Seeing and Observing in International Pharmacovigilance

Achievements and Prospects in Worldwide Drug Safety

Marie Lindquist

Published by *the* Uppsala Monitoring Centre

ISBN: 91-628-5588-3

Cover: Marie Lindquist
Printed by: Kopieringshuset, Uppsala, Sweden

Seeing and Observing in International Pharmacovigilance

Achievements and Prospects in Worldwide Drug Safety

een wetenschappelijke proeve
op het gebied van de Medische Wetenschappen

Proefschrift

Ter verkrijging van de graad van doctor
aan de Katholieke Universiteit Nijmegen,
op gezag van de Rector Magnificus Prof. Dr. C.W.P.M. Blom
volgens besluit van het College van Decanen
in het openbaar te verdedigen
op woensdag 11 juni 2003
des namiddags om 1.30 uur precies

door

Anna Marie Lindquist

Geboren op 21 December 1956 te Trollhättan, Zweden

Promotores:	Prof. dr. Y.A. Hekster
	Prof. dr. F.W.J. Gribnau
	Prof. dr. I.R. Edwards (Uppsala Monitoring Centre, Uppsala, Sweden)
Co-promotor:	Dr. R.H.B. Meyboom (UU, Netherlands)
Manuscriptcommissie:	Prof. dr. P. Smits
	Prof. dr. A.C. G. Egberts (UU, Netherlands)
	Prof. dr. V. Lepakhin (WHO, Geneva, Switzerland)
	Prof. dr. P. Routledge (University of Wales, Cardiff, UK)
	Dr. P. Koopmans

For my parents

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Scope and objectives of the thesis

Introduction

No drug is inherently safe. Consequently, no treatment involving medicines is free from the possibility of harm. A person taking a medicine is exposed not only to the likely benefits of such treatment, but also the risks of unwanted effects. The harm caused by medicines can range from mild side effects, leaving no permanent damage, to serious, sometimes fatal reactions. Sometimes a lack of effect or inadequate effect is the major problem. This is of critical importance in cases of serious illness, or where no alternative treatment is available.

When an individual experiences an adverse effect, the treatment can nevertheless be regarded as successful, provided that the actual benefits are perceived to outweigh the damage caused. However, since the outcome is not known before the treatment starts, a decision has to be made based on the available theoretical or empirical knowledge of the likely benefits of treatment, and an assessment of the level of risk involved. This poses several difficulties, both for the health care provider, and for the patient.

Prescribers need not only up-to-date knowledge of the disease and the available treatment possibilities, including medicines, but also good communication skills to convey this information to the patient in a way that the patient can understand and accept. The patient needs to take in new, often complex information, and assess what the consequences of treatment might be for her/him. The ability, and willingness, to accept risks with medicines vary between individuals, as does the ability to tolerate harmful effects once occurred. The seriousness of the treated disease plays an important role. A cancer patient might put up with hair-loss or bad nausea and vomiting if there is a chance of a cure, whereas someone with a trivial disease would, and should, not normally accept such adverse reactions.

Ideally, before any treatment starts, the patient should be involved in a thorough and open discussion about pros and cons of a particular treatment. During and after treatment, the effects, positive as well as negative, should be monitored and followed-up. Many adverse drug reactions (ADRs) can be prevented, or their negative impact reduced. This, however, requires knowledge of the pharmacological properties of medicines, the mechanisms of adverse effects, and an awareness of predisposing factors and the patient's susceptibility.

Given the reality of medical care in many countries, this could be seen as an unobtainable goal. Patient–doctor encounters often suffer from lack of time and resources, as well as from lack of knowledge and communication skills (which go both ways). A dialogue may be difficult if the patient has problems in understanding the often complex issues involved, or is not prepared to take responsibility, but prefers to leave all decisions related to the treatment to the

doctor. An open discussion also requires mutual trust – if this is absent, the whole idea of doctor–patient partnership falls.

Although new products are rigorously tested for efficacy and pharmaceutical quality, the safety information on a new medicine when first put on the market is limited to data from animal studies, in vitro studies, and preclinical and clinical trials involving humans. Listed below are some factors which indicate why these data are not sufficient to reveal the complete safety profile of a drug before its launch:

- animal toxicology is often not a good predictor of effects in humans;
- before marketing human exposure is such that only events with frequencies in the 'per thousand' range or higher are likely to be detected;
- events detected in clinical trials will be incompletely described and understood, since they are too few;
- particularly susceptible individuals are unlikely to be included in pre-marketing studies, and the effects of concurrent disease or medication are poorly assessed, since as far as possible study subjects are selected to be free of such complications.

With today's high level of sophistication in both medicine development and regulation it could reasonably be argued that new medicines generally are safer than those that they replace. It is also quite clear that the availability of modern medical treatment and an array of effective medicines have been hugely beneficial for individual patients, and for public health in general.

On the other hand, pharmaceutical companies' marketing efforts have in many countries become more forceful and widespread, including Internet advertising and direct-to-consumer promotion. The result could be that larger populations than in the past are exposed to drugs which have just been launched. Consequently, if there is a safety problem with a new drug, the magnitude of the public health impact is likely to be greater than in the past.

In the last decade, both companies and regulators have tried to make the pre-launch regulatory review process more expedient [Thomas, et al., 1998]. In doing so, there is always a risk that, instead of achieving greater efficiency, this could lead to sub-optimal safety review practices [Friedman, et al., 1999; Edwards, 2000; Suchard, 2001].

International pharmacovigilance

Much time, effort, and money is spent on drug safety, both before and after marketing. Even so, many reactions may not be detected until a drug is used after it is launched. This gives a strong a priori case for monitoring and assessing the safety of drugs after they have been marketed.

Pharmacovigilance is defined in a recently published guideline by the

WHO (World Health Organization) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems" [WHO, 2002]. The ultimate endpoint of such activities is to improve patient care and safety. Another motivation, mainly applicable on the societal level, is to reduce the substantial financial burden of adverse reactions upon the health care sector, and for society as a whole.

Drug safety concerns a whole range of individuals and groups in society: patients and health care providers, consumer groups, health economists, medical journalists and many others. Pharmaceutical companies are naturally interested in, and legally required to monitor their products' safety. National health authorities that are responsible for allowing medicinal products onto the market need to have surveillance systems in place to be able to fulfil their obligation.

Today, many countries all over the world have such systems in place, but this is a relatively new phenomenon in the history of medicine. The first national adverse drug reaction (ADR) reporting or 'drug surveillance' schemes were set up in the 1960s in some ten countries, to which doctors were invited to report cases of adverse reactions that they suspected were caused by medicines. These new initiatives were prompted by a major tragedy: thousands of cases of severe foetal malformations caused by thalidomide in the early 1960s. The schemes were voluntary, and the term 'spontaneous reporting' was introduced.

Since adverse reactions may occur in all countries and their early detection requires a reporting system covering large populations, the need for international cooperation in the safety area was recognised. Following recommendations by the WHO Scientific Group on Monitoring Adverse Reactions in 1964, and requests by the World Health Assembly in the following years, a pilot research project for the investigation of the feasibility of an international system of monitoring adverse reactions was started in 1968. The pilot project was based on a WHO drug monitoring centre, situated in Alexandria, the United States of America. Ten countries which already had started national drug monitoring centres agreed to participate in the project, and send their reports to the WHO centre.

The rationale for bringing spontaneous ADR reports from national reporting centres together into one, international, database, was that signals of suspected drug adverse reactions could be detected at an earlier stage than via national monitoring systems only, particularly for reactions occurring in low numbers at a national level. To meet the objective of enabling early warnings of drug problems, one of the primary tasks of the pilot project was to develop a signalling system.

After a successful conclusion of the pilot project, the WHO International Drug Monitoring Programme went into its primary operational phase in 1970. The WHO centre was relocated to WHO Headquarters in Geneva, Switzerland.

In 1978, the responsibility for the technical and scientific aspects of the

WHO Programme was transferred to the Uppsala Monitoring Centre (UMC), which was set up as a dedicated WHO Collaborating Centre for International Drug Monitoring, in Uppsala, Sweden.

Since then, pharmacovigilance has evolved from its early focus on detection of new adverse reaction signals towards the improvement of rational therapeutic practice throughout the world. To reach this ultimate aim, efforts are needed not only in the further development of pharmacovigilance as a science, but also in the areas of communication and education.

Objectives of thesis

Over a period of thirty years, important developments have taken place, in medicine and drug safety in general. The aim of this thesis is to demonstrate how the work done within the WHO International Drug Monitoring Programme, and, specifically, the Uppsala Monitoring Centre, has been instrumental in the introduction and enhancement of global pharmacovigilance, and how it has added to existing knowledge and thinking in the area.

For this purpose the thesis examines the global pharmacovigilance process from the perspective of the WHO Drug Monitoring Programme, as outlined in Figure 1.

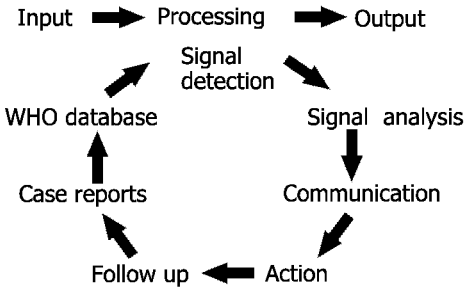

Figure 1. The WHO Programme signalling process

Maintaining and developing the database system, particularly its signalling function, was, and still is, one of UMC's core functions. There is no doubt that modern information technology (IT) has made data transfer easier and more effective. In theory, exchange of data between different systems could be an alternative to pooling data in a central database. However, one of the specific aims of this thesis is to demonstrate the advantages of a single independent,

international data source for signal detection and analysis.

The thesis describes and analyses scientific and methodological work carried out by the author and her team over the last twenty years. It concentrates on:

- the importance of good data processing
- the use of automated analysis tools to manage large amounts of data
- the use of other data to help set the case report information into a useful public health context, and, finally
- the need to communicate well at all levels and to be aware of consequences which may need revision of views as the processes evolve.

Chapter I, the Introduction, provides background information on the history of pharmacovigilance, the WHO Programme, and the Uppsala Monitoring Centre, and considers the complexity of international pharmacovigilance.

Chapter II, From data to signal analysis, deals with the international signalling process. The first three parts of chapter II describe signal sources, The WHO Programme reporting system, and the structure and contents of the WHO database. The fourth part discusses signals based on clinical assessment of case reports. The final two parts cover methods which have been developed by the UMC for signal detection and analysis, and show how the work done has contributed to the development of pharmacovigilance as a scientific discipline. The chapter will include discussions of strengths and weaknesses of the material and methods. Quality assurance issues are raised, and the impact of new technology is reviewed. Whilst the published papers included in this thesis are to be found in an appendix, they should be considered an integral part of this chapter.

Once a drug safety signal has been raised, its significance has to be assessed, communicated to relevant audiences, and acted upon. This demands a good deal of human thinking and effort, and requires the use of effective communication skills and methods, since the previous efforts will be wasted if the communication of the results is poor. For the foreseeable future, it is unlikely that computers will play a significant role in carrying out this type of work. The application of new technology will, however, improve the speed and ease with which communication can take place, and it can provide new tools that facilitate the work. Communication and follow-up will also be aided by quick and easy access to relevant information.

Communication issues of importance for international pharmacovigilance will be reviewed in Chapter III, From signal to balanced safety communication. The 'What, When, Who and How' of action and follow-up in relation to safety issues is analysed, and the roles of the different players involved are examined. The chapter ends with a discussion of possibilities for development of scientific methods for safety assessments taking into account benefits as well as harm.

Chapter IV, Towards safer use of medicines, is concerned with the

implications of the findings reviewed in the previous chapters, and discusses how the work done so far can be applied and further developed to enhance global pharmacovigilance as a science and contribute to a rational and safe use of medicines.

What is then the role of international pharmacovigilance, and the WHO Programme, in the near and more distant future? This thesis provides arguments to show that there is a continued need for an independent supranational body that will work in the interest of consumers, patients, doctors and other health care professionals around the world. This is as a complement to, and not in competition with the work done in this area by national and international regulators and pharmaceutical industry.

Chapter I – The Evolution of International Pharmacovigilance

This chapter provides background information on the history of pharmacovigilance, the WHO Programme, and the Uppsala Monitoring Centre, and considers the complexity of international pharmacovigilance.

Introduction

It is illustrative to record the history of pharmacovigilance as a series of milestones which introduced new thinking or rethinking to the discipline. This is done in Table 1, which is a listing of significant events in global drug safety and their primary and secondary effects. The changes before, and including, the benoxaprofen (Opren) incident in 1989 were mostly driven by disasters with high media profile throughout the developed world, and the responses were major rethinking of safety methodologies.

There are now safety systems in place around the world, which should allow for effective action and limit the numbers of individuals suffering. From the 1990s to date there has been a number of drug withdrawals, suggesting that the safety net works well. However, drugs being taken off the market cannot be seen as a straightforward measure of successful regulatory action. On the contrary, it could be seen as a failure. In the case of there being good alternative drugs available, patients could be exposed needlessly to a possibly dangerous drug. In other instances, patients not belonging to certain risk groups are deprived of a medicine that is being well tolerated by them.

One of the challenges for drug regulation is to get the balance right between, on the one hand, expeditious action with only limited and uncertain information to go by, and, on the other hand, a decision based on more solid evidence, but where the time spent on evaluation will cause a delay that in turn could result in unnecessary patient suffering.

The 'pill scare' in 1995 is an example of the difficulties involved. It has been suggested that, in this case, a rapid regulatory response caused unnecessary anxiety and a subsequent increase in birth rates and abortions in Europe [Skjeldestad, 1997; Furedi, 1999; Mills, et al., 1999].

Table 1. Important events and issues in international pharmacovigilance

Year	Issue	Primary and secondary effects
1937	**Elixir of sulphanilimide** Formulation defect results in poisoning	Improvements in pharmaceutical regulation
1961	**Thalidomide** Phocomelia in children of mothers who took this apparently safe drug	National and international collections of ADR reports Yellow card system, UK, 1964 WHO Programme in Alexandria, 1968 -attempt to create automatic signal generation ('Black box')
1969	**Clioquinol** New clinical syndrome reported from Japan (SMONS)	Ethnic susceptibility and drug use issues raised More realisation of complexity in drug safety Early work on pharmacogenetics
1970s	**Oral contraceptives** Venous thromboembolism	Realisation of underreporting being a major problem with spontaneous reporting systems Acceptance of the importance of epidemiological findings
1975	**Practolol** New clinical syndrome, recognised by UK expert (Oculo-muco-cutaneous)	Realisation that spontaneous reporting will not pick up 'events', not easily recognised as caused by drugs Prescription event monitoring introduced – IMMP in NZ. and PEM in UK. Causality algorithms developed
1978	**WHO Collaborating Centre for Drug Monitoring, Uppsala** No 'black box' signal detection solution found	Enhanced 'clinically useful outputs'-critical terms, WHO-ART, WHO-DD, quarterly summaries National collaboration enhanced under WHO Programme
~1980	**NSAIDs** Blood dyscrasias, GI bleeding a serious public health problem: high background incidence a problem	Development of pharmacoepidemiology Bayesian methods introduced
1982	**Benoxaprofen** Unusual photosensitivity Liver necrosis in the elderly UK takes action to remove drug from the market without US knowing	USA saw the need to have international industry ADR information - CIOMS I Need to have rapid alert system between agencies necessity for regular reporting CIOMS II – at risk groups WHO Programme invites more expert help WHO Programme begins to work towards greater openness France introduces regionalisation and a causality algorithm Start of thinking towards ICH

1989	**Fenoterol - beta agonists** Linked to death in asthma in case–control studies	Signals from case control studies debated strongly Use of data bases-nested studies become more accepted
~1990	**EU and ICH** Common European policies on pharmacovigilance promoted US, EU and Japan work on harmonised drug regulation	Rapid alert and common international decisions on signals Development of harmonised methods (ICH) and projects, eg. EPRG (European Pharmacovigilance Research Group)
1994	**ADR Signal Analysis Project (ASAP)** International drug usage data available from IMS and used in international signal analysis in WHO Programme	Development of methods for linking case report information in the WHO database with international drug denominators Increasing use of clinical databases Drug use data more widely used in drug safety
1997	**Bayesian Neural Network** An automated signal detection method with statistical information to aid expert opinion, in WHO Programme	Proportional reporting ratios (UK and Netherlands) Other statistical methods (USA and Australia)
1997	**Third Generation Oral Contraceptives** A small absolute increase in risk of death causes 'pill scare', followed by abortions and unwanted pregnancies	Focus on the need for good communications practice and consequence evaluation Re-opens debate on issues of evidence in pharmacovigilance

On the positive side, better systems and regulatory procedures means that safety issues on the whole are managed more effectively and expeditiously. Since the late 1980s, there has been a higher degree of pro-activity in pharmacovigilance, together with the development of more sophisticated epidemiological techniques and information technology (IT) support systems. Thanks to vastly improved computer capacity in recent years, it has been possible to develop techniques for automated quantitative comprehensive data assessment and signal detection.

1.1 The WHO International Drug Monitoring Programme

The need for systematic follow-up of drugs after their introduction into general use had been widely recognised after the thalidomide experience, and the appreciation of this need led to the establishment of national post-marketing

monitoring systems. Table 1 indicates that the UK 'yellow card system' was first, with several countries following suit.

The meeting of the Scientific Group on Monitoring Adverse Reactions in 1964 [Finney, et al., 1964] "sought to present more fully the requirements of, and benefits to be expected from, a world programme for monitoring and studying adverse drug reactions". The group concluded that "WHO should support the establishment of an International Centre for monitoring adverse reactions to drugs, and that there should be regular and systematic communication between the International Centre and recognized National Centres established for the same purpose".

Three main aims of monitoring of suspected drug reactions were identified:

- Early warning of serious adverse reactions to drugs, especially those previously unsuspected
- Evaluation of drug hazard
- Research into mechanisms of drug action, to aid the development of safer and more effective drugs.

Finney stated in 1965 that "monitoring is an important complement of, not an alternative to, formal clinical testing" and that the purpose of drug monitoring was "to ensure that observations on a large number of persons who receive a new drug are collated and used effectively; only so can a warning of any untoward consequences be given as early as possible" [Finney, 1965].

The Director-General of WHO referred in a 1966 report to the WHO Executive Board to the resolution WHA18.42 in which the 18th World Health Assembly requested the Director-General "to study further the requirements of an international programme for the collection, analysis, and dissemination to Member States of information on adverse drug reactions" [WHO, 1966]

After further resolutions by the World Health Assemblies in 1966 and 1967, a WHO Pilot Research Project for International Drug Monitoring was started in 1968. In a progress report to the 22nd World Health Assembly, the Director-General stated that 'the primary objective of monitoring drugs for adverse reactions is to define at the earliest possible time the capacity of a drug to produce undesirable effects' [WHO, 1969].

The scope of the WHO drug monitoring programme was to

- "assess the feasibility or otherwise of an international system of drug monitoring;
- develop the methodology for recording case histories of adverse reactions to drugs, systems for analysis and feed-back of data to national monitoring centres;
- undertake analysis of instored data on an experimental basis;
- provide facilities for searches by WHO staff and national centres on the

types and patterns of adverse reactions to individual drugs; and
- make a preliminary study of the contribution of drug monitoring to research in pharmacology and therapeutics".

The pilot phase started in 1968, with the participation of ten countries which already had developed national reporting systems. The project was funded by the government of the USA, which also provided offices and computer facilities. The WHO Pilot Project Centre was set up in Alexandria, USA, with a staff appointed by the WHO.

The pilot project was evaluated in 1970 and it was decided by the World Health Assembly to start a primary operational phase aimed at the establishment of an international system for monitoring adverse reactions. A WHO Drug Monitoring Centre situated within WHO Headquarters was established in 1971.

During the initial phase the staff of the WHO centre prepared and adopted methods of processing, recording, storing, linking and retrieving reports. A common reporting form was developed, together with a terminology for coding of adverse reactions, a system for coding of information on drugs occurring in adverse reaction reports and a computer system enabling storage and retrieval of the collected data. Guidelines on how to report were prepared, including a definition of an adverse drug reaction (ADR); "a reaction which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function" [WHO, 1972a].

A great deal of thought and effort went into the design and production of regular database output documents which would help finding new signals. These were scrutinised by professional staff at the WHO centre, and the findings discussed at international expert meetings.

Inter-country differences in reporting was identified as an important topic of study. At an expert meeting in 1972, the utilization of certain ratios for expressing differences of drug reaction experience between countries were discussed. It was recognised that "while such ratios may also be used to express differences in drug reaction patterns, no indication of absolute frequencies of adverse reactions to drugs can be presumed, as drug usage data would be necessary for this". However, "careful interpretation of resulting tabulations could reveal areas for further study and may be especially relevant for highlighting genetically mediated drug problems and possibly those related to environmental factors" [WHO, 1972b].

In the mid seventies a discontinuation of the Programme was considered, mainly due to financial constraints and changes of priority within the WHO. The survival of the programme was however secured when the Government of Sweden offered to meet the operating costs of the programme, and in 1978 the operational activities were transferred to Uppsala, Sweden, where a WHO

Collaborating Centre for International Drug Monitoring was established.

In order to be able to take over the process, the first task was to set up a new database system for the management of case reports of suspected ADRs from the then 24 countries participating in the Programme. Apart from maintenance and development of the database as an information and research tool, the main function of the new collaborating centre was to identify new adverse reaction signals. It was an early ambition of the Programme to develop a self-activating signal detection system. In 1974, Finney proposed a number of possible automated signalling approaches, based on statistical reasoning [Finney, 1974]. These were not implemented, mainly due to the heterogeneous and incomplete nature of the case reports forwarded to the database and computational constraints. Finney's work was seminal in much of what has developed since, however.

When developing methods for detection and analysis of ADR signals one must take into account the inherent limitations of spontaneous reporting systems. It is clear that case reports which are subject to various kinds of selection pressure and bias prior to being forwarded to the WHO database, and with various degrees of completeness and different national manipulation in format, do not make ideal material for statistical analysis. The biases that affect reporting, the fact that only a small , but variable, percentage of suspected reactions are reported and the incompleteness of the data have been major barriers to progress in pharmacovigilance. Some of these problems are accentuated in an international system with data pooled from many countries, with differences not only in spontaneous reporting systems, but also in medical practice. Also, lack of access to drug utilization denominators, particularly on the international level, has made assessments of risk levels difficult.

Although Finney's early pioneering work was not realised, the level of computerisation of the centre in Geneva was sophisticated for its time. During the initial phase of the Programme a number of standard output documents were introduced, containing summaries of the information held in the database. These listings, produced on a quarterly basis, provided information that was thought valuable for human review, and formed the basis for signalling of new drug–ADRs.

With some modifications and additions, the result of quarterly screenings of the database in the form of paper printouts continued to be the main signalling mechanism after the WHO centre moved to Sweden. In the mid-80s a programme for intensified review of the quarterly listings was introduced. Selected documents were sent to a panel of experts for scrutiny and identification of possible signals. After review of the individual case reports, a summary of the findings were published in a document *Signal* which was distributed to all national centres participating in the WHO Programme. In addition to production of the standard outputs and the intensified review process, the database was frequently screened on an ad hoc basis, using standard

search programs which had been developed by the WHO centre in Uppsala in the 1980s. These programs allowed quick and comprehensive answers to the most frequent types of questions, with the search results presented either as formatted tabulations, or as complete records in open text for the individual case reports selected by the given search criteria. Most searches were done by the WHO centre staff in Uppsala, but the same search facilities were also made available to national centres via on-line connections to the WHO database. For queries where none of the standard search programs were applicable, the WHO centre staff formulated search criteria using a computer query language built into the database system. When personal computers (PCs) were introduced in the late 1980s, sub-sets of data could be downloaded from the main database and processed further locally, with a wider range of data presentation and layout possibilities than before.

Over the years greater understanding of the nature of the data and its flaws, greater computer processing power and better analytical tools and approaches have allowed pharmacovigilance to move forward as a scientific discipline. Two major steps forward for the WHO centre and the Programme were taken in the mid-1990s when new methods for signal detection and analysis were developed. The Bayesian neural network approach for comprehensive data assessment and automated signalling, and the developments in the area of combining ADR data with drug usage information, are described in detail in chapter II of this thesis.

1.1.1 The role of national centres

From the start in 1968, the international drug monitoring programme has depended on the contributions of national centres. The forwarded case reports of suspected adverse drug reactions form the basis of the operations of the programme, also, national centres provide an essential pool of experience and competence which have been instrumental for the continuous development of the WHO Programme and pharmacovigilance as a whole.

The objectives of national centres were detailed in a WHO report of 1972 as "a) to identify as quickly as possible important or serious adverse reactions to drugs, and b) to attempt to establish the causal relationship between the drug and the adverse reaction. The centre should provide data and evaluations calculated to increase the safety of drug use."

"To achieve these objectives the national centre should develop and investigate methods for data acquisition, ensuring that information on the association between drugs and adverse reactions is as complete and reliable as possible. Techniques should be developed for data evaluation and interpretation, and for the distribution of information about adverse drug reactions to appropriate professional groups and bodies responsible for drug safety. The centre should also aim to provide other national centres and the

WHO centre with data and information in a suitable form".

The set up of a national pharmacovigilance centre depends on the organisation and development of the healthcare system in the country. In many countries, the national centre is part of the drug regulatory agency, whereas in others, the centre is situated in a hospital or academic department. In any case, a well functioning pharmacovigilance system requires "the presence of an effective drug regulatory body in the country that has the will and potential to react to signals emanating from the centre and to take proper regulatory measures. WHO considers this point as vital: a pharmacovigilance system must be backed up by the regulatory body." [UMC, 2002b]

Over the years the international network has developed from the original ten countries to the present 68 national centres which interact with each other and the WHO Collaborating Centre as the technical co-ordinator. Although the scope of global drug safety has changed, to include issues such as counterfeit drugs and non-orthodox medicines amongst many others (for a more detailed account, see 1.2 below), the basic operation of national centres remains consistent with the original role cited above. New guidelines for setting up and running a national centre have been produced, taking into account the current demands of safety monitoring [UMC, 2002b].

Basic steps in setting up a Pharmacovigilance Centre

1. Make contacts with the health authorities and with local, regional or national institutions and groups, working in clinical medicine, pharmacology and toxicology outlining the importance of the project and its purposes.
2. Design a reporting form and start collecting data by distributing it to hospital departments, family practitioners, etc.
3. Produce printed material to inform health professionals about definitions, aims and methods of the pharmacovigilance system
4. Create the centre: staff, accommodation, phone, word processor, database management capability, bibliography etc.
5. Take care of the education of pharmacovigilance staff with regard, for example, to:
    - data collection and verification
    - interpreting and coding of adverse reaction descriptions
    - coding of drugs
    - case causality assessment
    - signal detection
    - risk management
6. Establish a database (administrative system for the storage and retrieval of data)
7. Organise meetings in hospitals, academia and professional associations, explaining the principles and demands of pharmacovigilance and the importance of reporting.
8. Promote the importance of reporting adverse drug reactions through medical journals, other professional publications, and communications activities.
9. Maintain contacts with international institutions working in pharmacovigilance, e.g. the WHO Department of Essential Drugs and Medicines Policy (Geneva) and the Uppsala Monitoring Centre, Sweden.

1.1.2 The role of the WHO centre

The role of the WHO Drug Monitoring Centre when located in Geneva in 1971 was to function as "the operational centre responsible for the development of the international system on the basis of a two-way flow of information on suspected adverse reactions to drugs, in collaboration with national centres" [WHO, 1972a].

This role was maintained when the WHO Collaborating Centre was set up in Uppsala, Sweden, as stipulated in the agreement signed between the Swedish Government and the WHO:

The functions of the Centre shall be -

a) to collect, analyse, store, retrieve and tabulate reports on suspected adverse reactions to drugs received from national and other centres participating in the WHO Programme;
b) to follow the scientific literature and gather publications on adverse reactions to drugs;
c) to develop methods for assessing rate and significance of adverse reactions, and for obtaining early warnings of serious reactions;
d) to initiate retrospective and prospective studies on occurrence of adverse reactions to drugs;
e) to undertake scientific studies of problems related to adverse reactions to drugs;
f) to provide the World Health Organization with the results obtained under (a), (b), (c), (d) and (e), and to assist in preparing relevant information for distribution to national and other centres participating in the WHO Programme or to Member States, as appropriate;
g) on request by the World Health Organization, to assist in the establishment or development of national monitoring centres in developing countries and in the improvement of their monitoring systems;
h) in collaboration with the World Health Organization, to organize scientific meetings to review and evaluate the information collected by the Centre and to review its work.

Article 2 of the above agreement stated that "the activities shall be carried out withing policies determined by the World Health Organization which will retain full responsibility for coordination of the programme and for decisions on the participation of national and other centres".

It should be pointed out that the WHO Programme and the WHO Collaborating Centre/UMC are intrinsically linked, and therefore, throughout this thesis, it has not always been possible, nor desirable, to make a clear distinction between the two. When the 'WHO Programme' is used, it refers to the network of members in general, including the WHO Headquarters and the UMC. When the 'WHO Collaborating Centre' or 'UMC' is used, this mainly refers to technical and scientific matters co-ordinated and carried out by UMC staff.

1.1.3 The relationship with EMEA and ICH

The European Agency for the Evaluation of Medicinal Products (EMEA) started its operations in 1995, with the mandate to evaluate and approve new medicines for the whole European Union (EU) through a centralised authorisation procedure. Also, the EMEA co-ordinates the European pharmacovigilance system for centrally authorised medicinal products.

According to a European Council regulation, the EMEA "shall collaborate with the World Health Organization (WHO) on international pharmacovigilance and shall submit promptly to WHO appropriate and adequate information regarding the measures taken in the European Union related to the marketing authorisations of centrally authorised medicinal products which may have a bearing on public health protection in third countries" [EMEA, 1998].

Thus, the WHO and the UMC receive some information directly from the EMEA, but the reporting of adverse reaction case information to the WHO Programme is done by the individual European countries.

In all its communications, the UMC places the EMEA on an equal footing with the national centres participating in the WHO Programme. Any information provided to national centres is also sent to the EMEA.

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is joint project involving the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions. The project was set up to discuss scientific and technical aspects of product registration, with the aim to make medicines available to patients with a minimum of delay. The regulatory parties are committed to implementing the tripartite, harmonised guidelines and recommendations.
[ICH, 2000].

The WHO has observer status in the ICH work, and it thus is not directly involved in the decision making process, but expected to provide a link to non-ICH countries.

1.2 The widening scope of pharmacovigilance

A recent WHO publication highlights the new challenges for pharmacovigilance: "Within the last decade, there has been a growing awareness that the scope of pharmacovigilance should be extended beyond the strict confines of detecting new signals of safety concerns. Globalization, consumerism, the explosion in free trade and communication across borders, and increasing use of the Internet have resulted in a change in access to all medicinal products and information on them.

These changes have given rise to new kinds of safety concerns such as:

- illegal sale of medicines and drugs of abuse over the Internet
- increasing self medication practices
- irrational and potentially unsafe donation practices
- widespread manufacture and sale of counterfeit and substandard medicines
- increasing use of traditional medicines outside the confines of the traditional culture of use
- increasing use of traditional and herbal medicines with other medicine with potential for adverse interactions." [WHO, 2002]

According to the same publication, "the specific aims of pharmacovigilance are to:

- improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions,
- improve public health and safety in relations to the use of medicines,
- contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost–effective) use, and
- promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public."

As pharmacovigilance has evolved, the scope of the WHO Collaborating Centre has been extended accordingly, as reflected in the centre's new goals and vision, and the introduction in the mid-1990s of a new working name, the Uppsala Monitoring Centre (UMC).

The UMC vision

Our vision is to aid WHO's leadership by providing excellence

- in the science and concepts in all aspects of pharmacovigilance
- to prevent harm to humans from the effects of medicines
- to gather and share objective intelligence and opinion in the field of drug safety through open and transparent means of communication
- to support the promotion of the rational use of drugs, and the achievement of improved patient therapy and public health
- in global education and communications in benefit, harm, effectiveness and risk in medical therapy

In addition to managing and developing the core functions of data management and signal detection, the UMC has done much work in the areas of :

- Information and feedback
- Education and support
- Harmonisation efforts
- Development of tools
- Research

Over the years, the audience has also been widened from regulators only to a broader range of drug safety stakeholders, including pharmaceutical manufacturers. Active collaboration with other international organisations contributes to the extended profile. These organisations include:

- IMS Health – provider of drug utilization data for safety analyses;
- the Council for International Organizations of Medical Sciences (CIOMS) – produces guidelines and definitions in the drug safety are;
- International Society of Pharmacovigilance (ISOP) – a professional forum with an emphasis on the clinical aspects of pharmacovigilance;
- International Society of Pharmacoepidemiology (ISPE) – a professional forum with an emphasis on pharmacoepidemiological methods.

Table 2 summarizes a series of achievements of the UMC and the WHO Programme.

Table 2. Major achievements from the start of the WHO Programme for International Drug Monitoring

Year	What was accomplished
1968	Collection of international data made in a consistent and agreed-on way
1968	Development and maintenance of an international ADR terminology and a drug dictionary
1969	Definition of adverse drug reaction (ADR)
1971	Production of regular formatted output reports
1972	WHO Technical Report: International Drug Monitoring: The Role of National Centres
1978	Transfer of operational responsibilities to the WHO Collaborating Centre in Uppsala, and the setting up of a relational database system for storage and retrieval of information
1979	Organisation and running of regular national centres' meetings

Table 2. Major achievements from the start of the WHO Programme for International Drug Monitoring cont.

Year	What was accomplished
1981	Making a computerised version of the drug dictionary available outside the WHO Programme
1982	Coding of all medicinal products according to the Anatomical Therapeutic Chemical (ATC) classification
1982	Introduction of an Adverse Reaction Newsletter containing summaries of ADR information received from National centres
1985	Publications of studies in major medical journals
1985	Setting up of an international expert panel for intensive review of data
1985	Production of regular summaries of new safety signals, based on information in the database, provided to National centres in the *Signal* document
1991	Introduction of an on-line WHO database search programme available to National centres
1991	Agreement on definitions of adverse event, side effect and causality assessment terms
1993	Introduction of a Windows based client server programme for on-line database searches
1993	Organisation of regular training and educational activities
1994	Development of a methodology for the use of denominator data for calculation of ADR reporting rates
1995	A widening of the audience from regulators only
1996	Proposals of methods for benefit–harm assessment
1997	Implementation of a data mining tool for automated signal detection
1997	Promotion of communication as a necessary discipline
1998	Introduction of Internet discussion group for National centres
2000	Joint WHO–UMC guidelines for setting up and running a Pharmacovigilance Centre
2002	Implementation of a new database system enabling storage and retrieval of more detailed information, and with better handling of historical data

Chapter II – From data to signal analysis

This chapter deals with the international signalling process. The first three parts of chapter II describe signal sources, The WHO Programme reporting system, and the structure and contents of the WHO database. The fourth part discusses signals based on clinical assessment of case reports. The final two parts cover methods which have been developed by the UMC for signal detection and analysis, and show how the work done has contributed to the development of pharmacovigilance as a scientific discipline. The chapter will include discussions of strengths and weaknesses of the material and methods. Quality assurance issues are raised, and the impact of new technology is reviewed.

Introduction

Since the safety profiles of newly launched drugs are only tentative, it is essential to closely monitor marketed medicines in order to learn more about their effects, positive as well as negative. To this end, a number of approaches for data collection in routine clinical practice have been developed, all having their strengths and weaknesses.

After an initial adverse drug reaction (ADR) association has been identified, the accumulation of more information is needed in order to decrease the uncertainty and increase the level of evidence as to the character and extent of the problem. This signal evaluation phase can be seen as a stepwise process in which the use of different methods and/or data sources contribute to a gradual increase in knowledge (see Fig 3.) The risk of inappropriate action when drawing conclusions based on preliminary information must be weighed against the risk of exposing patients to drugs which, after extensive analyses, would show to have an unacceptable safety profile. Throughout this process, therefore, and depending on the issue under investigation, time and cost should be carefully considered against the need for more knowledge, and the limitation of harm to patients.

2.1 Signal information sources

Information about the safety of medicines can be derived from large, or even whole populations on a continuous basis, at the one extreme, or can result from in-depth analyses of specific risk situations. From the point of view of detecting signals the breadth of the coverage seems more important than narrow, detailed coverage.

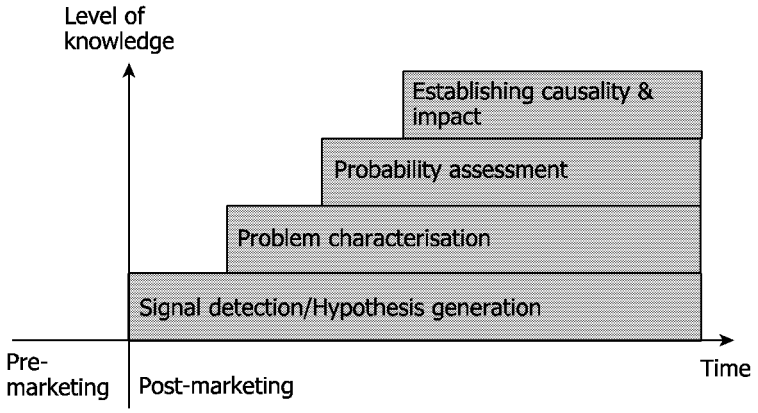

Figure 3. From hypothesis to harm–benefit evaluation; knowledge versus time

Post-marketing observational studies can broadly be divided into descriptive and analytical. The former include ad hoc case reports, case series, and systematic collection and analysis of case report data on a regional, national or global scale, often referred to as 'spontaneous reporting systems' (SRS). Prescription–event monitoring (PEM), intensive hospital monitoring, record–linkage studies, case–control and controlled cohort studies are examples of analytical studies.

Signals of hitherto unknown harmful effects can in theory be identified by any of the above methods, although in practice the first indications of a new adverse effect are most likely to come from descriptive data sources since they can cover broader, if not complete populations [Meyboom, et al., 1997]. On the other hand, analytical studies provide an incidence estimate, which one cannot obtain using descriptive data (case reports) alone, as well as focussing on specific problem areas [Strom, 2000].

Controlled experimental studies can, in addition to providing pre-marketing information on common adverse reactions, at least in theory be used to provide more definite evidence of causality than any of the other methods. A more detailed description and a discussion of the strengths and weaknesses of the different methods follows below.

2.1.1 Case reports

The first signal of a possible problem is often based on case reports, either communicated directly in professional journals by doctors, or detected through screening of systematically collected case reports in spontaneous reporting systems (SRS). Case reports of suspected adverse reactions are based on observation and concern by an individual health professional or patient, and may refer to any adverse effect. Descriptive data on the patients and the region

or country in which the reaction occurred can give an indication of a pattern, and possible etiology of an adverse reaction. Systematic collection of case reports in a spontaneous reporting system (SRS) has the advantage that the whole population in the region or territory covered can be monitored continuously, which allows for detection of rare reactions, and of changes in patterns or reporting frequencies over time. With the development of effective analytical tools, disease patterns can be identified and described for case series. Regular screening of case reports is the most cost effective and rapid way of detecting new signals of negative effects of medicines. This is the raison d'être of the WHO database, which, in addition to national SRSs, offers one international source of data.

In clinical practice, the presence of concomitant medication and/or other disease than that treated with the suspected medication is common. Therefore, there is an obvious risk of confounding, and causality assessments are not always conclusive. The likelihood of an accurate case assessment increases with availability of complete and correct information, and access to follow-up information. This still leaves the possibility of external bias due to e.g. publications in the general or medical media focussing the reporters' attention on a particular topic.

An initial signal evaluation can be made using case reports only. Accumulation of more cases with time may strengthen the signal, particularly if reports keep coming in from different sources (more than one country or from different reporters in one country). This reduces the likelihood of a chance event or selection bias by an individual reporter. Also, with more reports a better characterisation of the problem can be made.

The incidence of adverse reactions cannot be calculated from spontaneous reports only, the obvious reason being the lack of a denominator (the size of the exposed population). Furthermore, ad hoc case reports published in the literature do not provide a numerator that can be used for estimating the incidence of the reported reaction/s, whereas the reporting frequencies obtained from SRSs at least give an approximation of real occurrences of ADRs in clinical practice. However, such estimates are uncertain due to the under-reporting affecting SRSs, the extent of which is suggested to be up to 95% [van der Klauw, et al., 1993; Rawlins, 1995; Belton, 1997; Begaud, et al., 2002]. Also, there is often a bias towards unexpected and serious reactions. This bias is magnified in some SRS to which reporters are encouraged, or required, to send in only cases fulfilling certain criteria, e.g. newly marketed drugs, unlabeled and/or serious reactions. Thus, differential under-reporting can affect both the ADR profile for a drug (e.g. selective reporting of serious reactions), and comparisons of reporting frequencies for different drugs (e.g. selective reporting of problems with new drugs). The reliability of approximations made, and the conclusions that can be drawn, therefore depend on the level of background knowledge of the factors that may have influenced the reporting in a given situation.

2.1.2 Case reports together with drug usage information

Signals with better information as to their frequency of occurrence can be obtained by combining case report information with drug usage information. In such correlational studies the addition of sales or prescription data as a denominator allows for an estimate of the incidence in the exposed population. Also, it can provide additional descriptive information which allows a better characterisation of the affected individuals, particularly the treated diseases and dosages used, and the reactions. This methodology was used by the Food and Drug Administration (FDA) in the US when analysing ulcerogenicity of piroxicam and other NSAIDs [Rossi, et al., 1987]. Using systematically and continuously collected international data, as provided by IMS Health, together with the case report information in the WHO database, longitudinal analyses can be made including a large part of the world's population.

Although whole populations can be covered, most often drug usage data is collected using sampling methods, and therefore, in addition to the uncertainties affecting the numerator, the generalisability also depends on the validity of the methods used in obtaining the denominator information. There are other reasons why results must be interpreted cautiously, including the following:

- the numerator and denominator information are obtained from separate sources, therefore different biases may apply;
- correlational studies refer to populations rather than individuals, thus it is not possible to link an exposure to occurrence of an outcome in the same person.

New signals can also be found in correlational studies, although, at present, for this to happen some sort of selection, either of drugs or adverse effects, will have to been made. In the future, more systematic screenings could be made using combined data sets.

2.1.3 Prescription–event monitoring systems

Prescription–event monitoring as a method for postmarketing surveillance was pioneered by E.G. McQueen in New Zealand, and W.H.W. Inman in the UK, in 1977 and 1980 respectively [Coulter, 2002; Shakir, 2002]. Complete cohorts of exposed patients with more accurate numerator information allow for a better estimate of incidence in the exposed population, compared with using case reports alone or in combination with drug usage data. In PEM normally only a limited sample population is covered, which could make generalisation difficult. The ability to find new signals is also limited, both due to the fact that a smaller population is covered, and also these systems normally do not cover all medications, but rather focus on a selected group, usually newly marketed

drugs. Whilst unexposed patients are not included, other exposed cohorts can be used for comparisons.

2.1.4 Case–control and controlled cohort studies

Case–control and controlled cohort studies can add further information to the existing knowledge by giving an estimate of the incidence of the negative effect in both exposed and non-exposed populations, as well as controlling for some biases and confounding. Thus one can get an idea of whether the risk of experiencing a particular reaction is higher in a drug taking population than in a non drug taking population.

Although cohort studies can give a more accurate estimate of the relative risk (incidence in exposed compared with incidence in non-exposed) than case–control studies (unless the latter are population based), their cost and the time required limit their use. Case–control studies cover a limited sample of individuals with a particular target disease. Any new signals that would emerge would therefore be confined within this selection, but could provide additional information on already identified associations. Contrary to this, cohort studies could well be used for identification of new signals, provided that the study would not be limited to a specific target effect, and that the sample size was large enough to enable detection of rare reactions.

Ad hoc pharmacoepidemiological studies refer to studies where information on the study subjects is assembled specifically for the study. This is in contrast to analytical studies using information already gathered in computerised, longitudinal health care information database systems. Some of these are so-called record linkage systems, where data from several different databases are connected through a common patient record identifier. The use of such databases has an advantage both with regards to speed and cost as compared with ad hoc studies, but does not offer full flexibility of study design. Examples of such database systems are: the General Practice Research Database (GPRD) and the Tayside Medicines Monitoring Unit (MEMO) in the UK, the PHARMO system in the Netherlands, the Medicaid databases in the USA, and the Saskatchewan databases in Canada.

As with any epidemiological methodology, case–control studies and, to a lesser extent, cohort studies are not exempted from bias and confounding. The risk of selection and recall bias is low in cohort studies, whereas it is high in case–control studies. Also the probability of confounding is low in cohort studies, and higher in case–control studies. The main advantage with a case–control study, apart from cost and time, is that it offers good opportunities for study of rare diseases and for follow up.

2.1.5 Controlled experimental studies

The only way of obtaining definite evidence as regards incidence of an adverse reaction, with a control of confounding, would be to perform population based randomized controlled trials on every drug. This is however not feasible due to the time and costs involved, and therefore the use of clinical trials as a source of new post-marketing safety information is limited. On the other hand, once a signal has been identified, a clinical trial could provide more reliable information than any other method, but only for relatively common adverse reactions. Also, there are ethical issues involved and altogether the practical usefulness of experimental study designs for signal evaluation is limited.

Figure 4 summarises the relationship between level of evidence and the available methods for working with a hypothesis.

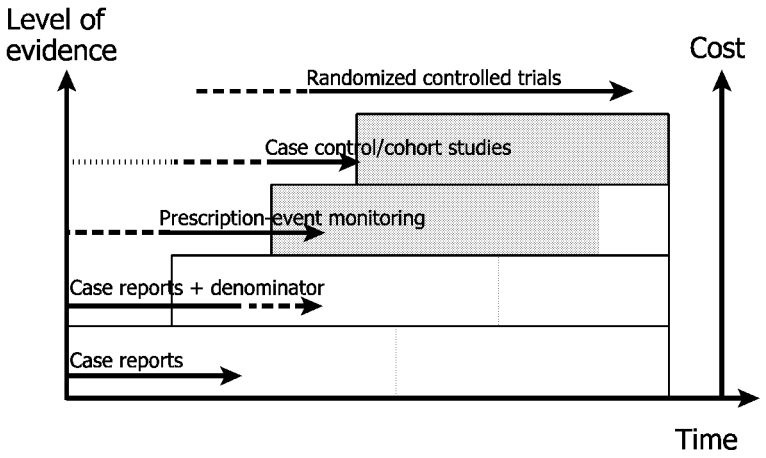

Figure 4. Data sources in pharmacovigilance – evidence of causality versus time and cost

2.2 The WHO Programme reporting system

Most national pharmacovigilance systems, when set up, were based on voluntary reporting, mainly from physicians – in particular general practitioners and internists. In some countries, hospital doctors are the stronghold of general medicine and also are the main source of case reports. Doctors are still major providers of reports, although many countries allow reporting from other health professionals in addition. Reports from doctors have the advantage of usually containing a medical diagnosis, which can easily be coded using a medical terminology.

In the past, pharmacists were not normally expected to be able to

contribute to the reporting of adverse reactions. However, in several countries clinical pharmacists now play a major role in ensuring the reporting of adverse reactions and the completeness of data, and pharmacist reporting is on the increase worldwide. The same applies to nurses.

Regulations on medicines and pharmacovigilance give in many countries pharmaceutical companies and their system of sales representatives an important role in the collection of adverse reaction case reports. In some countries a large proportion of the total number of reports have first been received by pharmaceutical companies, and from there sent on to the national pharmacovigilance centre. For instance in the USA, a vast majority of reports are provided by companies. Most countries forward company reports to the UMC for inclusion in the WHO database, but there are some exceptions, e.g. France and Japan.

Regulators' influence on reporting is strong, not the least since it is the regulators who decide not only who are allowed to report to the national centre, but when, what and how to report. According to a survey made in 1997 [Olsson, 1997] 41 countries of 56 responding to the questionnaire had voluntary doctor reporting, as compared with 9 where doctor reporting was mandatory and 6 which had a combination of voluntary and mandatory reporting. As can be seen in Table 3, forty-four of these countries also allowed reports from other health professionals, and 23 accepted reports from consumers. Forty countries accepted reports from marketing authorisation holders (MA holders) – but in contrast to the doctor reporting, reporting from MA holders were mandatory in most countries where such reports were received (28 of 40).

The issue of consumer reporting is interesting. In 23 WHO Programme member countries consumers can report directly to the national authority, or to the manufacturer, whereas consumer reporting is not accepted in 33 countries. There is an ongoing debate as to the feasibility, and relevance, of consumer reports. On the one hand, it is argued that consumer reports will only add 'noise', i.e. minor and already well known adverse reactions, which will overburden the systems and those who analyse the information. On the other hand, consumer reports could provide unique insights into what individuals taking medicines consider important effects for them, and also add new knowledge about possible drug related signs and symptoms, if not necessarily confirmed diagnoses [CRM – Policy and Practice, 2000; Editorial, Lancet, 2002].

Hence, an inter-country heterogeneity in various respects is built into the system already at the outset. This has to be considered whenever information is compared between countries, or indeed, when data is collected on a global scale. It is likely that doctors' reporting will differ from that of pharmacists and nurses, but particularly as compared with consumers or patients. Some studies have been done in this area, but much more needs to be done to elucidate how great the differences in reporting are, and what those differences consist of [Savage, 1985; Emerson, et al., 2001; Bäckström, 2002; van den Bemt, 2002].

Table 3. Type of reporting in countries participating in the WHO Programme

Type of reporting	Doctors	Other health professionals	Consumers	Marketing authorisation holders
Mandatory	9	5	1	28
Mandatory/Voluntary	6	1		4
Voluntary	41	38	22	8
Not accepted	0	12	33	16

In about half of the national reporting systems, doctors are encouraged or required to focus particularly on certain kinds of drugs or reactions. Table 4 shows that the emphasis may be on new drugs in general, or on selected drugs/drug categories. The selection can be predefined drugs or drug groups, or based on 'drugs of interest' from a safety perspective. This introduces another bias.

Table 4. Emphasis of reporting encouraged/requested in countries participating in the WHO Programme

Reporting emphasis	Type of reporting		
	Mandatory	Mandatory/ Voluntary	Voluntary
Selected drug categories			1
Selected drug categories and drugs of interest			1
Drugs of current interest/with safety issues			3
New drugs (in general)	2		4
New drugs and selected drug categories	1		2
New drugs and drugs of interest		1	3
New drugs and serious reactions			1
Selected new drugs		1	2
Selected new drugs and drugs of interest		1	1
Serious unexpected reactions	1		
No emphasis made	5	2	21

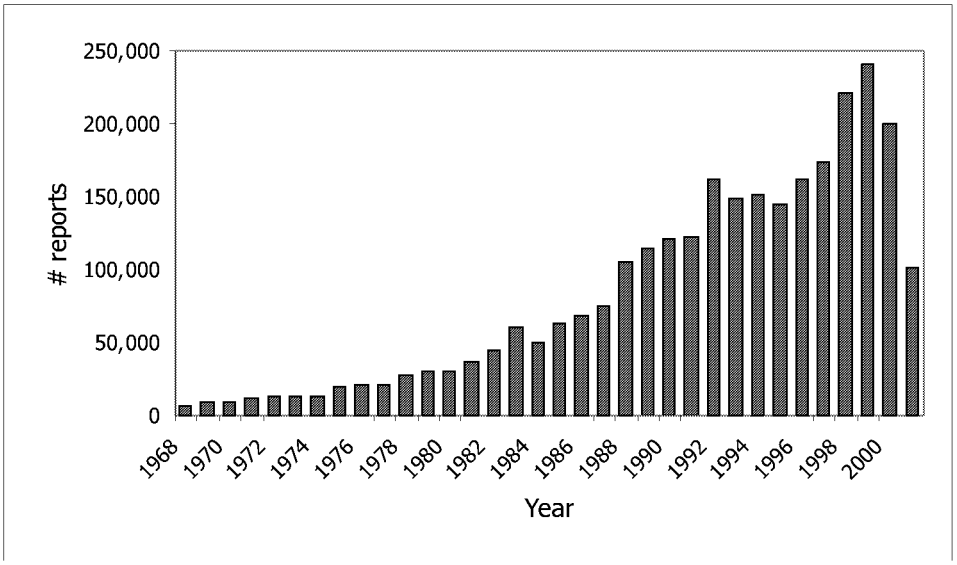

Figure 6. WHO database reports per year

In March 2002, there were 67 countries participating in the WHO Programme, as compared with the original ten countries (see Figures 7 & 8). Now, all continents of the world are represented, but, particularly in Africa, and South America, major countries are, for different reasons, still not in a position to join the Programme as full members.

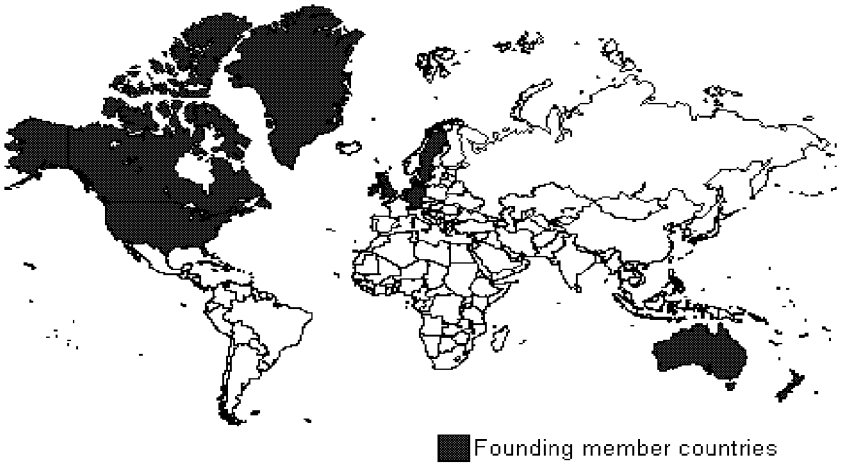

Figure 7. WHO Programme member countries in 1968

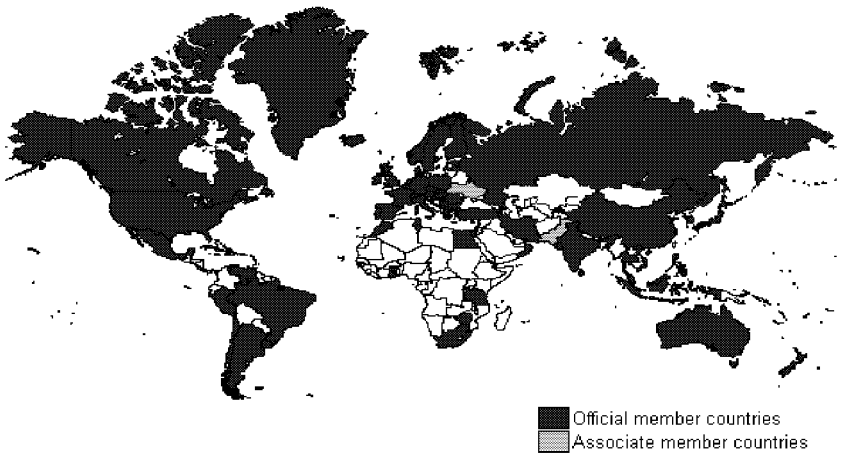

Figure 8. WHO Programme member countries March 2002

2.3.1 Technical aspects of the new database system

Over the years many technical modifications were made as to the ways in which the data held in the WHO database was processed and retrieved. New outputs were introduced, and systems for on-line connections to the database enabling remote retrieval were developed. However, the fundamental database structure, determining what kind of information could be captured, and how it was stored, remained unchanged from 1978.

In the mid-90s, the UMC decided to start the work on a new database system for the management of WHO Programme case report information. The main focus of the new software development efforts was to implement the progress made in international harmonization, with the specific aim to reflect the conclusions of the CIOMS 1A working party and the subsequent ICH–E2b working group, which defined pharmacovigilance information which was considered necessary, and suitable for international exchange. The goal set for the new system was to fulfil the needs of existing and future users in terms of internationally agreed data fields, and also an improved functionality, with more efficient solutions for report handling, data retrieval and analysis.

Paper II *Lindquist, M., The WHO Programme for International Drug Monitoring: The Present and Future, 1998* describes the technical structure and function of the new WHO database system, which is up and running as of September 2002. Remote access to the information in the WHO database will take place through Internet-based interfaces, a main advantage of which is that the user does not have to install the application interface software on the local

computer, but can run the programme from an Internet browser. As new search modules are added, or other improvements made, these become instantly accessible for all users, without the need for re-installation of software.

One lesson learnt during the development phase was that, no matter how thorough the initial work producing a user requirement specification was, it was impossible at the outset to anticipate the need for further specifications and modifications that were necessary as the project proceeded. Since information technology (IT) is an area where incessant change and a continuous flow of new versions of programs and tools is the norm, re-thinking of solutions and re-programming of already completed modules had to be done throughout the project.

The data is stored in a relational database, which can be regarded as filing cabinets for structured information. Unlike manual filing systems, it is easy to link one set of data to another, and to sort the information by any data category. Relational database management systems (RDMS) include the data itself, stored in tables linked by key fields, and tools for data entry and retrieval. The standard programming language used for this purpose in most RDMS is the Structured Query Language (SQL). SQL statements allow a user to define commands to the database, for instance to retrieve information from one or more tables. They can be executed separately, or be incorporated in data programs written in other programming languages. Such programs can be installed, and run, from a user computer (client), which communicates through the user interface with a remote host computer (server) where the database resides. The WHO database system belongs to this category. There are also personal computer (PC) RDMS, with the database residing on the PC, or on a local area network (LAN), instead of on a separate host computer.

Structured Query Language (SQL)
A language used for structure definition, retrieval and modification of data in a database system.

Recent versions of relational database management systems (RDMS) allow added functionality compared with older versions. For example, it is now possible to move computer program logic from the user interface to the server, by using so-called Persistent Stored

Persistent Stored Modules (PSM)
Collections of defined functions and procedures containing programming logic and SQL statements. PSM are stored in a database, and executed by a database programme.

Triggers
Procedures executed from within a database when data is added, modified, or deleted.

Modules (PSM) which are essentially programs stored and run from within the database. This has the benefit of minimising network traffic, and thereby increasing speed. In addition, PSM provide better structure, since SQL statements and programming logic is stored in the database itself and not spread in other programs.

'Triggers' are another new development. They protect the integrity of the information in the system by preventing erroneous, inconsistent or unauthorized data changes. 'Triggers' define SQL statements that are run when a user attempts to modify data in a table or a table view. As with PSM, these functions are built in to the database itself, and not only being executed when data is manipulated through a programmed user interface.

The need to make textual information available on the World Wide Web (WWW), or Internet, in a standard, structured, format has led to the development of 'mark up languages'. These allow blocks of text in documents to be ordered and headed, and the information is organised in a transparent way so that it can be searched and manipulated by anyone. A main technical event in recent years is the development of the Extensible Markup Language (XML) which can be seen as a simplified 'dialect' of the Standard Generalised Markup Language (SGML). Like SGML, XML is an international, platform-independent, standard based on plain ASCII text which allows document-based information to be shared and re-used across applications and computer platforms in an open, vendor-neutral format. Since the content is separated from presentation, multiple output formats are facilitated.

The fact that XML is a neutral, international standard is of course very valuable in an international pharmacovigilance system. The availability of XML has opened up a whole range of possibilities, from use in data retrieval and presentations to improved data transfer between systems.

The new web-based database search program that has been developed makes use of XML in presentation of the search results. So-called 'style sheets' are applied to enable different displays of the same data set. This means that the same information or pieces of information can be grouped together and presented in various ways. XML is also used for displaying the contents of the WHO Drug Dictionary, the Anatomical Therapeutic Chemical (ATC) classification and the WHO Adverse Reaction Terminology (WHO-ART) in inverted tree structures. The user can browse the contents of the classification, starting on the highest level for a broad overview, and continuing down the hierarchy to the most detailed level from which selection of individual code values can be made. This display provides a user friendly way of enabling the selection of search criteria.

Finally, when transferring data between systems, XML data files improve security and data handling since the file description and the identification of data fields are not separated from the data itself, as is the case when using fixed

length ASCII files, but part of the structured data document. Changes in format and layout are therefore directly identifiable, thus reducing the risk of errors.

Anatomical therapeutic chemical (ATC) classification tree structure

+ A : ALIMENTARY TRACT AND METABOLISM
+ B : BLOOD AND BLOOD FORMING ORGANS
+ C : CARDIOVASCULAR SYSTEM
+ D : DERMATOLOGICALS
+ G : GENITO URINARY SYSTEM AND SEX HORMONES
+ H : SYSTEMIC HORMONAL PREP, EXCL SEX HORM. AND INSULINS
− J : ANTIINFECTIVES FOR SYSTEMIC USE
  − J01 : ANTIBACTERIALS FOR SYSTEMIC USE
    + J01A : TETRACYCLINES
    − J01B : AMPHENICOLS
      + J01BA : TETRACYCLINES − *add to search*
    + J01C : BETA-LACTAM ANTIBACTERIALS, PENICILLINS
    + J01D : OTHER BETA-LACTAM ANTIBACTERIALS
    + J01E : SULFONAMIDES AND TRIMETHOPRIM
    + J01F : MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS
    + J01G : AMINOGLYCOSIDE ANTIBACTERIALS
    + J01M : QUINOLONE ANTIBACTERALS
    + J01R : COMBINATIONS OF ANTIBACTERIALS
    + J01X : OTHER ANTIBACTERIALS
  + J02 : ANTIMYCOTICS FOR SYSTEMIC USE
  + J04 : ANTIMYCOBACTERIALS
  + J05 : ANTIVIRALS FOR SYSTEMIC USE
  + J06 : IMMUNE SERA AND IMMUNOGLOBULINS
  + J07 : VACCINES
+ L : ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS
+ M : MUSCULO-SKELETAL SYSTEM
+ N : NERVOUS SYSTEM
+ P : ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS
+ R : RESPIRATORY SYSTEM
+ S : SENSORY ORGANS
+ V : VARIOUS

2.3.2 Statistics

General

As mentioned above, the WHO database contained in March 2002 2,791,906 individual case reports. The ten countries contributing most reports are shown in Table 5.

Table 5. Top ten reporting countries in the WHO Programme, by number of reports received in total from joining up to March 2002.

Country	# reports	Start year	EU member
United States	1,314,525	1968	
United Kingdom	391,868	1968	Yes
Germany	160,648	1968	Yes
Australia	146,116	1968	
Canada	136,192	1968	
France	113,713	1986	Yes
Sweden	77,058	1968	Yes
Spain	71,993	1984	Yes
Netherlands	48,472	1968	Yes
Denmark	44,196	1968	Yes

Reports from these ten countries add up to 90% of the total in the WHO database. It is interesting to note that all except two (France and Spain) were members from the start of the WHO Programme, and that seven of the ten are EU member states.

When looking at reporting by number of inhabitants (see Table 6), the picture looks slightly different, although seven of the ten countries with most reports also have the highest reporting rates by population. New Zealand, Ireland and Switzerland have more reports relative to their population than e.g. Germany, Spain and Canada. There are various reasons for the ten countries in the table having the highest reporting rates. It is known that the UK and the US have long established systems in large populations. In both countries there has been wide publicity of drug safety issues which have included high profile legal action. Overall the regulatory authorities in these countries have been active and promulgated much advice and information to medical practitioners. Moreover there are stringent requirements enforced on industry for them to collect reports, particularly in the US.

Table 6. Top ten reporting countries in the WHO Programme, by number of reports/million inhabitants/year (average 1996-2000)

Country	# reports/ mill. inhabitants	Start year
New Zealand	740.7	1968
Australia	479.7	1968
United States	416.1	1968
Sweden	312.0	1968
United Kingdom	310.8	1968
Netherlands	305.7	1968
Ireland	274.1	1968
Denmark	220.8	1968
Switzerland	170.4	1991
France	163.8	1986

The other countries, except France, have much smaller populations, and in all of them there have been great efforts made by the reporting centres in outreach activities to professionals. Noteworthy is the effort in responding to each reporter with useful feedback, something which is very useful in promoting interest in the systems. France, though it has a large population, has achieved the same intimacy of relationship between the reporting system and professionals by pioneering regional reporting centres. New Zealand found that the Intensive Medicines Monitoring Programme (IMMP) for new drugs had a striking effect on general reporting [Coulter, 1998]. The IMMP's operation requires that patients, doctors and pharmacists are alerted to special reporting requirements each time an IMMP monitored drug is prescribed. The Prescription Event Monitoring (PEM) system in the UK also involves regular contacts with doctors [Shakir, 2002].

In the total WHO database, the average number of adverse reaction terms per report was 1.9, and the corresponding figure for drugs were 2.1, whereof 1.2 drugs reported as 'suspected' or 'interacting' and 0.9 drugs reported as 'other', i.e. concomitant medication not suspected of having caused the reaction.

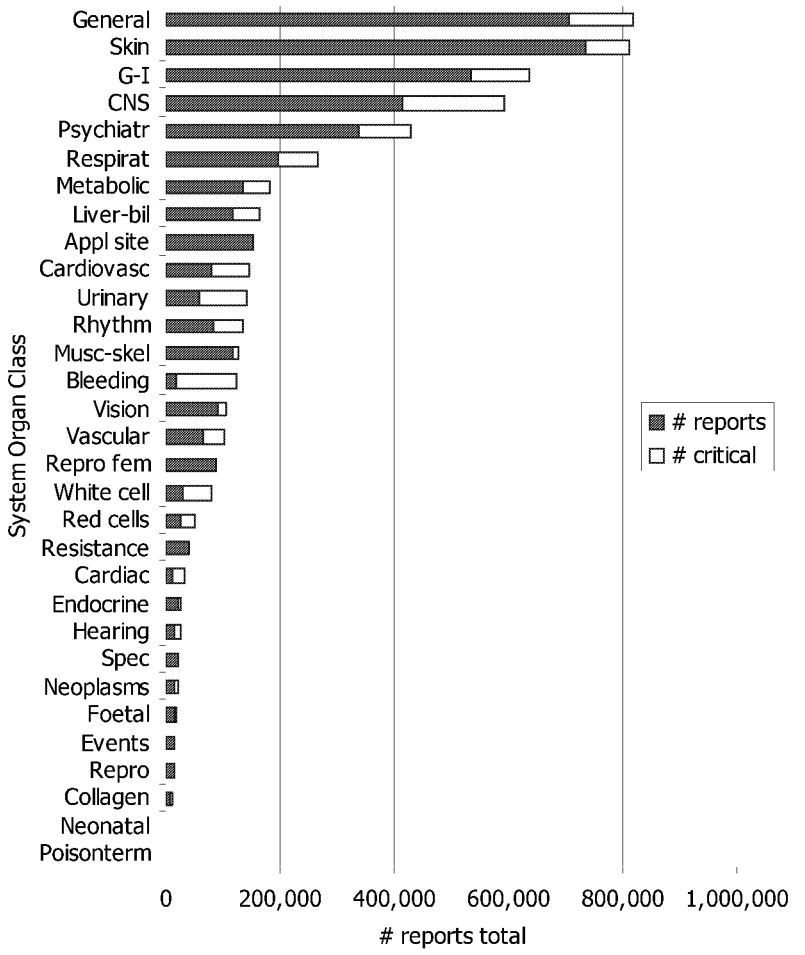

Figure 9. WHO database adverse reaction profile

The overall reporting profile by Body System Organ Class (SOC) (see Figure 9) shows that the two most commonly reported SOC's were General (15.2% of total) and Skin (15.1%), followed by G-I (11.8%), CNS (11%) and Psychiatric (8%).

Serious adverse reactions

The 'critical terms' in the WHO database represent terms which need special consideration when reviewing reports. By looking at reports by system-organ classes it should be interesting to see which SOCs are most likely to harbour

suspected ADRs of most significance.
Figure 9 shows the proportion 'critical terms' versus other terms for each SOC. The SOC's with more than 50% of the reported reactions being 'critical terms' were Bleeding (85% of reactions), Neonatal (70.8%), Cardiac (69.5%) and White cell (65.2%), Urinary (58%) and Collagen (53.6%).

A high proportion of reports of 'critical terms' for a particular SOC could be due to there being a higher number of *reportable* 'critical terms' in that SOC. This is indeed the case for the three first mentioned SOCs above, whereas for the others relatively few reportable 'critical terms' in the SOC account for a bulk of the reports. For instance, more than 30% of the reports in the White cell SOC were on the terms 'leukopenia', 'granulocytopenia' and 'agranulocytosis'.

There is a general trend to focus on the importance of expedient reporting of 'serious' cases, particularly in the ICH countries. Although the total reporting frequencies are not increasing in many countries, a result of an emphasis on seriousness could be that the proportion of serious to non serious cases have increased. In the past, the WHO database format has not included 'serious' as a recordable field. It is however included in the new database format, which will enable trend analyses of the reporting of 'serious' cases in the future. (See also page 93 for a definition of 'serious').

Concepts in Critical Terms

The word 'critical' is taken to mean 'relating to a crisis' or 'decisive' or 'crucial'. Thus the terms which are included in the new Critical Term List do not necessarily refer to serious conditions in themselves, but are terms which may be part of or lead to a serious syndrome.

The logic that underpins the choice of terms for inclusion is:

- that they should have been reported within the WHO Programme as adverse reaction terms
- that the terms either refer to or might be indicative of a serious disease state. A serious disease is one that may be fatal, life-threatening, involved or prolonged inpatient hospitalisation, or resulting in persistent or significant disability or incapacity (see also definition of 'serious' on page 93)
- that reports including critical terms warrant special attention, because of their possible association with serious disease states and may lead to more decisive action than reports on other terms

The frequency with which the terms has been used has not been taken into consideration in selecting 'Critical terms'.

The concept of 'critical terms' is different from seriousness, and is not the result of an individual case assessment ('serious' is linked to the patient outcome, whereas 'critical' is linked to a particular term, whenever reported). Nevertheless, since 'critical' terms are "indicative of a serious disease state" and "warrant special attention", the reporting frequencies of critical terms give an indication of whether reporting goes towards more and more serious cases relative to the total. The data shown in Figure 10 does not support this hypothesis.

The figure shows the overall frequency of reports of 'critical terms' by year for ICH and non ICH countries, expressed as a percentage of all terms. Although a minority in numbers (16/67 – Luxembourg is not a member of the WHO Programme, but contributes reports as part of the French reporting system), a majority of the reports in the WHO database comes from ICH countries.

Although the proportion of critical terms year by year is higher in the ICH countries compared with the non ICH countries, the long term trend (dotted line) has been towards a reduction. In comparison, the reporting of critical terms in the non ICH countries is more stable, with only a very slight reduction over the years. However, if one only considers the time from 1990, the trend is towards an increase of reporting of critical terms in both country groups.

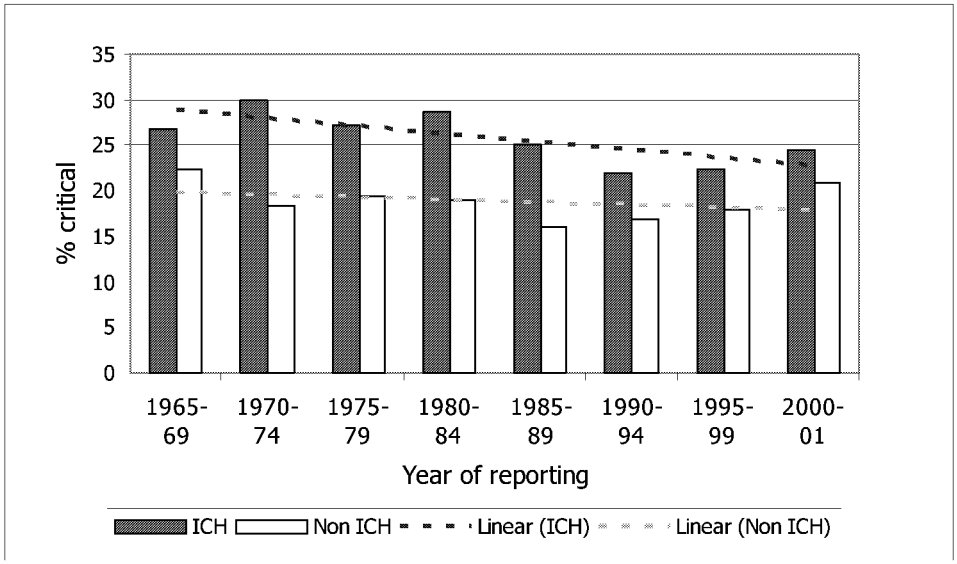

Figure 10. Proportion critical terms in ICH and non ICH countries as a percentage of all reactions reported

Table 7 shows the 20 most reported adverse reaction terms in the WHO database up to and including 2001. Of these, only 'death' is a critical term, and it is worth noting that although 'death' is an outcome, and recorded as such in the database, it is also included as a reportable term. Currently, the UMC is promoting the concept that 'sudden death' can be regarded as a reportable term, there being no other disease/event information. 'Death' on the other hand should always be accompanied by a reported disease/event e.g. hepatic failure, myocardial infarction, agranulocytosis etc.

Table 7. Most reported adverse reaction terms in the WHO database up to March 2002, coded by WHO Adverse Reaction Terminology (WHO-ART)

Adverse reaction term	Critical term	SOC	# reports
Rash		Skin	173,341
Fever		General	133,371
Pruritus		Skin	123,935
Nausea		G-I	118,154
Urticaria		Skin	116,664
Headache		CNS	106,689
Vomiting		G-I	94,359
Dizziness		CNS	92,410
Dyspnoea		Respiratory	75,214
Diarrhoea		G-I	74,453
Rash erythematous		Skin	74,189
Abdominal pain		G-I	72,093
Death	Yes	General	67,714
Injection site reaction		Appl. site	61,788
Rash maculo-papular		Skin	58,697
Pain		General	56,805
Therapeutic response decreased		General	47,132
Somnolence		Psychiatric	46,140
Hypotension		Cardiovasc.	45,055
Fatigue		General	44,170

Table 8 shows the 20 most reported drug groups, by ATC 3rd level codes. It is currently not possible to conclude how the reporting frequency is related to the usage of these drugs, since global utilization statistics on prescriptions summarised by drug groups are not generally available.

The ATC classification hierarchy

Level 1: Main Group
N Central Nervous System
Level 2: Therapeutic Subgroup
05 Psycholeptics
Level 3: Therapeutic Subgroup
B Tranquillizers
Level 4: Chemical/Therapeutic Subgroup
A Benzodiazepines
Level 5: Chemical Structure
01 diazepam

It is interesting, however, to note that five of the 10 most reported drug categories in the WHO database, namely antiulcerants, cholesterol and triglyceride reducers, antidepressants, NSAIDs and antipsychotics are among the 10 'leading therapy classes' in 2001 global sales (expressed in US dollars) according to IMS Health [IMS World Review 2002, 2002]. The remaining 5 most selling categories have the following ranking in the WHO reporting frequency list: calcium antagonists (28), oral antidiabetics (41), ACE inhibitors (12), cephalosporins (11) and systemic antihistamines (37).

This suggests that the five latter categories are relatively less problematic in terms of adverse reaction reporting in relation to their sales, although it should be kept in mind that the sales value is not directly related to the number of prescriptions issued. Newer drugs tend to have much higher price per prescription, which means that there for new products are fewer prescriptions per currency unit than with older products. It is not surprising that the top selling categories include many new products, but it is unclear whether the high reporting frequencies for these drugs are due to initial high interest, and therefore more complete reporting of new products.

Table 8. Most reported drug classes in the WHO database up to March 2002, grouped by Anatomical–Therapeutic–Chemical (ATC) classification (3rd level)

ATC code	Drug group	# reports
M01A	Non-steroidal antiinflammatory drugs (NSAIDs)	209,922
N06A	Antidepressants	204,956
J07A	Bacterial vaccines	163,230
J07B	Viral vaccines	162,589
N05A	Antipsychotics	102,138
J01C	Penicillins (beta-lactam antibacterials)	93,439
B01A	Antithrombotic agents	93,183
N03A	Antiepileptics	79,121
A02B	Drugs for treatment of peptic ulcer	74,607
C10A	Cholesterol and triglyceride reducers	72,083
J01D	Other beta-lactam antibacterials (excl. penicillins)	72,059
C09A	ACE-inhibitors, plain	70,514
G03A	Hormonal contraceptives for systemic use	64,064
N02B	Analgesics and antipyretics	58,851
A08A	Antiobesity preparations, excl diet products	58,747
V08A	X-ray contrast media, iodinated	58,561
G02C	Gynecologicals, other	54,076
N02A	Opioids	53,135
C07A	Beta blocking agents	52,831
D10A	Anti-acne preparations for topical use	52,611

As a contrast, the two categories antithrombotic agents and antiepileptics are not among the ten most sold groups, but are the 7th and 8th most reported categories in the WHO database. These groups have a relatively troublesome adverse reaction profile, with a high proportion of serious reactions. The remaining categories among the 10 most reported drug groups in the WHO database are bacterial and viral vaccines, and penicillins. For these categories the adverse reactions are mainly of a less serious kind, although frequently reported.

Trends over time

Table 9 shows the 20 most reported drugs in the WHO database, by WHO preferred name. The so-called 'Weber effect' (see also section 2.6.4) has been referred to when arguing that there is normally a higher initial reporting of adverse reactions in the first few years post-marketing, followed by a subsequent decline [Weber, 1984; Wallenstein, et al., 2001]. This is clearly not so

for international reporting of the drugs shown in the table. For the drugs shown in the table the average time from first report in the WHO database to the maximum reporting frequency was 16 years (median 18). Only two drugs reached their highest reporting so far within two years, namely Haemophilus B conjugate vaccine and etanercept, although for the latter the reporting frequency might continue to increase, since reports from 2000 and 2001 are still coming into the system.

Table 9. Most reported drugs in the WHO database up to March 2002, by WHO Drug Dictionary Preferred Name

Drug name	# reports	First report	Peak year
Diphtheria And Tetanus Toxoids And Pertussis	62,952	1968	1992
Fluoxetine	46,134	1988	1992
Hepatitis B Vaccine	40,329	1982	2000
Poliovirus Vaccine Live Oral	38,087	1968	1992
Bactrim (Co-trimoxazole)	36,340	1968	1993
Measles, Mumps And Rubella Vaccine	31,570	1975	2000
Clozapine	28,935	1973	1992
Sertraline	24,655	1990	1998
Enalapril	23,700	1983	1988
Paroxetine	23,417	1990	1994
Carbamazepine	21,618	1968	1990
Diclofenac	21,217	1975	1989
Ibuprofen	20,748	1969	1989
Amoxicillin	20,680	1972	1998
Diphtheria And Tetanus Toxoids	20,376	1969	1996
Levonorgestrel	19,583	1974	1993
Etanercept	19,537	1998	1999
Naproxen	18,926	1973	1988
Haemophilus B Conjugate Vaccine	18,794	1988	1991
Nifedipine	18,768	1974	1986

When looking at reporting frequencies by year in different countries the pattern is even more complex. As shown by the examples in Figures 11 and 12, a high initial reporting frequency did occur in Australia, Germany, the UK and the US for paroxetine, whereas for sertraline only the UK reporting showed an early peak.

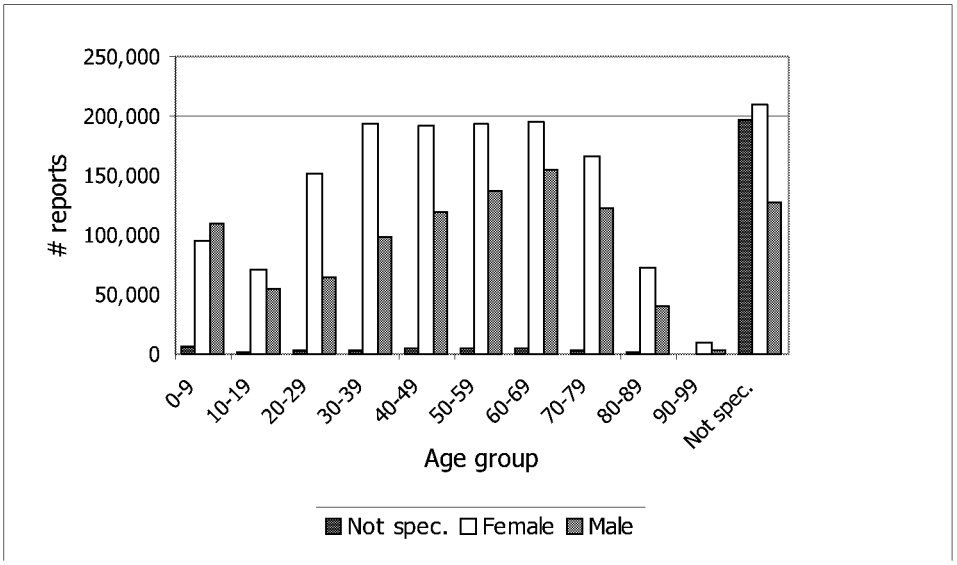

Figure 13. Reports by age group and gender

The fact that there is a substantially higher adverse reaction reporting frequency in women warrants attention, even given that drug use is overall higher in women. Taking out the more than 100,000 reports of contraceptives , the reporting frequency in the 20-39 year age group is still higher in women than in men. Since many clinical trials do not include female subjects there is a risk that drug treatment is not optimised for women. If the greater reporting is due to more women using drugs, then they should be represented in clinical trials. If there are more reports of adverse reactions per exposed population of women, this phenomenon needs full investigation. Only if women report their adverse experiences more than stoical males, is there no medical gender problem, but if this is the case it is still important to know more about the factors involved.

2.4 From case reports to signals

Whilst there is much interesting statistical data to be obtained from the WHO database, as given by the few examples in the previous section, the main function of the database is to serve as a source for finding new signals. Common criticisms of spontaneous reporting systems include erroneous causality attributions, under-reporting and the contribution of 'noise' by reporting of already known reactions. A 'spontaneous report' is the result of the reporting of a diagnosis of a reaction, suspected to be related to a medicine. Normally this

diagnosis takes place as part of a clinician's routine examination of a patient, and, like any other diagnosis, the conclusion of a causal relationship depends on the expertise and experience of the clinician, the availability of confirmatory tests, the time relationships, the development of the reaction, and the presence or absence of alternative explanations. Therefore, the causality assessment made by the reporting clinician is as good as any other careful clinical diagnosis. Furthermore, since there are studies which show that doubt about causal relationship is one of the common reasons for not reporting a suspected adverse reaction [Belton, 1997; Biriell, et al., 1997], this should reduce, not increase, the reporting of false causal attributions.

It has been argued that the term 'spontaneous report' does not do justice to the effort which underlies such reports which are the result of a health professional's (usually a medical doctor) analysis of a clinical situation. The term 'clinical concerns' was proposed as a better designation for this concept, with the added value of distinguishing these reports from those originating from non health professionals [Edwards, 1999].

In order to reduce under-reporting it might be worth concentrating on reasons to report, rather than the reverse. An international study showed that a motivation to contribute to medical knowledge, the reaction being previously unknown to the reporter, and the reaction being of a more severe nature than previously seen/expected were among the reasons for reporting [Edwards, et al., 1994]. As has been mentioned previously, studies have shown that if health professionals are encouraged to contribute their experiences, and receive positive feedback in return for their efforts, the level of under-reporting can be reduced [Scott, et al., 1990; Orsini, et al., 1995; McGettigan, et al., 1997; Coulter, 1998].

The concept of 'known' reactions merits some attention. Many experts are worried about a high number of reports of 'known' reactions flooding the systems and making it more difficult to identify new drug problems. The terms 'labelled' and 'expected' are used interchangeably in drug regulation, denoting a concept which, it could be argued, is the same as 'known'. However, there is a distinction in that the former two refer to a message that has been made available, but not necessarily received by the intended audience [Smalley, et al., 2000]. Also, a reaction known to experts in some countries is not necessarily known to members of the medical profession worldwide who prescribe. This can be due to inadequate information to health professionals, but perhaps more commonly, to a general information overload that makes it almost impossible for health professionals to keep up with all the current developments, including changes in product labelling. Instead of regarding reporting of 'known' reactions as 'noise' it could be considered as a sign that more effective communication is needed to prescribing physicians and other health professionals dealing with patients.

If the general level of under-reporting is to be reduced one must accept

some 'false' signals and 'noise'. This risk should be weighed against the risk of losing important information by not receiving reports. Although reporting frequencies cannot be taken as evidence of the true level of occurrence of an adverse reaction, they indicate the level of concern felt by those who report, and deserve to be regarded as 'valid' information.

Also, the reasons for delay or failure to diagnose adverse drug reactions in clinical practice must be addressed. Many ADRs are never attributed to drug treatment, and consequently will never be reported. To reduce this source of under-reporting, both education and communication efforts are needed.

2.4.1 Signals from international case reports

To achieve its main aim, the identification of international drug safety problems at the earliest possible stage, the WHO Programme must have a mechanism in place that produces effective and timely detection of new adverse reactions. The key issue is to find the relevant signals and to avoid generating too many unfounded suspicions. National regulatory bodies and pharmaceutical companies face the same challenge, albeit relating to nationally approved medicines and their own products, respectively.

Signal detection is a process which starts with the facts: the assembly of data and identification of 'what stands out'. After an assessment of the facts has been made, a hypothesis can be generated, refined and tested. The term 'signal generation' should be avoided since it can give the erroneous impression that a signal is not based on existing facts, but a proposition made 'out of the blue'.

The WHO Programme signal detection is based on adverse reaction case report data stored in the WHO database. The case reports have varying amount of detail, but the absence of some information does not mean that a case report can be completely discarded when it comes to signalling of possible adverse reaction problems. However, the plausibility of a signal depends on the range and quality of the information available, and to base a signal only on poorly documented case reports without the necessary information needed to exclude obvious confounding is open to criticism. On the other hand, such reports could be considered as supporting evidence, that, together with reports with more complete information, would add to the substantiation of a signal.

Paper III *Edwards, I.R., et al., Quality criteria for early signals of possible adverse drug reactions, 1990* devised criteria for the amount and type of information needed to produce a well-founded early drug–adverse reaction signal from the international database. The WHO reports were divided into different categories based on the amount of information given in the reports. Any report containing at least source and case identification, reaction description, date, drug and treatment date was classified as 'feasible', whereas those that did not fulfill these requirements were regarded as 'unassessable'. 'Substantial' cases were those that, in addition to the above, had information on

patient sex and age, doses and dates for all drugs, indication of treatment and outcome. Finally, 'index' cases were those 'substantial' cases which had a positive rechallenge, or the absence of confounding factors. A publishable 'signal' was defined as the equivalent of three 'index' cases, according to criteria set out in Paper III.

For the 19 studied drugs, there were 15 signals based on the criteria above. In only three instances were the signals based on data from an individual country. In two cases, reports from 5 countries were needed for a signal. When dates were compared, a signal was available in the WHO database before the corresponding literature report in seven cases. The fact that most signals were based on reports from several countries is a strong argument for continued pooling of international data.

Based on the results of Paper III, a new field 'documentation grading' was added to the WHO database. During the processing of incoming reports, each drug–ADR combination is automatically assigned a value, ranging from 0-3, according to predefined criteria. This grading facilitates the identification of well documented cases, and is used for signalling purposes.

Documentation grading of reports in the WHO database

Date of onset of reaction and dates of treatment:
If these dates are filled in (at least the month and year are required), the drug–ADR combination meets the criteria for documentation grade 1. Combinations for which any of these dates are missing or not specific enough are given the documentation grade 0.
Combinations meeting the requirements for grade 1 are checked further:

Disorder/reason for treatment (indication) and outcome:
Combinations for which the indication and outcome are filled in are meets the criteria for documentation grade 2.
If any of this information is missing or if the drug is not reported as a 'suspected' drug, the combination will remain as a grade 1. Combinations meeting the requirements for grade 2 are checked further:

Rechallenge
If rechallenge is positive the combination is given documentation grade 3. If rechallenge is negative or not performed or the information is missing the combination will remain as a grade 2.

Paper IV *Lindquist, M. and I.R. Edwards, Endocrine adverse effects of omeprazole, 1992* is an example of a published signal consisting of a case series from the WHO database, from the period when no automated signal detection was yet in place. It illustrates that it is possible to identify signals using manual scrutiny, and clinical thinking. Many potential signals, though, can not be substantiated enough for publication using the WHO database information alone. As can be seen in Table 10, less than half of the reports in the WHO database had a level of information corresponding to documentation grade 1, and only a small fraction (11.5 and 10.6% in 1995 and 2000, respectively) fulfilled the documentation grade 2 criteria.

Table 10. Report documentation level in the WHO database 1995 and 2000

Data fields filled in	% of reports 1995	% of reports 2000
Onset and treatment dates (= documentation grade 1)	44.1	43.1
Onset date, treatment dates, indication and outcome (= documentation grade 2)	11.5	10.6

In most instances, more detailed information on individual cases is available from the national centres, albeit not always in a computerised format. The signalling potential of the WHO database would increase if more case details could transferred to the international database. One basic technical requirement for this to happen is already fulfilled with the design and implementation of the new WHO database system, but additional efforts have to be put into enabling the transfer of high quality information from national centres to the UMC.

Another area of the utmost importance for the WHO Programme's signalling efforts is to focus on reduced delays in transfer of information from the national level to the international system. The whole concept of 'early signalling' depends not only on good quality data, but also on the data being available in time for the signals to be detected before there is a major drug problem.

In addition to all the above, the effects of possible reporting bias also need to be taken into account when assessing potential new drug problems. Widespread publication on safety issues increases reporting, but it is difficult to know whether there is a real increased incidence of the adverse reaction, or if the increased reporting frequency is the result of reduced under-reporting, or an increased reporting of false attributions. A consideration of the type of drug, the kind of patients it may be used in, and the nature of the adverse reaction may

help in deciding the most likely explanation. But any assumptions may be erroneous.

The fact that case reports may be subject to bias and confounding, and that spontaneous reporting systems suffer from under-reporting, lack of information and delay, does not reduce their value for signalling of possible drug related problems. The difficulties involved make the information complicated to interpret, but careful analysis with an understanding of the limitations, together with an extensive background knowledge can reduce the risk of mis-interpretations. The low level of evidence available at the first hypothesis generating stage should be weighed against the low cost of spontaneous reporting systems, and the speed with which new safety issues can be brought to the attention of the medical community for further consideration.

However, even with careful assessment there will always be problems with imperfect data, but with the development of better IT solutions for storage, analysis and transfer of information, it is possible to minimise the imperfections and maximise the usefulness of the data. Paper III and IV show evidence that the WHO database is useful in finding signals of new safety problems, but there is room for improvement. Since the limitations of using heterogeneous data and missing data will exist also in the future, there is a need for some way of data mining and grouping in order to find significant information. The next section of this chapter will discuss the work that has been done to supplement clinical case review with automated methods for signal detection.

2.5 Systematic signal detection

2.5.1 The early years

The use of statistical methodologies in drug monitoring had been recommended before the start of the WHO pilot project by Finney [Finney, 1965], who also wrote that "computer scrutiny of a far greater number of records will direct attention to striking disproportionalities in the incidence of side-effects". In this paper, Finney described a logic for trend analysis of a disproportionate increase in reporting. Following a similar logic, adapted for the data held by WHO, Patwary proposed a method [Patwary, 1969], the essential features of which were implemented in one of the regular data outputs produced during the pilot phase of the WHO programme, *Increase in reporting*. This tabulation, together with other database outputs, formed the basis for the signalling system in the early 70's.

However, at an informal meeting of advisers, held in 1971, it was stated that, from the statistical point of view, interpretation was difficult due to the small number of reports presented, the small number held in the master file, irregularity of reporting and national centre selection of reports. It was agreed

that data in this form would not be suitable for strict statistical analysis [WHO, 1971a]

Later in 1971, it was agreed by a group of experts and the WHO centre staff that methods to extend and enhance the value of the signalling system should be explored during the primary operational phase of the project. The hope was expressed that some of the manual approaches used so far could be transformed into automated signalling.

In 1974, Finney stated that "the deficiencies in and heterogeneities of the data appear to make any strict probabilistic basis for statistical inference almost inconceivable. Yet the data seem to contain information that, in combination with medical understanding, can draw attention to particular dangers". In this paper, Finney suggested developments of the signalling system used by WHO at the time, including the proposal of a 'Reaction Proportion Signalling'; an extension of the trend signalling; a 'Dose Signalling'; and national comparisons, all based on statistical methods, and intended for automation with the help of computers. These theories were not put into practice at the time, in part due to lack of enough computer capacity to handle the complex calculations involved.

2.5.2 The intermediate years

The combination of standardised tabulations together with manual selection of drug–ADR combinations of interest continued to form the basis for signal detection in the WHO Programme for the years to come. When the operational responsibility for the Programme was transferred to the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden in 1978, a re-programming was needed to produce tabulations from the new relational database management system implemented at the time of the move.

The new database system was one of the first of its kind in the world, and provided state of the art technology when it came to storage and retrieval of information. However, the newly established Collaborating Centre had very limited resources, and at the start the efforts were concentrated mainly on the data input side. Furthermore, the Collaborating Centre in Uppsala did not have medically trained staff employed, thus the WHO Programme was to a greater extent than in the previous years reliant on experts in national centres for the assessment of the information contained in the signalling documents which were distributed.

After the move of the operations to Sweden, the first step towards a more systematic signalling approach was taken when, in 1985, several national reporting centre experts agreed to form a panel for intensified review of the quarterly output documents. The *New to the System* document was separated into sub-documents, by System-Organ Class. Each expert undertook to review one or more System-Organ class printouts, according to their expertise and interest. Their case summaries, with comments, were printed in a new document

called *Signal*, and sent to all national centres participating in the Programme. his activity is still ongoing, with a review panel of more than 30 experts, some of which are clinical experts from outside the WHO Programme reporting centres appointed by special agreement.

WHO Programme regular database output in 1978

Yearly output documents
Report Type A: all reactions reported, by year

Drug Reference List: printout of information held in the drug database

Quarterly output documents
Tabulations of drugs associated with:
- death
- foetal malformations
- neoplasms
- dependence

New to the System document: drug–reaction associations not previously reported

Follow-up document: reporting frequencies of selected associations

2.5.3 Towards an automated signalling system

A signal detection system which is based on human review of data is bound to have a high level of subjectivity in the selection and analysis of information since it depends on the reviewers' background knowledge, experience and interest. This subjectivity can to some extent be balanced by the recruitment of experts with different expertise, monitoring the same data set, but a performance analysis is very difficult to make in the absence of a 'gold standard' against which the results can be measured.
The inherent weakness of human review of data is also its strength, in that clinical knowledge, experience and interest, often together with a 'signal instinct' or intuition, are unique human qualities which cannot be replaced by computer systems. However, the sheer size of new information coming in to the

WHO database makes it impossible to rely solely on manual review, and, as was early recognised, some sort of an automated system was needed to aid the signal detection process. This idea of an automated system was never abandoned, but it was not implemented until the latter half of the 1990's.

With the appointment of a medical Director of the UMC in 1990, and the subsequent increase in staff enabled by the sales of computerized versions of the Drug Dictionary, the UMC had in the early 90's the sufficient resources to realize this long held ambition of the WHO Programme. The first step of this process was the development of a data mining tool for the WHO database. This work started in 1995, together with mathematical, statistical and computer technology experts from the Stockholm University in Sweden.

The new tool, the Bayesian Confidence Propagation Neural Network , was designed to identify statistically significant disproportionalities in a large data set, and had a performance which would allow automated screening of all drug–adverse reaction combinations in the whole database. Bayesian logic was chosen as the basis for the system since it supposes that probability of any defined single or complex outcome constantly changes, as more of the considered information is added. Thus, a system based on Bayesian logic is well suited to monitoring trends of probability over time and also to consider the effect of adding variables. Missing data can be handled, either by an increased uncertainty of output probability, or, if desired, predicted values can be inferred from a limited data set to the whole. The methodology is fully reproducible and transparent, in that every step can be checked by an independent observer.

When the first full-scale tests were run on the WHO database as of the end of 1995, it contained more than 1.7 million individual case reports, and almost 13,000 preferred drug names (denoting unique combinations of drug ingredients), and 1,600 preferred level adverse reaction terms.

Paper V *Lindquist, M., et al., From Association to Alert – a revised approach to International Signal Analysis, 1999* describes the revised signalling process and the initial testing thereof.

Paper VI *Bate, A., et al., A Bayesian neural network method for adverse drug reaction signal generation, 1998* describes the development of the BCPNN methodology.

Paper VII *Lindquist, M., Ståhl, M., Bate, A., Edwards, I. R., Meyboom, R. H.B., A retrospective evaluation of a data mining approach to aid finding new adverse drug reaction signals in the WHO international database, 2000* analysed the signalling capacity of the new system.

Paper VIII *Coulter, D.M., et al., Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: data mining study, 2001* provided an example of how the new signalling system can be used in practice.

The Bayesian Confidence Propagation Neural Network (BCPNN)

The BCPNN methodology uses a neural network architecture to measure dependencies between variables (e.g. drugs and adverse reactions) within the WHO database, and how dependencies vary over time. The dependencies are selected using a measure of disproportionality called the Information Component (IC). Positive IC values indicate that a particular combination is reported to the database more often than expected from reports already in the database. The higher value of the IC, the more the combination stands out from the background. An IC value of zero means that there is no quantitative dependency.

The IC value is based on:

- the number of case reports with variable X (C_x) ; and
- the number of case reports with variable Y (C_y); and
- the number of reports with the specific combination C_{xy}); and
- the total number of reports (C).

The distribution of the IC, expectation and variance values are calculated using Bayesian statistics. The standard deviation for each IC provides a measure of the robustness of the value. The higher the C_x, C_y and C_{xy} levels are, the narrower becomes the confidence interval.

Other approaches for signal detection based on statistical disproportionality measurements have been adopted by several national pharmacovigilance centres, including the Netherlands, the UK and the US [DuMouchel, 1999; Evans, et al., 2001; van Puijenbroek, 2001], and also by some pharmaceutical companies. A recent paper analysed the concordance between different measures (Proportional Reporting Ratios (PRR), Reporting Odds Ratios (ROR) and the BCPNN Information Component (IC)). The result was that no clear differences were present, except for when there were less than four reports per drug–ADR combination [van Puijenbroek, et al., 2002]. The methods all have their somewhat different advantages and disadvantages. Before implementing an automated signal detection system it is therefore recommended to carefully consider the possible alternatives to use one that is most practical and appropriate in a given setting.

2.5.4 New developments

The continued developments of the UMC's signalling system are mainly focussed on work in two areas, as outlined below.

The neural network architecture is not necessary for the relatively less complex screening involving drug–adverse reaction pairs, although the high performance of the BCPNN system makes these calculations exceptionally quick. However, the intention when the system was designed was to allow for multi-variable screenings, and, eventually, unsupervised pattern recognition. The rationale for this was to extend the capacity of the signalling system to predict unexpected correlations between any variables in the database, rather than only considering the relationships between drugs and adverse reactions, thus enabling the identification of more subtle patterns and complex risk situations.

In August 2001, the first results of the further development of the BCPNN system in order to find and highlight previously unknown patterns in the WHO database were presented at the ISPE conference held in Toronto, Canada.

The requirements for a pattern recognition system were that the method:

- had to be able to handle discrete variables, since most fields in the database are of that kind;
- should find patterns without a priori information as to the pattern of interest;
- should be capable of inferring dependencies between variables even if these are not reported together (in the same case report);
- should generate reliable patterns also when there is data missing, or unrelated information distracting the pattern ('noise'), or a combination of the two;
- should be computationally manageable; and
- should produce calculations reasonably fast.

Experiments were run on a theoretical test set of eight predefined patterns within a two dimensional matrix of units, with those units being part of the pattern highlighted ('on'). The neural network was trained to recognise these patterns, also when there was missing data (some units 'off' when they should have been 'on'), and with the introduction of 'noise' (some units 'on' in spite of not being part of the pattern).

Predictive values were calculated to determine the accuracy in correctly predicting a trained pattern. The system was run ten times, with a variable degree of completeness of information (60-80 %), and 'noise' (0-50 %), resulting in a positive predictive value of 80.4% and a negative predictive value of 99.1%.

The method was then implemented on a subset of data from the WHO database, all reports (8,468) of haloperidol being reported as the drug suspected of having caused the reaction. The results from this test showed a pattern consistent with the neuroleptic malignant syndrome, which is highly associated with haloperidol.

The early results of using the BCPNN for pattern recognition have thus been encouraging, and the UMC intends to continue developing this method for implementation on the whole database [Bate, et al., 2001].

Further refinements of the signal detection process

With the large number of reports entered into the WHO Database (more than 250,000 reports per year) an automated way of picking up drug–ADR combinations for assessment is essential. In the signal detection process, which was introduced in 1998, the UMC has used the BCPNN methodology to produce quarterly line listings of new associations. The associations were sent to the around 30 members of the UMC international expert review panel who were asked to make selections of drug–ADRs of potential interest. The reviewers sent requests for case reports to the UMC that in turn retrieved the requested case reports from the WHO Database and sent them back to the reviewer. If the reviewer, after assessing the cases, found the issue worth signalling, a summary was written which was sent to the UMC for inclusion in the *Signal* document.

After two years of operation, a major limitation with the system was identified: there was still too much information provided for human analysis. In 2001, a further modification of the signal detection approach was therefore needed to improve the likelihood of picking up important signals. For this purpose, a triage strategy was elaborated together with a group of experienced evaluators. The triage is a filtering process, in which different algorithms are applied to narrow down the number of associations for review, and to focus on the areas of greatest importance. After filtering, the retrieved drug–ADR combinations are checked at the UMC for occurrence in the available product information literature. For the drugs where the reaction is not found or fully described, complete case reports in the WHO Database are retrieved and sent to the appropriate expert in the review panel with a request to assess the evidence for the reaction being related to the suspected drug. The reviewer, as has been the case before, drafts a signal text and the UMC includes it in *Signal* for distribution to all national centres. In making the preliminary selection of associations of possible interest at the UMC, instead of putting the onus on the external reviewers, the time consuming and ineffective process of sending line-listings, case reports and other information back and forth between the reviewers and the UMC has been avoided.

evidence as to the real extent of the problem among the exposed population, nor of the prevalence of the treated or concomitant disease in that population. Therefore, in order to investigate the magnitude of an ADR both numerator data and drug use denominators are needed.

2.6.1 Adding denominator data to case report information

The report from a meeting in 1971 of WHO Drug Monitoring Programme advisers and staff of the WHO centre, then in WHO Headquarters, Geneva, stated that "whenever 'increase in reporting' is found, an approach to establish incidence figures would be justified as a main step in validating the result. In this context drug consumption figures and incidence figures obtained from intensive drug monitoring schemes are of particular importance" [WHO, 1971b].

Today, such schemes are operational on a routine basis, for new drugs, in only three countries (New Zealand, the UK and, recently, Japan), and, whilst providing useful national denominators, have some limitations. Generalization from local data can be problematic, moreover, only one of these schemes (New Zealand) involves continuous signal detection. The New Zealand Intensive Medicines Monitoring Programme (IMMP) can therefore relate new signals immediately to drug use. Apart from this, periodic analysis of the cohort is done. The profile of adverse reaction rates can be generated, but there is no population control. Controls can only be found in other cohorts of drugs concurrently examined in the systems.

For the follow up of international signals, comparable drug use denominators, country by country, are needed for global review, as well as for analyses of country differences. There is also a need to be able to examine signals relating to all drugs in use, not only new products, and to analyse subsets of the total use of drugs to identify higher risk situations. This takes signal analysis a step forward in focussing on risk groups and practices related to drug prescription and use.

IMS Health has collected drug use data for many years in the major markets of the world. Their database contains the only internationally comparable data which is relevant to the problem of denominator definition, with the exception of ex-manufacturer sales. The IMS sales data allow for the application of an international denominator as well as cross country comparisons; the medical index data has the same multi-country capability as well as offering detailed prescription data.

A project was started in 1995 to develop a method for combining numerator data from the WHO database, denominator data from the IMS Health drug utilisation database, and international demographics data. The aim was to examine if the different data sets could be concatenated and used for the investigation of international drug safety signals. The ADR Signal Analysis Project (ASAP) was funded by the European Union (BIOMED grant BMH1-

CT94-1301), and the development team included UMC, IMS Health, and other experts.

The project was successfully concluded in 1997, after a number of analyses of current drug safety problems had been made. It was agreed that the collaboration between IMS Health and the UMC would continue on an ad hoc basis also in the future.

Although no definitive algorithms could be applied to every analysis, a number of standard tabulations were developed, together with methods to concatenate the data and recalculate sales and prescription figures into internationally comparable measurements. The analyses made showed that the methodology can be used for a wide range of drug safety problems, and it was concluded that, for the initial analysis of international signals, this method provides a quick and cost-effective complement to formal epidemiological studies.

As soon as one begins to analyse aggregated case report data, for whatever reason, one must confront the nature of the data and understand the ways in which it can be processed without distorting information or hiding inadequacies in the data. The merging of two different data sets can further magnify the problems, unless there is a detailed knowledge of the characteristics of each set.

Some of the methodological issues are described below, followed by a summary of the findings during the course of the ASAP project, and a description of how this approach was developed into a new pharmacovigilance service.

2.6.2 Considerations when using WHO data for signal analyses

Below is a summary of the more important points, which should be considered in any study using data from the WHO database.

Missing data

Only 'adverse reaction', 'drug', 'country', 'year' and a report identification number are obligatory fields in the WHO database. Whenever any other data field is chosen as a study parameter, it has to be considered to what extent useable information in that particular field is available.

An analysis was made as to what extent the different fields in WHO reports were filled, by examining reports stored in the database in 1990, and in 1995. Some problems were identified:

- onset of reaction was recorded in 74 - 79% of the reports, though not always as a complete date;
- treatment dates were recorded for 48 - 52% of the drugs reported as 'suspected', though not always as complete dates;

- indication for treatment was recorded for 20 - 26% of the drugs reported as 'suspected';
- dosage was recorded for 49 - 56% of the reports, but not always as a daily dose (sometimes the total dose was given).

Statistics produced in March 2002 showed that reports from the year 2000 had a similar degree of completeness for the first three variables. However, dosage information expressed in amount, unit and frequency (e.g. 5 mg daily) was only available in 24% of the reports. Dosages expressed as number of 'dosage forms' without indication of amount and unit were available in an additional 12%.

The 'year' field in WHO reports was in the past derived from the year of onset of the reactions as recorded in the reports sent by national centres. If the onset date was missing, the year was recorded as the year when the report was stored in the WHO database. Due to the transmission delay from national centres to WHO, this had implications on analyses of trends over time. The new WHO database format includes additional dates; the date of receipt by the UMC will be stored for each report, together with the date entry into the WHO database. For studies based on these dates there will always be complete information. However, if one wishes to base a study on the date of onset of the reaction, the problem will be the same as in the past. Some countries do not always submit their reports on a regular basis, mainly related to problems with computer systems. The resulting reporting delays might have the same implications on secular trend analyses.

Free text versus structured information

As from the end of 1998, one of the major contributors to the WHO database, the USA, transmit reports from the FDA Adverse Event Reporting System (AERS) in a format, agreed for use in the ICH countries, which uses one free text field for all dosage information. This type of data cannot easily be automatically entered into the structured WHO format, and is currently therefore not stored in the WHO database. This means that any calculation involving dosage, when submitted in this way, has to be done manually. In connection with the implementation of the new WHO database, the UMC has started investigating how this issue can be solved.

Another problem identified when comparing detailed dosage data with that available from IMS Health was that the dosage in the WHO reports were recorded by amount, unit and frequency of dosage, and route of administration, but lacked information on dosage form, and amount per dosage form. This problem has been solved in the new WHO database format, but it is likely to take time before this information will be routinely transmitted, depending on the information recorded nationally.

The WHO adverse reaction terminology (WHO-ART) is not always immediately updated with new terms - a new symptom may be recorded using a more general term for some time. This causes problems with retrospective analysis (reports are "hidden"). An example of this problem was an analysis made on muscle disorders, particularly rhabdomyolysis, with lipid lowering drugs of the 'statin' group. The term 'rhabdomyolysis' was not introduced as a reportable term until 1992, and many of the early reports were coded under the more general term 'myopathy'. Only by going back to the original case data in each country would it be possible to determine whether some, or many, of these reports were indeed rhabdomyolysis.

The introduction of the Medical Dictionary for Regulatory Activities (MedDRA), mandated for use in ICH countries, does not remedy this situation, since, like the WHO-ART, the MedDRA terminology is open-ended and new terms are added when appropriate. It would be very resource demanding to go back and check historical data whenever a new term is added, and it seems unlikely that this would happen routinely in all countries.

Each WHO report may contain several different adverse reactions, and each reaction term belongs to a body system organ class (SOC). When analysing counts of reactions, it is important to keep in mind that 'number of reactions' is not the same as 'number of reports'. For instance, if a report mentions two reactions and the count is made on the reaction level, this will result in two counts for this report. In those reports mentioning several different reactions, two or more of which belong to the same system organ class, the counting can be done in two different ways: a report of rash (SOC Skin), urticaria (SOC Skin) and hepatitis (SOC Liver) can be counted as one occurrence of 'Skin' and one of 'Liver', or as two occurrences of 'Skin' and one of 'Liver'.

The first method puts an equal weight on the System Organ classes, irrespective of the number of terms reported for each, whereas the other method puts more of an emphasis on the individual terms. Whenever an adverse reaction profile is produced which involves System Organ class counts, it is important that it is stated how the count was made. Throughout the ASAP project, the former method was used.

The WHO terminology includes specific syndrome terms, e.g. 'anaphylactic shock' and 'Cushing syndrome'. It is however also possible to describe a syndrome by the individual symptoms which together constitute the syndrome. The usage of syndrome terms varies between countries, and, to some extent, also within countries (different report assessors). Whenever a syndrome is involved in a database search, the individual terms, with which the syndrome might be described, have to be identified. Criteria have to be defined for allowed combinations of the terms, e.g. 'serum sickness' could be defined as (rash or urticaria or erythema) + (arthralgia or arthrosis) or (myalgia + fever).

2.6.3 Considerations when using IMS data for signal analyses

Sales data

IMS drug sales data is available from more than seventy national pharmacy and hospital sales audits, measured in number of packs, units (e.g. tablets), amount (e.g. kilograms), or defined daily dosages (DDDs). The information can be broken down by brand or generic drug name, form/strength/pack, drug category, pharmacy/hospital, time period and country. This kind of data is well suited for general analyses of reporting rates across countries. However, for more detailed analyses involving patient age, gender, indication or dosage, projections from prescription data have to be made instead.

From the sales data, single ingredient products can be retrieved by the substance name ('molecule'). This does not apply to combination drug products. These are recorded by the product brand name and the 'International Product Name', which is a grouping name for all products with the same combination of ingredients and the same manufacturer. Thus, whenever combination products are included in analyses using sales data, mappings of drug product names to ingredients have to be made (unless the analysis is made on the product name level).

Prescription data

IMS prescription data is available from more than forty IMS continuing indexes of primary care. It is available in a computerised format for the current year and quarter, and 10 quarters back. This means that data from the first years of marketing is limited to recently introduced drugs. It also does not allow for long term secular trend analyses.

Since the prescription data is available from fewer countries than the sales data, analyses of reporting rates by age, sex, indication and dosage will not cover all countries for which the more general profiles (using sales data only) can be produced.

Information on amount, doses/day or units/dose is not always available. In the study examples this information was missing in up to 25% of the prescription records.

Dosage is a composite field (amount followed by unit in the same field). In order to make computer calculations the amount must be separated from the unit. The same dosage form can also be recorded using different terms, which necessitates some manual editing.

Drugs are not recorded by their active ingredients, but by brand names which are grouped so that all products made by a certain manufacturer, containing the same ingredients in the same amounts have the same "International Product Name". Since international analyses usually are made on

the generic drug level, and including different compounds, the active ingredients have to be identified for each product name. To some extent this can be done automatically, by mapping product names in the IMS files to those in the WHO drug dictionary (where drugs are recorded with their ingredients). Not all IMS product names are however available in the WHO drug dictionary, and sometimes the corresponding 'International Product Name' is given as 'unallocated'. The latter applies mainly to Germany and France, and is the case when a product is either not sold internationally, or is a locally named generic. In all these cases, the ingredients for each product must be identified manually, by searches in drug databases and drug lists from different countries and different years.

The prescription data does not include information on the duration of prescriptions. Therefore, when using prescription data to project onto sales, the assumption was made that there is no variation in the lengths of prescriptions within the groups that are studied. This limits the usefulness of the method in that it cannot be used when such a variation is known or suspected to exist. It should also be noted that the figures derived this way are estimates, and more uncertain than reporting rates calculated directly from sales data.

In some cases figures derived from prescription data can not be projected onto sales data. An example of this was the study on oral contraceptives (OC). The duration of OC prescriptions does vary between the countries studied, and therefore, in the study made, it was not possible to calculate estimated reporting rates by age groups. The age distributions had to be done separately for WHO reports and IMS data.

2.6.4 ASAP project findings

Four of six studies in the ASAP project resulted in publications in scientific journals. Paper IX *Lindquist, M., et al., New Pharmacovigilance Information on an Old Drug – an International Study of Spontaneous Reports on Digoxin, 1994* was the first publication. It provided a very useful public health signal concerning the safe use of digoxin, even though this is a very old drug. This emphasizes the importance of keeping an eye on all drugs, not only those recently marketed.

The omeprazole study [Lindquist, et al., 1996] showed a 'positive' negative result; the signal raised in one country could not be confirmed by international data, suggesting that in this case it was a phenomenon peculiar to one country. Also the possible public health risk, compared with two other drugs in the same therapeutic group, was indicated with a 'worst and best case' scenario. This was supplemented by drug use and case information which confirmed the special national nature of this signal.

The result of the analysis on 'withdrawal syndrome' reported with selective serotonin reuptake inhibitors (SSRIs) [Stahl, et al., 1997] suggested that the withdrawal reactions were different as to their character for the drugs in this

category. This finding added to the information which should be generally available to prescribers.

Paper X *Lindquist, M., et al., How does cystitis affect a comparative risk profile of tiaprofenic acid with other non-steroidal antiinflammatory drugs? An international study based on spontaneous reports and drug usage data, 1997* demonstrated that the public health impact of the signal of cystitis could have been recognised internationally earlier than was the case, had the ASAP methodology been applied.

Another main finding related to differences in reporting between countries and between drugs:

- the reporting frequency varied between countries, and to some extent within countries (over a period of time);
- the source of reports varied (the proportion GP/hospital/industry reports were different);
- the reporting frequency was influenced by publicity;
- recently introduced drugs generally had higher reporting rates, possibly due to better recognition of problems to new drugs in recent years.

One conclusion was therefore that direct comparisons between reporting rates in different countries should not be made lightly. However, a relative increase in reporting rate was suggestive of a new drug safety concern in the country in question, which could have been due to increased awareness or publicity. The advisability of comparing drug reporting rates at similar times in their marketed lives was also re-affirmed. Another insight gained through the project was that it was wise to include a 'worst and best case' evaluation of the data to address the subjectivity of some of the decisions made in the process.

The so-called 'Weber effect' refers to a rapid increase in ADR reports following the launch of a new drug, and the subsequent decline when the drug becomes established [Weber, 1984; Wallenstein, et al., 2001]. The reporting rates in the ASAP project study examples showed that this phenomenon is very variable. The variability of this phenomenon deserves further study, since the early period of a drug's use is the most critical in establishing information on its safety.

Since the most useful public health result will be to give pointers in considerations of risk–effectiveness decisions, the use of appropriate comparator drugs was seen to be very important. Moreover, the national and temporal changes in reporting rates seemed to be more easily understood with a comparator.

Under-reporting of adverse drug reactions constitutes a basic limitation of the ASAP approach; as do some aspects of the sampling of prescribers for drug utilisation information; and drug sales through channels other than retail and hospital pharmacy (e.g. family planning clinics). Against these drawbacks is the advantage of multinational comparability; continuously obtained data and

therefore the ability to examine secular trends; and the richness of the denominator data available.

Another problem, common with observational studies, is that the information on drug use as it has been ascertained by the reporting health professional does not always reflect the drugs and doses actually used by the patient.

IMS data is regularly used throughout the pharmaceutical industry for analysis of their market penetration and other sales and business support. However, during the project it was found that companies do not seem to use IMS data routinely for analysing safety issues. The skills needed to manipulate the data in order to provide a useful denominator can no doubt be learned by others, but the impression was that the kind of insight into drug use data needed for pharmacovigilance was best left to professionals whose main perspective was drug safety.

The international situation needs to be assessed in countries where the drugs are used widely, i.e. those accounting for the bulk of the international sales, and who have an ADR monitoring programme). Surprising and informative national variations can be seen, and sometimes explained on medical practice, media influences or other grounds, such as historic knowledge of reporting practice.

With more reports, adverse reaction case report data is more of epidemiological importance - factors such as age, drug indication, co-prescribing etc. can be examined. This extra numerator data should cause consideration of more refined medical denominators being used and other aspects such as demographics, which may affect reporting rates, being considered. The demographic data may sometimes be used earlier in analysis to throw light on some aspects of reporting differences between countries. Clearly the numbers of doctors per population may be relevant, and the population age distribution, for example.

The merging of two data sets requires an in-depth knowledge of their structure, definitions, and the way the data has been recorded. The many years of experience by the WHO and IMS project team members in using the respective data sets for periodic surveys and analyses allowed the avoidance of many possible pitfalls in the course of the ASAP project.

For each study example, considerable manual data transformation was necessary. Originally it was thought that concatenation of the two sets of data could have been achieved at a level allowing a 'push button' result. In the event this was not realistic, since it was not possible to develop one algorithm that would fit all situations. Also, the signals chosen for investigation required different approaches. The insights gained during the two years of processing and analysing the combined data in a critical way added to the previous expertise of the group, and at the end of the project a unique combined team resource had been developed.

2.6.5 The development of the ASAP strategy as a pharmacovigilance service

The strategic importance for the ASAP type of analysis lies in the gap between finding an early signal with possible important clinical and public health implications, and the performance of expensive case control or cohort studies. Being able to quantify the problem further and perhaps indicate risk factors or patient groups is of importance.

The studies in the ASAP project are examples of the usefulness of this methodology, and subsequently the UMC and IMS Health have used the method on a couple of signals annually. Paper XI *Lindquist, M. and I.R. Edwards, Risks of non-sedating antihistamines, 1997* was written because of a view put forward by the ASAP team that a drug adverse reaction signal that threatens to take a drug off the market should not be evaluated in isolation, but that one should always include drugs from the same therapeutic group and/or those used for the same indication in the analysis. The paper indicated that other antihistamines, apart from terfenadine, could possibly cause heart rate and rhythm disturbances.

Apart from that kind of ad hoc study, it is envisaged that key newly marketed drugs could be monitored using the two data sets. This would help to spotlight any evolving safety problem during the first years of the drug's life on the international market, in much the same way as the national intensive post marketing surveillance systems described above.

2.7 The link between case reports and further pharmaco-epidemiological studies

Signal analysis is bound to have an iterative quality to it. The initial signal is likely to be of the type 'Hepatitis has been associated with drug X, in 3 cases'. The characteristics of such a few cases are unlikely to allow for any other question than: 'Is this a real problem?' This question breaks down into causality, seriousness, frequency and comparative risk–effectiveness issues. The first two points can be considered on the basis of the reports alone. The frequency needs at least a crude use denominator.

In order to look at the signal for a particular drug versus other drug treatments for the same indication, the exposure parameters must be comparable. It is clearly of value to take considerable care in selecting relevant drugs as comparators (eg. same chemical group, similar effectiveness in an indication, likely substitutes). Also the whole risk profile of the signalled drug versus the comparators must be considered.

There are a number of information sources and methods for the detection and study of drug adverse reactions. As has been argued previously, the WHO

database provides the most cost and time effective source for identification of early suspicions, signals, on a global scale. The *signal detection* phase is the first step in the signalling process – the result of which is the generation of a hypothesis.

After this initial phase follows the *signal evaluation* or *signal strengthening* phase, where the next steps are to better characterise the problem and to try to establish the magnitude of the problem analysed. The case reports collected from countries all over the world can, combined with drug usage data, cast some light over the character of the problem analysed, and give preliminary information as to the frequency of ADRs and their possible public health impact. A main advantage is that these studies can be done quickly, and at a low cost.

However, in many situations, to test the hypothesis, there may be a need for further epidemiological studies. These can better quantify the problem and establish its public health impact, as well as determine a probable causal relationship. What is the most appropriate method and data source depends on the issue, but there seems to be a trend towards more frequent use of multipurpose health care information databases containing continuously recorded patient data, often referred to as automated databases, at the expense of ad hoc case–control or cohort studies.

The choice of appropriate method for hypothesis testing is an issue that has been of concern for pharmacoepidemiologists for years, be it in the regulatory, industry or academic setting. Much work has been done to improve the speed and efficacy with which the transition from signal detection to quantification is made. It is outside the scope of this thesis to examine the results of these efforts in detail.

However, it should be mentioned here that some steps have been taken to bridge the gap between signal detection in the WHO Programme and further epidemiological follow up. A joint project together with the Saskatchewan group in Canada led to the successful follow-up of a signal of verapamil and depression [Blackburn, 1988; Biriell, et al., 1989].

Since then, international meetings organised by e.g. ISPE, ISOP and Drug Information Association (DIA) have provided good opportunities for discussions on how to move forward. Recently, a more formal co-operation has been established between the UMC and prescription event monitoring groups: the Drug Safety Research Unit (DSRU) in the UK, and the Intensive Medicines Monitoring Programme (IMMP) in New Zealand. These collaborations are in their early phase, and much more effort is needed in this area.

Throughout the scientific signalling process there is a need for communication of findings. The demand for information and action varies depending on the issue and the role and interest of those concerned. The next chapter will discuss the *signal communication and action* phase which completes the signalling cycle.

Chapter III – From signal to balanced safety communication

This chapter reviews communication issues of importance for international pharmacovigilance. The 'What, When, Who and How' of action and follow-up in relation to safety issues is analysed, and the roles of the different players involved are examined. The chapter also includes a discussion of possibilities for development of scientific methods for safety assessments taking into account benefits as well as harm.

Introduction

The previous chapter dealt with the input and processing of pharmacovigilance information. It is clear that the development of pharmacovigilance as a scientific discipline has lead to better tools and methods for signal detection and analysis.

The next critical step in the signalling cycle is the output process: the transformation of new information into knowledge that is available to, understood by, and acted upon, not only by those immediately concerned, but also by the community as a whole. The key to the output process is good communication practice.

The UMC and WHO has a natural concern that signal information should reach the appropriate audience and be used wisely. Some years ago a paper [Edwards, et al., 1996a] showed that this was not always the case, prompting the UMC examine the issues around the communication of pharmacovigilance information specifically.

3.1 Communication principles

Communication in its simplest form means transmitting a message. One has to decide what the message is, to whom it should be directed, and how and when it should be transmitted. However, for an effective communication to take place, a two-way interaction between sender and recipient needs to be established. Only when there is an exchange of information will it be possible to find out if the message has not only been received, but understood in a way that was intended. A follow up will give information as to the usefulness of the message for the recipient, and whether it has been acted upon appropriately. After an impact analysis has be made, the message can be finetuned and adjusted as necessary to better serve its intended purpose.

Edwards and Hugman [Edwards, et al., 1997] raise the following points for consideration when planning a communication activity:

- What is the purpose of the message?
- What is the state of mind of the intended recipient(s)?

- What is the general context or climate in which the message will be perceived?
- What medium or media of communications should be used?
- What feedback mechanisms are needed to assess the extent of receipt of the message and its subsequent effects?
- How should the impact be monitored and evaluated?

Basic principles of good communication practice

- The correct message
  - at the right time
- To the right audience
  - by the right medium
- Consequences
  - Message received?
  - Message understood?
  - Followed up?
  - Acted upon appropriately?

A major difficulty when it comes to good communication practices being established and applied to pharmacovigilance is that the result of efforts in this area leads to new information that is generally both complex and with a degree of uncertainty associated with it. It is based on varying levels of evidence, usually ranging from a highlighted association between a medicine and a reaction, to a well founded, statistical probability of a causal relationship. In the absence of hard facts, there is often a high level of subjectivity involved in the assessment of the available evidence, also affecting the dissemination of messages based on these assessments. The decision as to the content of the message, when it should be communicated and how it will be followed up will depend to a high extent on the motivations and agenda of the sender, not necessarily taking into account the needs of the recipient.

The risks of producing obscure and confusing messages are even more pronounced in an international setting, with different cultures and legal and regulatory systems. Furthermore, varying availability of medicines, and different indications for use might magnify the problems of communication across countries.

What can then be done to overcome these problems? New safety information is invariably associated with uncertainty, and therefore open to questioning and the possibility of different interpretations. A first step is the awareness of this being the case, by all those participating in transmission and exchange of such information. Secondly, there should be transparency of the methods used and the decision making process involved. Available facts, and the sender's arguments and motivation should be disclosed. Such openness has to be based on trust, and honesty, in all interactions.

3.2 Concepts and definitions

In its global normative function, WHO has generally been very much concerned with definitions that are understandable by a variety of cultures and can be translated into the main language groups. Over the years the definitions of some fundamental pharmacovigilance terms have been agreed within all the countries belonging to the WHO Programme for International Drug Monitoring.

Definitions agreed in the WHO Programme

Side effect
Any unintended effect of a pharmaceutical product occurring at doses normally used in man which is related to the pharmacological properties of the drug.

Adverse event/adverse experience
Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse reaction
A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis,diagnosis,or therapy of disease, or for the modification of physiological function.

Serious Adverse Event or Reaction
A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- results in death
- requires inpatient hospitalisation or prolongation of existing hospitalization
- results in peristent or significant disability/incapacity
- is life-threatening

There are, however, some key terms which have not so far been agreed internationally, and which cause some difficulties in international pharmacovigilance practice. Terms such as 'signal', 'alert', and 'warning' are used in connection with information being communicated (the noun forms: a signal, an alert, a warning), or in relation to activities undertaken (signal detection, signal generation, and the verb forms: to signal, to alert, to warn).

Within a given setting, these might be understood and applied consistently, but when it comes to communication between and outside confined areas, there is a risk of misunderstanding. Ideally, to avoid confusion, one should seek to establish agreed-on definitions of terms and concepts used and referred to. A definition should be easy to understand and provide a concise and unambiguous description of a word or an expression. Accurate and clear definitions facilitate interpretation between different professional areas and groups, and translation, which is essential in an international setting.

Oxford dictionary definitions:

Detection: The finding out, or discovery of what is unknown, hidden or disguised; detective work. Exposure, revelation of what is concealed.
Generation: Bring into existence, produce; cause to arise; give rise to
Signal: A sign or indication of a fact or quality, a future occurrence; intended as a sign to convey warning, direction or information
Alert: A sudden attack or surprise; a warning call; an alarm. Make alert, warn (v.)
Alarm: Frightened anticipation of danger; a state of frightened surprise; apprehension. To warn of danger or to attract attention (v.)
Warning: Indication, intimation or threatening of impending misfortune or danger; a sign or message of this. Deterrent counsel; cautionary advise against neglect of duty or imprudent or wrongful action. Notification of a fact or occurrence.
Information: Knowledge or facts communicated about a particular subject, event etc.; intelligence; news
Knowledge: Acquaintance with facts; a state of being aware or informed; awareness; consciousness

This is the theory, but what about the practice? There are several reasons why the above ideal is difficult to reach in the signal detection area. The concepts are abstract; they do not represent easily identifiable or recognisable objects, but refer to a quality, a state or action. The terms are often used seemingly interchangeably; it is difficult to establish whether by using different terms the same or indeed different concepts are intended. The terms have developed as part of a jargon; they form a convention or code with an assumed meaning used only by those who are 'in the know', therefore not considered necessary to explain to outsiders.

Despite the above, some efforts have been made to describe what these terms mean when used in pharmacovigilance, albeit not with the aim of seeking agreement outside the drug safety area.

3.2.1 Signal

Finney wrote in 1974: "a signal is a basis of communication between WHO and national centres; only rarely will it carry the force of a proven danger". " Signals are intended to arouse suspicions and to stimulate deeper investigation"[Finney, 1974].

The WHO Programme members agreed in 1991 on this definition: "Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously". The following note has been added to aid interpretation: "Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information" [Edwards, 1997] .

[Amery, 1999]: "a signal may be defined as new information pointing to a previously unknown causal relationship between an adverse event, or its incidence, and a drug: the information must be such that, if confirmed, it may lead to action regarding the medicine". "Thus signal generation aims at timely identification of previously unsuspected adverse effects, but any signals require further evaluation as they themselves do not prove that there is a safety problem".

The term signal is referred to by EMEA in the section headed Procedures for Transmission and Management of Detected Signals as "a potentially serious safety problem (e.g. a series of unexpected or serious ADRs or an increase in the reporting rate of a known ADR report)" [EMEA, 1999].

According to Meyboom [Meyboom, et al., 1997] a signal is a "set of data constituting a hypothesis that is relevant to the rational and safe use of a drug in humans", with the addition "such data are usually clinical, pharmacological, pathological or epidemiological in nature".

The examples given above do not provide an exhaustive listing but serve to illustrate the complexity of the concept of a signal, and that there are subtle but important differences in the views of experts in the field. One conclusion that can be drawn from the descriptions quoted is that there seems to be agreement on the general principle level: a signal is essentially a hypothesis based on reported clinical concerns or other data. This gives an indication of the nature of a pharmacovigilance signal, although on the broad conceptual level; and as a definition it is brief, but not comprehensive, nor very clear. For communication purposes, using this as the only description would be more confusing than helpful, in that it is open to wide interpretation.

A further analysis of the different descriptions shows that this problem has been recognised. In most, attempts have been made at clarifying and explaining the more precise meaning of the signal concept. This is done in form of added qualifying statements or notes. However, these additions in turn need further clarification to be meaningful. What does 'incompletely documented' mean? Whether an adverse reaction is potentially important, new, under-

recognised or serious is a matter of relativity and/or judgement. The criteria for these assessments are not clear. Also, there are differences as to the inclusion and emphasis of certain characteristics. This could be because the description was not intended to be exhaustive, or due to real differences in views. However, it does not facilitate interpretation.

In addition to the common thread of the quoted definitions of a 'signal', (a hypothesis based on facts), a signal also relies on more or less subjective assessments of these facts and their significance. A *communicated* signal is an opinion reflecting the view of the sender of the message, and the reason for communicating it is that, in the sender's view, an action is warranted (though this is not explicit except in Amery's definition). The characteristics of a signal, and the opinion and recommended action put forward in a message, depend on the context, the particular setting and the agenda of the person or group that formulates the message.

For communication purposes, a proposal for a more helpful general definition of signal in the domain of pharmacovigilance is: 'A signal is an opinion that a hypothesis based on facts and assessments warrants an action'.

When formulating the message, one should also keep in mind that the sender's opinion may not necessarily be the same as the recipient's. Therefore, in an actual communication situation something more than a general definition is needed in order to avoid misunderstandings and to enable the recipient to make a realistic interpretation of the information received. To facilitate interpretation and to enable discussion a practical suggestion is to provide the recipient with a description of the information content of the signal in each communication situation. The source of the facts, frequency measurements and their probabilities, as well as criteria used for the assessments, should be clearly stated. The level of uncertainty depends on the type, amount and quality of the available information, and is related to time and the origin of the signal. All this needs explanation, to go with the information. Also, a signal message should inform the recipient if absence of any of the information items is due to missing data/no assessment having been made, or if this information is available but not included in the message that is communicated.

Based on the above approach, the UMC *Signal* document incorporates background information including the WHO definition of a signal, but with more explanation. There is also a brief description of the UMC's signalling process, including a description of the data mining technique used. The intended recipients of the document are identified, as well as its purpose. The contributing reviewers are identified. They are asked to separate and describe the facts, and then to give an opinion. Discussion is invited from recipients, particularly from the producers of a drug product if a single producer can be identified.

Signal facts

Type	Description of reaction/s
	Number of cases
	Country/ies
	Number of cases with drug as only suspect drug
	Concomitant medication
	Age/gender distribution
	Dose
	Route of administration
	Indication
	Other concomitant disease/risk factors
Timing	When did it occur; immediate or delayed
Duration	How long did it last
Severity	Magnitude/intensity of reaction
Outcome	What were the consequences of the reaction? Was it reversible? Sequelae?
Dechallenge	Was the medication stopped, and if so, what was the outcome?
Rechallenge	Was the medication reintroduced, and if so, what was the outcome?

Frequency measurements and their probabilities

Reporting frequency	Number of occurrences (numerator)
Incidence	Number of occurrences/exposure information (denominator)
Absolute risk	Risk in an exposed population
Relative risk	Risk in an exposed population compared with risk in a non exposed population

Signal assessments

Validity and evidence of signal:

Documentation level	Are all relevant facts present/missing?
Confounding	Other risk factors than drug present?
Bias	Selection or measurement bias present?
Credibility of cases	Result and accuracy of individual causality assessment
Credibility of signal	Enough cases? Causality assessment of signal
Importance of signal	Seriousness/intensity of reaction: individual case (patient assessment; medical assessment); importance for public health

Other factors:

Predictability	Can the reaction be predicted? Are there any early indicators?
Prevention	What measures are needed to avoid the reaction? Identifiable risk groups?
Treatment	What treatment is available? Is it effective?
Alternatives	What therapeutic alternatives are available? Are they equal/better/worse?

3.2.2 Alert or Warning

Both the EU and the FDA use the term 'alert' in relation to the communication of safety information, in the sense of making alert, or attract attention to a safety issue. There is no agreed definition of the use of this term as such, but there are defined criteria for providing information, and to characterise the reports themselves. In the EU guidelines an 'alert' denotes information on "identified signals which may impact on the risk–benefit balance of a medical product". A 'rapid alert' should then be sent to member states, EFTA countries concerned, the EMEA and the European Commission. Upon receipt, it is up to each member state to contact the MA holder/s in their country. The communication criterium is "the concern about a change in the balance between risks and benefits that could lead to major changes in the authorisation such as urgent suspension or withdrawal of the marketing authorisation, the introduction of major contraindications, restrictions in the indications or availability of a product" [EMEA, 1999].

In the US, post-marketing 15-day 'alert reports' refer to adverse events that are both serious and unexpected, and which should be reported by the

manufacturer, packer, or distributor to the FDA within 15 days of receipt. The term 'alert' is also used in the US in connection with FDA publication of product withdrawals and labelling changes.

One difference between the two territories is that the information in the EU 'alert' is primarily directed to the national drug regulatory authorities, whereas in the US the term is used for reports that should be transmitted from the manufacturers to the FDA. Another difference is that the EU 'alert' refers to information sent at the pre-regulatory decision stage, but a US 'alert' can be either pre- or post-decision information, the latter available to the public.

'Drug alerts' as found on the WHO homepage cover a range of safety concerns raised in different countries or territories, from signals to drug withdrawals.

It is confusing that the term 'alert' is used to refer to three different concepts:

- the characterisation of certain information (as fulfilling certain criteria)
- the need for action
- the kind of action to be taken given this information.

The criteria for what warrants the action are different (in at least two major territories). In the US, 'serious and unexpected' reports in themselves should initiate the action. In the EU, it is the reports plus a subsequent assessment that there is an altered risk–benefit balance that should cause the action. Also, the kinds of action to be taken following an 'alert' vary, although normally associated with a degree of urgency. From a linguistic point of view, and for a better understanding, the most unambiguous use of 'alert' would be when referring to *the need for an action*.

The use of the term 'warning' is not straightforward either, in that it can refer to both the need for an action and the kind of action to be taken. The use of 'warning' in 'early warning system' belongs to the former category, whereas a warning to prescribers against giving a certain drug to a pregnant patient, or against using drugs with the potential for interactions together belongs to the latter. Conceptually related to 'warning' in this latter sense are the terms 'caution', 'restrictions for use' and 'contraindications' , which, like 'warning,' can be found in national drug lists or other prescription information and serve the purpose of recommending or imposing a certain action.

3.3 The communication of signals

3.3.1 Strength of evidence

The main task of the WHO Programme signal review panel is to identify drug–ADR associations of regulatory, public health or scientific relevance. In the assessment of whether or not a drug–ADR association should be disseminated

as a signal, a variety of criteria and considerations play a role [Meyboom, et al., 1997] and Paper III. Together these criteria determine the strength of a signal, but their individual importance may differ strongly from signal to signal.

As has been argued previously, signals are not only uncertain as to the level of evidence, they are also preliminary in nature. The situation might change substantially over time: more evidence could strengthen or weaken the association. Furthermore, a signal does not necessarily mean that the association between a drug and an ADR has not been made before: it could provide more documentation based on new information. Thus some signals add to existing knowledge by giving information on the range of severity of the reaction or its outcome, whereas others may postulate a mechanism, indicate 'at risk' groups, or suggest a pharmaceutical group effect or the lack of such an effect by a particular drug.

The signals which are the result of evaluations of summarised case data in the WHO database are sent by the UMC to national pharmacovigilance centres, in the 'Signal' document. The topics discussed are varying levels of suspicions derived from examination of the data in the WHO database, primarily intended for information. National pharmacovigilance centres and regulatory authorities may in turn consider the needs for possible further action.

At each step of the signalling process, the available information has to be disseminated and further actions to be taken. In determining the appropriate audience for the information, the signal should be judged by its seriousness, frequency, and whether it relates to widely used drug/s. Many signals included in the *Signal* document are based on a preliminary analysis of case reports in the WHO database. This kind of information would normally not warrant a wider publication, although exceptions could be made if the signal concerns a major public health issue.

On the other hand, some signals are the result of a more extensive investigation, normally involving national centres and/or the companies concerned. Again, further action has to be decided based on the importance and urgency of the new information. The WHO has no mandate to take regulatory action, so its role can only be advisory. There is no reason however why discussions on possible actions and how to proceed should not involve the WHO, particularly if the early signal was detected by WHO experts.

Another type of signal that conforms to the definitions mentioned earlier is a case report or case series report by a medical professional, published in the literature. Again, not necessarily referred to as a 'signal', but a concern expressed by someone who has diagnosed or treated one or more patients for what is suspected to be a new adverse reaction. This type of signal is often the earliest indication of a safety problem going direct to health professionals. It has been argued that, historically, most safety problems were first identified as published signals by vigilant doctors [Venning, 1983; Venulet, 1986]. One reason for this could be that these signals are the result of first-hand, clinical

observations, and thus are very early suspicions which have not gone through a lengthy evaluation or regulatory process.

In summary, the UMC *Signal* document includes signals which have different character, different amount of information and level of evidence, but with the common denominator that they need consideration and possible further action by regulators and concerned companies.

3.3.2 Actions based on signals

The decision to communicate a signal involves consideration of the appropriate action to be taken by the recipient, and also the sender. Depending on the mandate of the sender, the action can be proposed or demanded.

Possible actions following a signal include those listed below:

- Wait and see
- Seeking information (to strengthen signal or to test signal hypothesis)
  - asking for more case reports
  - initiating further studies
- Raising awareness
  - information via bulletin, medical or other media
  - Dear Doctor letter
  - change in product information
- Restriction
  - warning/contraindication for use
  - restriction of availability of drug
  - temporary suspension of drug
  - withdrawal of drug

Regulatory bodies are responsible for safety monitoring of the medicines they have approved for use in their countries. Signal detection results in considerations of appropriate action, along the lines of the above categories: this takes some time. The end results of regulatory signal evaluation are generally circulated to the medical profession in the country, e.g. in form of monographs in a national drug bulletin, issued by the authority, or as revised product information. Earlier in the process, communications with the companies concerned will normally have been initiated, and information sent out to other regulatory authorities.

Sometimes, a signal is published in the medical literature, before or after its inclusion in the authority publication. Such a publication may not be labelled 'signal', but presented as a review of received case reports. It could however be referred to as a signal, for instance in communication between authorities. For instance, the EU regulations require that the member state authorities and MA holders should 'inform each other of signals which may impact on the

risk–benefit profile of the medicinal product' [EMEA, 1999]. As means of communication within the EU the so-called rapid alert system has been devised. It is also stated that these communications should take place before a decision is taken in a member state.

Although many pharmaceutical companies have well established internal signal detection systems in place, the complete results of the initial screenings are rarely communicated as 'signals' outside the company. As is the case with regulators, it is generally only when the information will lead to altered safety information in the medicinal product information, or at worst (from the company point of view), the withdrawal of a product from the market, that the effects of signal detection, internal or external, are visible to an outside audience. In the case of externally identified signals, there is however normally some communication between the initiator of the information and the company concerned. Following from this, it is evident that although pharmaceutical industry representatives may agree on the above concept of a signal, new safety information from a company is rarely, if ever, published as 'signals', but communicated in other ways.

3.4 Communication throughout the pharmacovigilance process

The pharmacovigilance process consists of many steps: at each step the relevant communication issued should be identified and acted upon. Many different players are involved, not only regulators and the pharmaceutical industry, even though they will most often be the first recipients of information constituting a signal. Figure 15 gives an overview of the processes and communication issues.

but also as providers of information back to health professionals, and, in some countries, by reporting adverse reactions to the pharmaceutical companies or a national pharmacovigilance system.

3.4.3 The UMC and communications issues

The UMC has published two monographs, *Effective Communications in Pharmacovigilance* and *Dialogue in Pharmacovigilance*. The first of these was the result of an initiative was taken in Verona in 1997 to bring representatives of all the players in drug safety together to explore ways of enhancing drug safety communication. This initiative, and a subsequent meeting in Erice which resulted in a declaration on communicating drug safety information, were the start of a process with the potential to bring individual drug safety to the patient and the general issues to the public. The second monograph takes the main communication challenges defined by the first meeting, giving the results of an expert group's examination of those issues. The details of this work are out of the scope of this thesis, but education of adults and children, taking account of their perceptions of drugs and safety were to the fore, as was the topic of crises in drug safety [The Erice Report, 1997; UMC, 2002a].

A further publication by the UMC is called *Viewpoint*. In two volumes, the first of these is an attempt to introduce the ideas of benefit and harm to the general public, in a way that they can relate them to the normal experiences of life. The second volume will be more technical in the description of the global system, and the role of the UMC.

In addition to the above the UMC staff have provided help in the development of guidelines for the setting up of pharmacovigilance centres and for reporting by doctors, produced by the WHO.

A summarised account of communication issues in the signalling process is shown in Table 11. The players involved are listed in the left column. The right column indicates communication considerations.

Table 11. Communication issues in pharmacovigilance

Diagnosis of a suspected ADR	
Prescribers, patients and other health professionals involved in patient care	Interaction between players involved, and access to up to date, relevant information
Filling out a case report form or otherwise making a notification	
Prescriber or other health professional	Awareness of the existence of a reporting scheme, and access to reporting form/other means of reporting
Filing report locally (e.g. in hospital or in pharmaceutical company database)	
Report originator or	Transfer of information from originator to pharmaco-vigilance responsible person
Appointed pharmacovigilance responsible person	Interaction with report originator
Sending report to a regional pharmacovigilance centre	
Report originator or	Transfer of information from local site to regional centre
Appointed pharmacovigilance responsible person	Interaction with report originator
Sending report to a national pharmacovigilance centre	
Report originator or	Transfer of information from regional site to national centre
Appointed pharmacovigilance responsible person	Interaction with report originator
Collecting and entering report into a national pharmacovigilance system	
National pharmacovigilance centre	Interpretation of content of report, and interaction with report originator and local or regional pharmacovigilance responsible person
Sending report to UMC	
National pharmacovigilance centre	Transfer of information from national site to international centre, and interaction with UMC
Collecting and entering report in the international database	
UMC	Interaction with national pharmacovigilance centres
Screening of collected data to identify possible signals	
Pharmaceutical company, national pharmacovigilance centre, UMC	Interaction between players involved, and making strategy and methods used known and accepted
Preliminary analysis of evidence	
Pharmaceutical company, national pharmacovigilance centre, regulatory authority, UMC	Interaction with players involved; and interpretation of results, decisions about dissemination, and consideration of further action

Further studies	
Pharmaceutical company, national pharmacovigilance centre, regulatory authority, UMC, academia	Interaction with players involved; and making strategy and methods used known and accepted; and initiating and carrying out study
Analysis of evidence from study	
Pharmaceutical company, national pharmacovigilance centre, regulatory authority, UMC, academia	Interaction with players involved; and interpretation of results; and decisions about dissemination; and consideration of further action
Effectiveness–risk assessment	
Pharmaceutical company, national pharmacovigilance centre, regulatory authority, UMC, academia	Interaction with players involved; and interpretation of results; and decisions about dissemination; and consideration of further action
Changes in regulatory status	
Regulatory authority and/or pharmaceutical company	Interaction regulator–pharmaceutical company, and decisions about dissemination of information
Follow-up and impact studies based on new knowledge	
Regulatory authority, pharmaceutical company, UMC, academia	Making sure information is available to prescribers, patients and general public; and making sure new information leads to behavioural changes
Individual benefit–harm assessment	
Prescriber, patient	Interaction patient–prescriber, and access to up to date, relevant information

3.5 How to balance negative and positive information

3.5.1 The positive aspects of therapy

Modern drug therapy is based on pharmacological knowledge of how a medicine can work in alleviating symptoms, altering physiological or pathological processes, or functioning as a diagnostic tool. This describes its *utility.*

The next step is to see if the medicine works in healthy individuals, or selected patients, which allow for the clearest, most uncomplicated analysis of *efficacy*. How frequently, to what extent, and with what duration the medicine works is usually compared with that of a control group, which further defines efficacy compared with a placebo or another treatment.

More and more concern is raised about the *effectiveness* of medicines in day-to-day clinical practice, as opposed to the *efficacy* [Bombardier, et al., 1999] measured in the confined and selective clinical trial situation. Although the two words are often used interchangeably in everyday language, increasingly a

distinction is made between the two in epidemiology. It is also implied, or stated in some studies, that effectiveness is a better measure of the benefit of treatment. Whilst this is probably true, benefit depends upon effectiveness (and efficacy) but is not the same as either.

Benefit is 'an advantage; a good' and 'something that aids or promotes well being'. It is a subjective value judgement. One can guess at benefit to an individual or society, one can even devise some efficacy measures that many would agree indicate that benefit has been gained, but these do not measure true benefit, particularly in an individual. The target outcome when measuring efficacy/effectiveness is a carefully selected, intended main indication for treatment, whereas benefit can be a whole range of positive effects, many of which would be unknown and therefore unexpected and not included in a study of efficacy/effectiveness. A consumer or patient may well benefit from a placebo: or may judge a medicine to be inadequate in spite of its efficacy being established in clinical trials or the effectiveness shown in normal clinical use. Benefit to the individual can only be judged if it includes that person's expectation and completely measures the subjective fulfilment of that expectation.

3.5.2 The negative aspects of therapy

On the negative side of therapeutics it is evident that all treatments present a *hazard*: there is a potential for harm. Before clinical trials have been started the hazard is usually defined by toxicological information.

In clinical trials, we obtain information on possible harm in humans; the frequency, degree, and duration of harmful effects can be measured in a defined population. The process is analogous to that defining efficacy, although harm is more complex to define. When studying negative effects one has to take into account all events indicating harmful effects possibly related to the medicine, many of which would not be expected from previously available information. Also, the rare negative outcomes are less well quantified, if at all detected, in the small study population of a clinical trial.

Once the medicine is used in regular clinical practice, and a larger number of patients have been treated, one can get a much better idea of the probability (risk) and extent of harm on the population level, but also more information on individual harm as experienced by patients. On the individual level, harm is the true converse of benefit. Though harm has objective qualities, the full extent of harm to an individual is very much a subjective issue: only an individual can determine how harmed they feel.

3.5.3 Balancing positive and negative effects of medicines

Pharmacovigilance can result in two practical levels of regulatory and pharmaceutical industry activity. One level is simply to control the availability of drugs, the second is to provide information for their safe use. The information can be of a mandatory or advisory nature. Pharmacovigilance activity also results in publications which health professionals may read, and also in some output in the public news media.

It is currently supposed that removing a medicine with many adverse effects from the market is in patients' best interests. If the assumption is that doctors and patients cannot make an informed selection amongst alternatives then such an approach is justified: it may also be advantageous to withdraw products that are clearly inferior to available alternatives. On the other hand, the fine differences between individual patients' needs must demand, above all else, that information on the positive as well as negative effects of medicines can be useful in helping individual patients and their doctors to reach the best therapeutic decisions.

The doctor should have the detailed knowledge of a patient's illness(es) and is primarily responsible for the discussion of what therapy should meet that individual's needs. Therefore, the doctor is the main medium for transmitting information about therapy which will empower the patient to make a decision about the management of their disease.

Pharmacists and nurses play different and supportive roles in the therapeutic process, and may be the main suppliers of information to the patient in some circumstances. However, as part of a health team, both nurses and pharmacists can add to a successful therapy by providing information to the doctor about the patient and the medication (respectively). The involvement of the pharmacist in clinical practice could, and should, increase. The pharmacist has skills which complements the more therapeutic aspects of medication, and allows doctors and nurses to concentrate on the patient and the patient's disease.

The information sources generally available to doctors and other health professionals are national drugs pharmacopoeias, pharmaceutical industry information, package inserts, access to drug information centres and various text books. These resources provide useful basic information, but they are usually lacking detail on adverse drug reactions which, by their rare nature, are not usually part of the regular experience of most doctors, one exception being in the area of treatment with cytostatics. Since doctors do not get experience in ADRs (because most of them are not seen as part of daily practice) it is important that references give information on the frequency and severity of ADRs, when available.

Having become partners in practical pharmacotherapy at many levels and with the emergency of clinical pharmacy and pharmaceutical care, also pharmacists have become major users of pharmacovigilance information. In

addition to having become a source of information, e.g. in the form of reporting adverse reactions, pharmacists need to receive feedback information regarding the findings of pharmacovigilance. Depending on the position, be it retail, hospital, information or research pharmacists, this information is used in different ways. Dspensing pharmacists are in many countries a first contact for the patient, and they need prompt information regarding new adverse reactions or other medicine safety issues. The same is true for hospital pharmacists, for the medication monitoring as well as for preparing guidelines, formularies or the improvement of monitoring strategies.

Information sources are very variable throughout the world in their inclusion of suspected ADRs, but there is usually nothing on the strength of relationship between a drug and an ADR. There is often little information on the mechanisms of specific ADRs. Even the indications for use give little indication on how effective a drug is likely to be. Drug costs are quoted as prices per quantity only and not usually as cost of treatment in defined daily doses. There is thus very little which helps a decision on the relative effectiveness of drugs, let alone how to work out the overall relative merits of medicines.

Since interpretation is such an important factor in assessing the merits of a medicine in different contexts, it is essential that the conceptual framework is clear, and that communication is complete. The expression 'benefit-risk' is in widespread use to indicate the positive and negative attribute balance for a medicine or other treatment. As outlined above this expression is unequal, since benefit is a concrete positive outcome, whilst risk is the *probability* of a negative outcome.

The risk of harm can be measured in a clinical trial, or estimated in studies reflecting normal clinical use. The full extent of harmful effects will not be known until the medicine has been used by a large population. Correspondingly, the chance of achieving a target positive outcome can be quantified in a clinical trial (efficacy) or in epidemiological studies (effectiveness). The full extent of possible or perceived benefits are not usually covered, neither on the population nor on the individual level.

It *is* possible to talk of 'benefit' in a population sense but then it must be something that improves the *general* health status of a population or is more efficient and reduces costs to society. More attempts are made to do this, but they fall short of comparing all therapies for the same indication, their outcomes and consequences, which would be necessary to decide on a societal benefit.

The individual perception of benefit and harm have other aspects than frequency or likelihood, namely degree of relief on the benefit side versus the degree of severity of harm, and also the duration of one or the other [Edwards, et al., 1996b].

Even the bench science which gives us the 'hard' utility and hazard information has a subjective quality in interpretation, but the more human subjects are involved in the outcome of research studies, not only is there more

subjectivity involved in some of the outcomes, but more subjectivity should be taken into account. After all, any therapy has the aim of satisfying the individual: not society, not the government, not academics and not the pharmaceutical industry (vaccination can be considered as an example of exceptions to this). Subjective information should enhance, and be interpreted alongside the more quantitative information on hazard and utility, and their probabilities.

The nature of risk from drugs and the issue of probabilities in assessments of negative, and positive, medicine effects should be more widely promoted to those directly concerned. It is still too often said that practising doctors do not make 'correct' decisions about drug therapy: this may be true, but are they allowed to have the right information in a useful format? It is also often said that patients may be put off taking drugs (which someone decides for them will be beneficial) if they know about possible adverse reactions: this may also be true, but is there any attempt to generally educate people about what they can expect from drug therapy? How is the information on safety of medicines given to consumers and patients?

Both regulators and pharmaceutical industry have an important role to play in communicating information about medicines. This role is particularly critical when it comes to decisions involving restrictions for use, or withdrawal of a medicine. Such messages can only be understood if there is better disclosure of the risk assessment process and its results. When health professionals and patients feel they can trust that the decisions are based on considered and careful assessments they are more likely to act appropriately.

Less efforts have been put into development of risk assessment, communication skills and crisis management as compared with developments on the input and processing side of pharmacovigilance. This is a great challenge for the future, but necessary in order to avoid, or at least reduce the number and extent of, crisis situations in relation to new information on negative effects of medicines. In a crisis, with ensuing panic, there is a high risk of excessive or unreasonable decisions being made. The third generation oral contraceptive relationship with venous thrombo-embolism is an example of this [Mills, et al., 1999].

Media also has an important role in giving balanced information, and to try to avoid sensationalism. Recent developments of information on the Internet is both promising and worrying. It is not easy to judge whether the information presented is reliable or not. Efforts to limit the freedom of the media are not appropriate at all, but the frequent open and sometimes acrimonious debates in the media between experts on such emotive and technical issues as pharmacovigilance does not engender public confidence.

In the clinical setting, we should try to find out more about what our patients want from their therapy, try to explain the efficacy and risks of treatment, so that they understand that there may be a difference from their

expectations. We must reassess the patient for benefit and harm, objectively and as perceived by them.

3.6 Feed back communication

The final step in good communication practice is to ensure that it is two-way. Feed back on the impact of communications and actions are essential to see that what has been done is effective and appropriate.

Communication of issues relevant to all aspects of drug therapy is improving with better efforts being made to give balanced information in a readable format in modern monographs and drug information leaflets. This work is being pursued by many groups, but the efforts are far from being an established norm in consumer and patient information requirements.

The 'what, when and how' of communication are increasingly being considered by the pharmaceutical industry and regulators, with good initiatives being taken with patient orientated information, and better summaries of product characteristics.

These initiatives could be much improved by more involvement of consumers, patients, prescribers and other health professionals, both in finding out what would be most helpful and in checking the information for utility.

When it comes to consequences and impact analysis, there is a need for much more information and action.

Message received

A simple tear off addition to 'Dear doctor' letters to health professionals would give an indication of how many of these important communications had been received, and at least looked at. The cost would be only that of design return postage, and analysis. The need for repeat messages could be assessed and the need to target certain audiences for education (eg. Is it mostly hospital doctors who reply? If so then efforts should be taken to improve the response of others).

More sophisticated follow up could be undertaken as part of a distance teaching continuing education programme: one is already in operation through the University of Cardiff, Wales, UK.

Message understood

This is clearly an aspect that can be followed during continuing education. Other possibilities are:

- Epidemiological follow up of the use of the drug in question or of the disease with which it is associated for changes which reflect action on the information given

- A randomly distributed questionnaire seeking information on actions taken as a result of the message. (This overlaps with 'acted on appropriately' see below)

Message followed up

After getting information on the receipt of information and the level of understanding, there needs to be follow up which will ensure that any defects in the communication are remedied. This will not necessarily be a simple repeat of the message!

Message acted on appropriately

It may be that action taken after a message has long term consequences which are not obvious. For example, a message which results in a change of prescribing towards second-line therapy, may result in the substitution of a more problematic drug. Epidemiological follow up and drug utilisation studies are the best ways to detect this.

Pharmacopoeias and SPCs should be reviewed to ensure:

- Sufficient clinical detail on ADRs to allow for good diagnosis and management when there may be situations which are not covered by basic medical knowledge (eg. If liver function tests are elevated is it safe to continue the drug?)
- New information should be highlighted in new editions

There are many other style and layout issues which can be considered.

More work needs to be done to get the patients' perceptions of benefit and harm to themselves. Currently, there is much emphasis on quality of life indicators, but these are based on standard questions decided on by professionals to cover the main issues as they see them. Individual patient perceptions may include other questions and emphases which receive little or no attention in quality of life instruments, since they are difficult to evaluate in a study environment.

In the end, a broad, honest and objective assessment of the result of action and communication is the only way to improve. At the moment this is a much neglected topic, and we tend to assure ourselves that removal of a drug from the market shows that pharmacovigilance is working: this self-congratulatory approach does not take into account those who might be well pleased with a specific drug, and what inconvenience they have, and even loss of benefit they experience on its removal.

Chapter IV – Towards safer use of medicines – Discussion and Conclusions

This final chapter is concerned with the implications of the findings reviewed in the previous chapters, and discusses how the work done so far can be applied and further developed to enhance global pharmacovigilance as a science and contribute to a rational and safe use of medicines.

Introduction

The link between thalidomide and birth defects was discovered by a very astute, observant medical doctor. He was curious enough to ask himself the question 'Why?', and intelligent and persistent enough to find the link. That kind of curiosity and interest is still the basis of finding adverse reactions which are too rare to have been seen when a medicine is first marketed.

Individuals taking medicines and health professionals are the essential start and end of pharmacovigilance. Over forty years there has been a concentration on the middle - the science, epidemiology and regulation. These developments have not brought about, as much as they should, improved information, education and other support systems that health professionals and patients need to secure the best and safest treatments. In view of the lack of time and support for health professionals, it is possible that a thalidomide problem might go unreported for too long, if it were to happen again.

Although information on medicines is available from many sources, much of it is unbalanced, scaring and unchecked for quality. In today's circumstances where doctors have less and less consultancy time, they need more useful information, not just more! They also need more time, and sometimes interest and knowledge, to follow up patients to make sure that their treatment is working as it should. Very little is taught to medical students about the diagnosis and treatment of adverse drug reactions, and how to follow up patients.

Pharmacists have a detailed and specific knowledge about drug effects and pharmacokinetics, and could contribute a vital link in the building of health care teams with complimentary skills in the different aspects of drug therapy. This competence is often not used at all, or not optimally, in the clinical setting.

Since the start of pharmacovigilance systems forty years ago a number of epidemiological methods and techniques for post-marketing study and follow-up have been developed and refined. The main focus has been on public health impact and regulation, and major decisions as to whether a medicinal product should be on the market or not have been based on their perceived value for the public in general. However, this is of limited value to the prescriber who makes individual treatment decisions, and needs to be able to diagnose an adverse

reaction in an individual patient and then decide how to manage that patient's treatment afterwards, including being able to explain what is happening and keeping the patient as a trusting partner in any future therapy.

Much work is needed to make sure that pharmacovigilance activities that are undertaken have the best impact on public and individual health, and that the focus for the future should be on the areas that need improvement.

This thesis has covered the pharmacovigilance process from the international perspective; from the first identification of a safety signal, through further analyses and quantification of the problem, to communication, action and the weighing of benefit against harm.

4.1 Implications and recommendations

In pharmacovigilance the process of determining harm from a drug most often starts with a case, or several cases, each of which has been evaluated to the best of a health care practitioner's observation, intelligence and experience. This is therefore a deductive, but also an inductive process; there is a mix of a priori logical reasoning, and the use of a variable amount and type of experience and science. Moreover, intuition plays a part in this context meaning the inferential aspect of a diagnosis, using inputs which are not consciously considered by the diagnosing clinician, as well as holistic knowledge of the total patient's context.

It is important to realise the nature of the diagnostic process to understand its variability and in which situations it may be more or less reliable. Every day vast numbers of patients around the globe trust to clinical diagnosis to determine possible risky further investigations and treatments, or indeed that they should not have treatment. The diagnosis of any disease is not a random assignment, but each diagnosis carries a variable probability of accuracy normally in excess of 0.5. If this were not so, no one would trust the practice of medicine.

Epidemiology is population based, and can only answer questions in terms of probability. Very often the results of epidemiological investigations can only point to where further investigation is most likely to be profitable, in the sense of what next step may add most to knowledge. On the other hand the deductive nature of controlled epidemiological studies limits the effects of variables which can influence the issue under investigation. Cohort studies and randomised trials do this to a high degree, whereas case–control studies can only sieve out unwanted influences. In general, the greater the prospective control the more clear the result and the less external validity: the more observational the less clear, but more representative of real life.

Pharmacoepidemiology can provide scientific evidence to aid the process of diagnosing adverse drug reactions. Understanding and evaluating the various factors within any study which may influence the outcome, and the ability to

consider the probabilities described in a context external to the study, are an essential part of a diagnosis. The deductive aspect of a diagnosis adds another dimension in the consideration of many other factors surrounding an individual patient. Such a process adds information to the broad epidemiological information already available, giving a fine-tuning as well as finding new hypotheses for further evaluation by another method. The collection of individual case reports should not be seen as a part of pharmacoepidemiology, because each case report is the result of a deductive process which is completely different from that of an epidemiological study. Each diagnosed case is an actual incident where 'harm' has been considered to occur, whereas an epidemiological overview describes 'risk', by considering one defined treated group against a control.

Whilst there has been considerable development in the understanding and use of pharmacoepidemiology, there is little work that has improved pharmaco-diagnosis. The main approach has been along the decision-tree line, with the development of algorithms. Many have been produced, none has easy application in all situations, and, where they have been tested, they seem to have the effect of ensuring that a body of information is considered more consistently. This usually has the result that firm decisions of is – or – is not drug related are lessened to either 'probable' or 'possible'.

Bénichou and others have been strong proponents of the view that better results might be achieved if better definitions were used and the diagnostic process analysed for outcomes in various specific clinical areas [Bénichou, 1994; Benichou, et al., 1998]. This whole area of pharmaco-diagnosis must be considered as a major challenge for the future, in a discipline whose current gaze is mainly upon epidemiological method and regulation.

4.1.1 Patients and the Public

For the sake of emphasising that the only true beneficiaries of pharmacovigilance are those taking medicines, one can start with the general public. People need to be educated into what they may expect when they become patients. In respect to medicines this needs to include a view of effectiveness of treatment which may not be 100 percent. Nor is effectiveness the same as benefit. The latter is much more a subjective judgement: it is what good has actually been achieved, for that particular person.

Apart from potential effectiveness all medicines carry a risk of harm. People make decisions about effectiveness and risk and benefit and harm every day of their lives. What people need is a context in which to place benefit and harm information about medicines. Many people are interested in the effects of medicines, for instance, the national drug formulary, Patient FASS is one of the most sold books in Sweden. Much more might be achieved through general education in health and medicines and concepts of effectiveness–risk and

benefit–harm. This should use the general media to aid the process. Acquiring the necessary background knowledge and concepts can commence already in childhood [Bush, et al., 1999].

Once individuals become patients it should be much easier to explain about their new medicine in their particular situation. This should include a reminder, or first information, on reporting any adverse experiences to their doctor, or other health professional. The basic concept should be a part of a patient's normal ideas about treatment, just as it should be a part of the health professional's discussion with the patient. In this way only can there be a realistic expectation on medicines and reporting of adverse events and reactions by patients.

The public's (and possibly the health profession's) concern over safety does not rationally encompass a true assessment of effectiveness and potential benefit against the risk and possible harm from a drug. Perhaps this is not surprising given the multitude of diseases treated by a large array of drugs. The treatment of disease by drugs is a much harder knowledge base to grapple with than, say, the travel industry and safety. It is also more personal and emotive: public perception of risk, at least as portrayed by the media, seems to suggest a much greater adverse sensitivity to risk with drugs as compared with other risk taking activity of similar proportion [Bennett, 1999].

4.1.2 Health professionals

Doctors also need education. They need to be taught about how to diagnose, manage and report ADRs as undergraduates, and then they need regular reinforcement and reminders of their responsibilities later, throughout their professional lives. It is not necessarily that any new lessons need to be learnt, it is that the old should be applied more rigorously.

In many countries, pharmacists play an active role in the clinical health care team, whereas in others this resource is underutilised or completely overlooked. The contribution of pharmacist's skills and expertise could allow the doctors and the nursing team to concentrate on the overall medical treatment and care of the patient. Some of the responsibilities currently held by doctors and nurses would be better suited for a pharmacist, who has a comprehensive training specifically in drug effects and behaviour. Once the therapy has been decided, and a medication prescribed, the pharmacist could be responsible for making sure that the correct drug was given to the patient, at the correct dose and at the correct time. With their knowledge in pharmacokinetics and drug metabolism, pharmacists could be responsible for the optimization of the medicines' effect and tolerability. Consideration of the risk of interactions, given the total medication load for an individual patient, is another task well suited for pharmacists.

Pharmacists' role in drug dispensing and information has been well

established for a very long time. Also, the setting up and running of national pharmacovigilance systems have in many countries seen active contributions from pharmacists. However, when it comes to the reporting of ADRs, pharmacists in many countries have played only a minor role. An exception is the Netherlands, where a pharmacist initiative led to the creation of the Lareb foundation, which now maintains the national reporting system. The foundation is run by doctors and pharmacists, and pharmacist reports account for around 40% of the total reports received by Lareb [van Grootheest, et al., 2002]. The active involvement of pharmacists in promoting safe and responsible use of medicines sets a good example which more countries would do well to follow.

It seems reasonable, and is supported by some actual evidence, to postulate that increasing awareness of ADRs and ADR reporting schemes, and active and timely feedback to health professionals will create active involvement. By applying their complementary skills where they are most appropriate, the whole process can be made more efficient, and more professionally satisfying for those involved. Both patients and health professionals should then come to a full participation in the progress towards better therapy.

4.1.3 The pharmaceutical industry and regulators

In contrast to the health professionals and the general public, who are 'patient driven', the primary focus of the pharmaceutical industry is to protect their investment. This, of course, does not mean that safety is not taken seriously by pharmaceutical manufacturers, on the contrary, it is both a responsibility and in the companies' interest to have detailed and up to date knowledge of all possible effects of drugs that are marketed. In many countries this responsibility is enforced by strict legislative requirements. It should also be made clear that the difference in focus (patients versus drug) within a company is often extensive, and can be the cause of considerable friction, in particular between the marketing and the safety departments. The prevailing practice, however, for dealing with new safety signals is that the evidence needs to be strengthened, and that too early a warning will harm the drug concerned. It seems that there is a risk that this real dilemma is biassed unethically in favour of the drug rather than the patient.

The need to protect an investment should not be completely overlooked when it comes to regulators and their stance in drug safety matters. When a drug has been approved for use by the regulatory authority, there are no direct financial gains involved, but time and resources have been spent in trying to ensure that the drug is adequate for use in the population of the authority's control. Regulators with their public health perspective have less of an individual patient focus, since public health concentrates primarily on issues that relate to population effects and society norms. Drug safety problems could

be regarded as a failure to safeguard the public, rather than a positive result of surveillance. The normal response, to feel sure about a signal, and to establish its public health impact, could lead to very long evaluation times. Paradoxically, there is a risk of too swift a regulatory response, particularly if controversial information on individuals harmed by ADRs are reported in the media leading to political pressure. Neither are in the patients best interest, and regulators therefore have a difficult balancing act.

The relationship between the UMC and the other two major international groups involved in pharmacovigilance is open, if uneasy. Both the ICH and the EC/EMEA invoke regulation to ensure that countries comply with their decisions and agreements. The WHO, in contrast, works through recommendation and consensus. WHO is an observer at key meetings relating to pharmacovigilance of both other organisations. Observer status means that WHO, even thought it is the only truly global organisation, does not take part in the decision making process. This observer situation is however sought by WHO, since it must reserve the right of full consultation with member states; WHO has no remit to agree on their behalf in technical meetings. Practically speaking, this can make WHO seem a slow, weak, and even uncooperative negotiator.

The ICH has not concerned itself with postmarketing issues until quite recently, but it is not surprising that its work in premarketing safety has had an impact on the work of the WHO Programme and the UMC. This has mainly involved the use of MedDRA as a terminology, the M2 protocol on Electronic Standards for the Transfer of Regulatory Information and Data and the E2b format for electronic transmission of case report information. This latter was pioneered by the UMC, and the WHO/UMC/CIOMS has had a major input into all the ICH work. Recently, periodic safety update reports, good case management practice, and 'risk management' have become ICH projects in the postmarketing area.

The main area of real difficulty with ICH has been the introduction of MedDRA in conflict with WHO-ART, and a general feeling in developed countries that WHO/UMC has little relevance in spite of the major pioneering work which is done in the WHO Programme for International Drug Monitoring and by the UMC.

The EC/EMEA act both within and in addition to the ICH. The creation of a European ADR database and the strong possibility of a Drug Dictionary for Europe make for an overlap, and competition with the work of the UMC. If a European Drug Dictionary would be promoted as an ICH standard, as MedDRA was for ADR terminology, this would very seriously undermine the WHO's work in global harmonisation in pharmacovigilance.

Overall it seems a shame that more resources are not put into the WHO for the development of its global activities. It seems wasteful not to build on the work and services that already exist in the WHO Programme, and are

considered largely satisfactory by the global community. This is particularly true when it creates confusion where none previously existed, as well as subsuming WHO's role as the global standard setting agency in pharmacovigilance.

4.1.4 Weighing information

The evaluation of the first signal is the start of a process, the aim of which is to refine the place of the target drug in a context of its effectiveness in treating the indicated disease, and considering the risks of the disease and those of the drug. The idea of this therapeutic context needs to be widened to take account of other competing therapies for the same indication.

Ultimately, the knowledge we have on effectiveness versus risk must be harnessed to two distinct ends. The first is to try to define the overall place of a particular drug therapy in the overall therapeutic armamentarium, and the second is to provide information which allows for the diagnosis and management of drug induced disease. In each situation the statistical information needs to be supplemented by a view of the benefit and harm experiences of individuals. As mentioned before, there is a need for wisdom in deciding on how the available information should be used. At the moment this holistic viewpoint is not commonly held, there being a tendency for criticism to lead to some information being totally disregarded rather than trying to see how it can be better interpreted, and used to identify better ways forward.

Some examples may help to illustrate the above points. An increase in the number of cases reported on a particular drug and adverse reaction combination can often be dismissed as 'bias' if there has been some publicity on the issue (a 'Dear Doctor letter', a journal article, or some general media coverage). The true situation might however be in four different categories:

- there is bias leading to false causal relationships being made where chance may bring a coincidence of drug use and a common background disease;
- there is greater recognition of the drug–ADR link which was previously missed due to lack of knowledge;
- there is a another factor (e.g. an interaction, new uses for the drug) which has affected the reporting; or
- there is some mix of the previous factors.

The truth is not helped making any one of the above assumptions without the relevant information.

A second example may be when case reports indicate an early drug–ADR signal. Often there can be a situation where there are, say, 20 reports from 5 completely different sources. The information is incompletely filled in on 16; on ten, other drugs were co-prescribed; there were three in which the target drug alone was prescribed with plausible de-challenge, and in one of those there was

a recurrence of symptoms when the drug was accidentally given again. A common view is that this is not a signal because of the poor data. This is illogical, since it assumes that 'poor data' equates with 'no causal effect'. It is equally justified to say that in the 16 cases there was possible positive de-challenge or even a positive result on re-exposure. Which view is taken simply depends upon whether one wishes to give the drug or future patients the benefit of the doubt.

A third example may occur when case reports indicate a causal relationship based on a number of individual diagnoses, but the relationship is not seen in a study. In this instance one needs to question the power of the study versus the likelihood that the clinical diagnoses may be mistaken. It is often stated that clinical diagnosis cannot prove a causal relationship, whereas epidemiological studies can. The truth is that both give a degree of probability which is based upon the nature of the ADR, strength of data, various technical aspects and upon interpretation. A case report can be very indicative of causality in an individual case: and several reports from different sources can be suggestive of more than coincidence.

In each of the above examples the uncertainties can be identified and an interpretation possible that can lead to further action. Sometimes, patient confidentiality or other sensitivities are used as an excuse for keeping information secret, as if there were a contradiction between protecting individuals and full disclosure of information necessary to make informed decisions. Transparency does not mean the exposure of individuals, but the willingness to share incomplete information, opinions and projections and discuss them openly for the sake of society at large.

The 'benefit–risk ratio' has been much talked about, but there seems to be little progress in critically translating data into useful information. There is much academic debate over such issues as quality of data, bias, confounding, generalisability, and so on relating to epidemiological studies, but little seems to be done that makes an individual's treatment decision easier. Certainly, the precision that the term 'ratio' implies is a target far from achieved. Much has been made of the Cochrane Groups and their efforts at meta-analysis of double blind controlled clinical trial information on efficacy. These analyses are good at defining whether *efficacy* is present or not, but they may give little guidance over the *effectiveness* in the patient groups most likely to be treated. And on the safety side there is not enough that brings together the risk profile of a drug. This profile is left as a limited number of common ADRs, from controlled studies; information from pharmacoepidemiological studies on a single (or a few) outstanding ADRs; and a bulk of information based upon case reports. It is common for those who evaluate such safety 'profiles' to downgrade the latter information on the grounds that it is 'too soft'. Yet it is this same information which is often taken out of any reasonable effectiveness–risk context, and used to remove the drug from the market.

Before trying to analyse how to modify the cycle of harm, risk, effectiveness–risk analysis, action, consequences, impact, more information on harm, it is important to distinguish between 'public health' and 'summation of individual experience'. The first obvious difference is that reduction to a set of statistics removes any subjective description. Thus a frequency of harmed individuals gives no idea of the extent of harm as experienced by an individual. Quality of life assessments are an attempt to summarise this information, but great care must be taken to avoid the trap of constructing tools which by their structure bias responses. This is a dilemma, since unstructured responses may be difficult to analyse, and perhaps impossible without post hoc judgements being involved. A second point is that public health is to do with the norm. Outliers tend to be excluded from consideration, unless there is a prior intent to look for 'at risk' groups. Thus public health tends to work for the 'average', but little consideration is given to those that fall outside such an average range, however that may be defined.

Benefit is likewise an individual subjective judgment, and the sum of individual benefits cannot be translated to public health averages, because the benefits are weighed differently by individuals.

4.1.5 Data quality and outcomes

For the foreseeable future we will have to contend with very heterogeneous data. It seems wise that we try to do a much more descriptive and critical analysis, not leaving anything out, but weighing the data carefully and attempting to point the way ahead for practical studies that may clarify the situation.

New disciplines do need to be introduced in pharmacovigilance: particularly the assessment of outcomes and follow up. Neither of these essential quality assurance and feed-back steps are today part of routine pharmacovigilance science. A major criticism of spontaneous reporting schemes is that there is considerable under-reporting. Whilst such under-reporting may be quite low for serious and medicines specific events, it would be much better if the situation could be improved. Undoubtedly greater awareness by the public, patients, and doctors and other health professions would aid this aim. It has been shown that good feed back to doctors is very important in encouraging reporting. There is a link between high reporting rates per capita, and the effort which has been put into feed back with useful information on the case in question, and an active education and publication policy.

Over the years the outcomes of pharmacovigilance have been changes in the summaries of product characteristics (SPCs), or 'Dear Doctor letters' when there has been an urgent situation, and, in extreme cases, drug withdrawals. In addition, drug safety articles have been published in medical and scientific journals and pharmacovigilance methodology and regulation has been

evaluated and modified. Where any outcomes research has been done, it supports the view that 'Dear Doctor letters' on their own hardly influence prescribing behaviour at all, though the results are variable [Oxman, et al., 1995; Smalley, et al., 2000; Weatherby, et al., 2001].

Morbidity and mortality from iatrogenic drug related disease seems to change very little overall, though the drugs involved do change. Broader outcomes research suggests that medical misadventure in many therapeutic areas is significant [Leape, 1997; Kohn, et al., 2000]. Even the 'hard' endpoint of a drug withdrawal may not be a success if the patients who were happily taking the drug in question were seriously disadvantaged when the drug was withdrawn. This is particularly true when an ADR has an early time window for its appearance and patients taking the drug chronically may have had a very low risk of developing ADRs.

This should be contrasted with the often considerable length of time from first signal to significant action to deal with a drug–ADR problem. The lag time may be years, in the case of cisapride and arrhythmia it was 7 years [Suchard, 2001]. During long periods of evaluation of signals and epidemiological investigation, patients may be at unnecessary, and possibly serious risk.

4.1.6 The role of the UMC in the future

The UMC's vision for the future is built on continued contributions to, and enhancement of global pharmacovigilance. Listed below are key areas for the future:

- international signal detection and analysis
- development of new tools and methodologies
- research
- international harmonisation
- support and training
- establishing and maintaining partnerships with other organisations

The national pharmacovigilance centres provide the basis for the UMC operations. From the start of the WHO Programme an important role of the WHO centre has been to aid the establishment of new national centres. This work has been very successful: there are now centres in all continents of the world which collaborate with each other and the WHO, with the UMC as a connection point. There are however countries, particularly in Africa, where there is not yet a national centre in operation. Continued work is needed to provide support and training in how to set up and run a national centre, and to stimulate pharmacovigilance activities in these countries. The UMC has run training courses in Uppsala, participated in training activities in different regions of the world, and produced guidelines. These, and other training and support activities should continue also in the future, for the benefit of new as

well as established national centres. Directed mainly to national centres, but also to wider audiences, are a variety of services such as advice on communications, crisis management and media relations, provided by UMC consultants.

Direct contacts with health care professionals are not part of the UMC's normal work. However, the combined expertise of the national centres, the UMC, and its network of consultants, could be an important resource for the promotion and integration of pharmacovigilance training in under- and post-graduate university curricula.

The maintenance and development of the WHO database is one of the core functions of the UMC. The new database system allows much more, and more detailed, information to be stored and analysed than in the past. However, this is just the starting point: the overall potential of the WHO database as a source of international safety information depends on the information received from national centres.

Increased reporting, better data quality and timeliness of sending the information is a collective responsibility of the WHO Programme. The UMC can help by providing technical assistance and better IT tools and solutions in the whole data management area, including terminologies and classifications in useable formats, and the setting up of systems for direct exchange of data between national centres and the WHO database. A collaborative project with the Swiss national centre and the UMC, initiated in 2001, is an example of the latter. Swiss doctors will be able to report to their regional centres using an Internet application; the case reports are assessed and sent on to the national centre and then to the WHO database, from where they are available for retrieval and analysis, together with the information from all other countries in the WHO Programme.

Although resources are limited, the UMC will be able to assist other national centres with similar developments, of particular interest for those who are in the process of implementing new, or modernising existing, software systems for ADR reporting. The advantages are clear: the costs are relatively low since the development builds on existing technology, and an existing database. Also, data quality can be improved, and the reporting delays minimised.

Advanced analytical tools such as data mining are increasingly made available on-line, so that every country in the WHO Programme can participate on an equal footing. Further developments in the data mining area are important, both from the point of view of providing tools for quantitative data assessment, signal detection and analysis; and to enable research e.g. on more complex ADR patterns and chemical structure function relationships.

Intensified monitoring of special or novel drug groups, e.g. vaccines, herbals, biopharmaceuticals and oncolytics is another task which is becoming more and more important. Also, WHO has several public health programs for the treatment of HIV/AIDS, malaria and infestations. The UMC is increasingly involved in the safety monitoring of new medicines or new combinations of

medicines used for these diseases. A possible new area for WHO is that of medical/medication error, which could become part of the UMC's co-ordinating responsibility.

Of particular importance for the review of case data held in the WHO database is the availability of as detailed information as possible. In the past, only summarised, structured case information could be captured, but the new database allows free textual information to be stored with each case report. The UMC needs to encourage national centres to provide case descriptions and other findings, when available.

The use of drug exposure data needs to expand in the future. The work done so far together with IMS Health has provided a cost–effective methodology for signal analysis. In order to optimise signal analysis and follow-up, more collaboration is needed with groups that can provide exposure data, and links should be established with pharmacoepidemiologists and other researchers in the drug safety area.

The core UMC network consists of the national centres, international pharmacovigilance experts serving as consultants to the UMC/WHO and other groups within WHO. Other important communication partners include drug regulatory authorities, academia, international professional and consumer/patient organisations, pharmaceutical industry and the medical media. Through these partners, the UMC can reach those who should be the ultimate beneficiaries, patients and health care providers; and get feed-back as to their needs. The intention is to continue, and improve, collaboration with existing partners, and to extend the network by future collaboration with other groups, such as:

- drug information centres
- poison control centres
- national independent drug bulletins and the International Society of Drug Bulletins (ISDB)
- hospital (and other) formulary committees
- health insurance and reimbursement organisations
- undergraduate and postgraduate teaching organisations.

The UMC should continue to play an important role in international harmonisation, with work ranging from definitions of terms used in the area, to the development of accepted tools and methods in pharmacovigilance.

4.2 Conclusions

Trying our utmost to capture health professional and consumer concerns about possible ADRs must be pursued. This is the only practical way of developing new hypotheses on safety issues. The process needs much higher prominence in

the way we all consider medicines, and the collection of experiences needs to be facilitated by better IT methods of recording information during routine medical practice.

At the moment we are in the position of slowly accruing information, sometimes in a haphazard way, which could take years, and then turning to the next therapeutic suggestion without anything other than a vague baseline of efficacy data and miscellaneous harm stories to go on. The effectiveness–risk assessment of therapy should be a continuous process, with *all* relevant information being available for comparative analysis. Even when we have information, and even if we were to do a useful comparative effectiveness – to – risk analysis, we have a penultimate hurdle of turning this activity into practice. Not until we have managed the final challenge of checking what impact this may have on public health and on multiple individual's health, have we come full circle!

From the time of first drug launch, there should be a plan in place to move from information on efficacy to information on effectiveness and to move from the pre-marketing hazard information to a more complete picture of risk. Subjective case experience should be harnessed to provide more clinically useful information. Thus the merits of any drug should be continuously compared with alternatives, and this should lead to a merit assessment plan for a therapeutic indication. Since such a plan is updated each time new useful information becomes available, it will provide all the available information for professionals and patients alike. Whenever needed, targeted studies should be performed to fill in gaps in order of priority for both public health and to aid individual patient management. As new therapies become available, so they will slot into the merit assessment plan, thus finding their place depending on evidence.

It might be thought that such a scheme is unworkable, but the alternative is our current situation of therapeutic and public health decisions being based on incomplete and incompatible data sets, and analyses that are not holistic. This situation probably wastes large amounts of money and leads to unnecessary morbidity and mortality. The true situation cannot, however, be assessed until there is some better factual basis for determining outcomes and consequences of any actions taken to modify the therapy of diseases.

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Summary

This thesis concerns the safety of drugs used in clinical practice. It is particularly about the effort of grouping case report information on suspected adverse drug reactions from around the world in one place. The principle is that even rare adverse reactions are more likely to attract attention, and provide useful information on analysis, if this mass of global experience can be put together.

The work examines the development of the system for doing this job, as carried out by the WHO Collaborating Centre for International Drug Monitoring, in short Uppsala Monitoring Centre (UMC), Sweden, on behalf of the WHO. The main part demonstrates the complexity of the data collection system, and how it can be made to work to produce hypotheses on drug safety issues. There is also consideration of the use of such information and hypothesis to improve drug safety in public health and individual clinical practice. A final part gives recommendations and looks towards future developments.

Chapter I – The evolution of international pharmacovigilance

No drug is inherently safe. Before a drug is marketed a good deal of effort is made to ensure that drugs are as safe and efficacious as possible. However, only a limited human exposure to drugs occurs and even serious adverse reactions to drugs at rates of less than about 1/1000 patients exposed may never have been seen prior to marketing. This level of safety is less than public expectation. In order to meet this expectation, efforts must therefore be made to gain more information from routine clinical practice after the drug has been marketed.

The WHO Programme for International Drug Monitoring involved 10 countries at its inception in 1968 and now has 68 members, all of whom provide their case data to the UMC in Sweden. The evolution of the system has been driven by a number of drug safety issues, starting with the thalidomide disaster which caused fetal malformation in children born of women taking this sedative drug.

Alongside the modifications caused by major safety issues, the science of data collection, management and analysis has developed steadily, within the international collaboration. Standards for data collection and transfer to the central database were essential. Definitions, standard terms for adverse reactions, and a classification system for medicinal products were necessary, as was the development of various ways of analysing the data and providing useful periodic outputs.

National centres were committed to sending their data to the international database, and exchanged views, experience and regulatory information at annual meetings, and the UMC was charged with coordinating all this activity.

Early on it was seen that the international data was heterogenous, and

developments in information technology (IT) were necessary if full use was to made of such problematic data.

Nowadays, the finding of rare new adverse reactions is but a part of a broader spectrum of pharmacovigilance, which now includes counterfeit drugs and non-orthodox medicines, amongst others. Effectiveness–risk analysis has become a part of the work of pharmacovigilance which also entails detailed knowledge of drug use in society. Communication science is now essential to convey the complex messages regarding the benefit and harm of drugs to health professionals and the public. Indeed, it is not only health professionals and the public that are the interested parties: lawyers, the media, the pharmaceutical industry, and various professional associations have an interest in international drug safety work.

Chapter II – From data to signal analysis

Since the major thrust of international drug monitoring is to find new signals from international data, the process of data collection and analysis is core to the function of the UMC. However, whilst case reports often initiate a hypothesis, other information and methods are needed in order to reach an understanding of the nature of the risk, its magnitude, and indeed whether the proposed risk has a real causal link to the drug in question.

Case reports are created and used in an inductive way: reasoning to a general conclusion based on a set of observations, mainly from experience or experimental data. Conclusions can be biased and confounded; case report data is often incomplete; and there are also limitations to the generalisability of such an approach.

Adding drug use information helps to refine the hypothesis and give a rough idea of the potential magnitude of the risk. Even so, the hypothesis ideally should be tested in a more rigorous system which includes more complete numerator and denominator data, as well as control comparisons. This allows determination of the probability of a chance, or causal, association.

Prescription event monitoring provides much better information on the nature and extent of the risk, but still has limitations, including lack of good control information.

Case–control and cohort studies with control information may be performed within health care information database systems. Experimental studies may also be used in testing some hypotheses. All of these methods have a place, but they can be costly, and careful judgement must be used in choosing a particular method.

The case reports are sent from many countries, and it can be shown that the characteristics of reports vary considerably from country to country. There are also many other factors that influence reporting:

- the time period after a drug is marketed,

- whether doctors are urged to report serious ADRs, or not,
- how well the system is established in a country, and
- the patterns of drug use.

All reports are entered into a relational database which uses the latest IT, to store the agreed useful data fields. A study was made which related the completeness of information on reports to their potential to add to a signal. Whilst it abundantly clear that the best quality of information is vital, it is also clear that any system must have a defined approach to incomplete data.

To find signals, data must be grouped in meaningful ways. From the beginning of the WHO Programme, various experts have decided on the kinds of output they felt were most useful to find at least the most important signals. At the start it was hoped that some automated way could be found to highlight groups of reports that might constitute a signal, but the diversity in the data and the limitations of computer processing power then, amongst other things, led to this idea being abandoned. Quarterly analysis of the database following simple algorithms and producing printed tables was the method used for many years until the volume of information grew, so that human scanning of tabular data became impracticable.

Now, the use of a neural network using Bayesian logic to assess disproportionalities in the data is used to aid the signal finding activities of a panel of experts. This methodology has the capability of finding hitherto unrecognised patterns within the data fields. The addition of various new algorithms largely based around the neural network results has further enabled the power of the Programme to find the unexpected. Moreover, an agreement with IMS Health has allowed the UMC to set the WHO signal data against international drug use information. This allows for much better definition of the signal as a guide to further study.

Increasingly, links are being made between this international case data analysis and the work of other players in the field, to ensure that signals are found and analysed as expeditiously as possible.

Chapter III – From signal to balanced safety communication

Finding a signal not only leads to a cascade of techniques designed to refine information and establish risk, but also to a need for communication with a variety of players in the drug safety arena. The intermediate aim is to be able to balance effectiveness and risk for a particular drug and to compare that result with other therapies for the same clinical indication. The ultimate aim is to allow patients to make decisions, with their health professional advisors, on alternatives which suit them and their personal concepts of benefit and harm. Also, the safety information needs to be adequate to allow for the best possible diagnosis of ADRs.

First class communication is paramount. A very serious signal may need communicating , even though tentative. As more information becomes available the message may be changed. Not only may the information change, it may change the effectiveness–risk balance. Thus, messages can be very complex both depending upon antecedents and also the audience.

Since there are many players with an interest in safety, the message and the medium of communication need to be tailored with the recipient(s) in mind. In addition, these important and complex messages require acting upon, and it is therefore incumbent on the sender to try to ensure that they are both received and understood. Once messages have been received, action should be taken: good communication helps to ensure that the action is appropriate.

One communication requirement is that terms used be defined. In an international setting with many social and language groups involved, definitions terminologies are an indispensable part of the WHO/UMC's work.

It is very instructive to understand the number of players that communicate into the phamacovigilance network and those that are involved in some sort of action related to drug safety. Ideally, all players should be thinking in terms of balancing the positive side of the drug (efficacy, effectiveness, benefit) with the negative sides (hazard, risk, harm). The terms in brackets denote potential, based on pre-marketing information; public health impact, based on epidemiological information; and individual perception and experience, on the good and bad sides of the equation.

Of all the pharmacovigilance activities, the assessment of the impact of our work, both on public health and at an individual level, has received the least scrutiny. Much more attention needs to be paid to this, so that we may improve local, national and international pharmacovigilance according to observed results.

Chapter IV – Towards the future – Discussion and Conclusions

An important issue for the future is to consider how work done so far can be applied and further developed to enhance global pharmacovigilance as a science. With the endpoint of a rational and safe use of medicines in mind, where should international efforts be directed in order to be of best use? For all those concerned with pharmacovigilance it is of vital importance to focus on areas that need improvement, and to seek to ensure that activities undertaken have the best impact on public and individual health.

Pharmacovigilance starts, and ends, with individuals taking medicines and the health professionals involved in their care. Since the start of the first spontaneous adverse reaction reporting schemes over forty years ago, and the subsequent evolution of pharmacovigilance in the wider sense, there has been a concentration on the development of the science, the application of epidemiological techniques and the need for regulation. From now on, there

needs to be much more emphasis on improved information, education and support systems for health professionals and patients. These developments are needed to secure the best and safest treatments, and to avoid another thalidomide disaster in the future.

The general public needs education to have a realistic view on what to expect from medicines; treatment may not be 100 percent effective, and all medicines carry a risk of harm. Through general education in health and medicines, starting in childhood, people will have a context in which to place the concepts of benefit and harm, and a better understanding of medicines and treatments. This process can be aided by the general media, which also have a responsibility to provide balanced information in an accessible way.

Doctors need education about how to diagnose, manage and report ADRs, first as undergraduates, followed by regular reinforcement and reminders of their responsibilities throughout their professional lives. The contribution of pharmacists' expertise could allow the doctors and the nursing team to concentrate on the overall medical treatment and care of the patient. Pharmacists could be responsible for the optimisation of the medicines' effect and tolerability, and for making sure that drug interactions are considered, and prevented when possible. Also, pharmacists can play an important role in the reporting of adverse reactions.

If doctors and other health professionals are aware of pharmacovigilance schemes, and receive active and timely feedback when they do report, one can expect a much more active participation in the future. Of benefit to both patients and health professionals, the active involvement of health professionals in pharmacovigilance will contribute to a safe and responsible use of medicines.

Regulators and the pharmaceutical industry have key roles in responding of safety signals. The normal response, to feel sure about a signal, and to establish its public health impact, could lead to long evaluation times and delayed action. On the other hand, there is a risk of premature measures as a response to direct or indirect political pressure. A fundamental problem in pharmacovigilance is that much of the decision making has to be based on tentative information, and not on firm evidence. In order to improve the situation, the pharmacovigilance community as a whole needs to address these critical issues:

- the level of under-reporting needs to be reduced, and data quality improved;
- the use of case data and epidemiological techniques need to be optimized, and closer links established between spontaneous reporting systems and pharmacoepidemiology to bridge the signal detection–signal testing gap;
- the impact of work done and measures taken need to be assessed, and better systems for follow-up introduced.

Since we also in the future will have to contend with incomplete and heterogeneous data, assessing and balancing positive and negative information will never be an easy and clear-cut matter. However, much can be achieved if there is a willingness to share information and thinking among all those involved, and if there is transparency along the decision-making process.

The WHO has a crucial role in setting global standards based on recommendation and consensus among all member countries. The remit of the ICH, on the other hand, is restricted to Europe, US and Japan. Although these countries represent the major part of the global pharmaceutical market in economic terms, the great majority of the worlds' population resides outside the ICH territory. Standards and regulations that make sense in the industrialised world might not be appropriate for developing countries. This must be taken into account whenever a standard is proposed, or de facto mandated, on the global level. Good communication, and collaboration, between bodies involved in international harmonisation and standard setting are therefore essential in order to get the broadest possible agreement. Such cooperation also helps avoiding possible conflicts of interest and duplication of efforts.

The core UMC network consists of the national centres, pharmacovigilance experts from around the world and other groups within WHO. The UMC's vision for the future is built on continued collaboration with these, and the other main players in the pharmacovigilance area. To provide further insights and possibilities for feed-back, the network should gradually be extended to include new partners in the broader health care sector. One possibility is for the UMC to serve as a resource for promotion and integration of pharmacovigilance training in university curricula. Establishing a more direct communication channel with those who report adverse reactions will be of mutual benefit.

A main function also in the future is to promote pharmacovigilance and help establishing new national centres. The UMC will continue to provide training and support to newcomers, and to more experienced centres alike. Further services include advice on communications, crisis management and media relations.

The UMC has, in collaboration with the Swiss national centre, recently developed a software system which allows report entry over the Internet directly into the WHO database. This opens up exciting opportunities for improvements as regards the timeliness of reporting, the amount and detail of information, and the quality of the data. It is envisaged that more countries will take advantage of this option in the future.

As has been emphasized in this thesis, international signal detection and analysis is the primary function of the UMC. The ambition is to continue to be in the forefront when it comes to development and fine-tuning of tools and methodologies for signalling. Research on complex adverse reaction patterns has already been started, and it is planned to expand the research capabilities to

include unsupervised analyses of chemical structure–function relationships. Finally, the UMC continues to support WHO's leadership in international harmonisation. With previous work ranging from definitions of terms used in the pharmacovigilance area to the development of accepted tools and methods, the UMC is well equipped to take on new challenges also in the future.

The thesis concludes that it is an essential task to pursue the capture of health professional and consumer concerns about possible ADRs. This is as yet the only practical way of developing new hypotheses on safety issues. The process needs much higher priority in our assessment of medicines, and the collection of experiences, positive as well as negative, needs to be facilitated by better IT methods of recording information during routine medical practice.

The assessment of therapy should be a continuous process, with *all* relevant information on effectiveness and risk being available for comparative analysis. For each drug, there should be a plan in place to move from information on effect in theory or from pre-marketing studies (efficacy) to information on effect in clinical practice (effectiveness) and to move from the pre-marketing hazard information to a more complete picture of risk. Whenever needed, targeted studies should be performed to fill in gaps in order of priority for both public health and to aid individual patient management. As new therapies become available, they will slot into the merit-assessment plan, thus finding their place depending on evidence.

The current situation of therapeutic and public health decisions being based on incomplete and incompatible data sets, and analyses that do not contribute to a holistic perspective, must be improved in the future. This requires better factual basis for determining outcomes and consequences of any actions taken.

Samenvatting

Dit proefschrift heeft betrekking op de veiligheid van geneesmiddelen bij gebruik in de praktijk. Het is toegespitst op de mogelijkheden die worden geboden voor het verkrijgen van relevante informatie door het centraal bij elkaar brengen van meldingen van vermoede bijwerkingen uit alle streken van de wereld. Uitgangspunt hierbij is dat door accumulatie van ervaringen uit de gehele wereld eventuele zeldzame onbekende bijwerkingen eerder opgemerkt kunnen worden. Het promotieonderzoek beschrijft en analyseert de ontwikkeling van het centrum dat voor de uitvoering van dit internationale rapportagesysteem zorgdraagt, het WHO Collaborating Centre for International Drug Monitoring in Zweden, kortweg het Uppsala Monitoring Centre (WHO-UMC). Allereerst gaat het proefschrift in op de complexiteit van het systeem voor het verzamelen en verwerken van de gegevens en hoe het gebruikt wordt voor het genereren van hypothesen die van betekenis zijn voor de veiligheid van geneesmiddelen. Daarnaast wordt aandacht besteed op welke wijze vermoedens en signalen op dit gebied kunnen worden gebruikt om veilig geneesmiddelgebruik te bevorderen en de volksgezondheid te beschermen. Vervolgens worden aanbevelingen gedaan en wordt een blik in de toekomst geworpen.

Hoofdstuk I – De ontwikkeling van internationale farmacovigilantie

Geen geneesmiddel is helemaal veilig. Alvorens een geneesmiddel op de markt wordt gebracht is veel onderzoek gedaan om zo goed mogelijk de werkzaamheid en veiligheid ervan vast te stellen. Het aantal patiënten waarmee in onderzoeksverband ervaring wordt opgedaan is echter beperkt, waardoor een zeldzame maar ernstige bijwerking die bij, bijvoorbeeld, minder dan één op de 1000 gebruikers optreedt onopgemerkt kan blijven. Om de kennis van de veiligheid te vergroten is het nodig dat na de toelating van een geneesmiddel verder onderzoek plaatsvindt hoe het in de praktijk wordt verdragen.

Bij de oprichting door de Wereldgezondheidsorganisatie van het WHO Program for International Drug Monitoring in 1968 werkten 10 landen samen. Nu stellen de nationale bijwerkingencentra van 68 landen de gegevens ter beschikking aan het WHO-UMC in Uppsala. De ontwikkeling van dit internationale systeem werd in grote mate gestimuleerd door een opeenvolging van ernstige bijwerkingen die pas na de toelating van het geneesmiddel werden ontdekt. De epidemie van aangeboren afwijkingen bij kinderen waarvan de moeders het slaapmiddel thalidomide (Softenon) hadden gebruikt is hiervan een van de eerste en ernstigste voorbeelden.

In de loop der jaren heeft het WHO-UMC zich toegelegd op het op een wetenschappelijke manier verzamelen, verwerken en gebruiken van gegevens op dit gebied, waarbij veel aandacht is besteed aan standaardisatie. Er waren

terminologieën nodig, voor zowel bijwerkingen als voor geneesmiddelen, en er moesten methodieken worden ontwikkeld voor analyse van de gegevens en periodieke presentatie van de resultaten. Op jaarlijkse werkbesprekingen met de participerende landelijke bijwerkingencentra, die door het WHO-UMC werden georganiseerd, werden resultaten besproken, ervaringen uitgewisseld en verbeteringen voorbereid.

Van begin af aan is de grote heterogeniteit van de internationale gegevens onderkend en is geprobeerd om dit met behulp van Informatie Technologie het hoofd te bieden. Aanvankelijk was farmacovigilantie hoofdzakelijk geconcentreerd op de 'early warning' functie, het zo snel mogelijk op het spoor komen van nieuwe en onverwachte bijwerkingen. Tegenwoordig is het aandachtsgebied van farmacovigilantie veel wijder geworden en omvat bijvoorbeeld ook onorthodoxe geneesmiddelen (zoals kruidenpreparaten) en falsificaties. Het gaat er nu vooral om de mogelijke schadelijkheid van een geneesmiddel te beoordelen in samenhang met de te verwachten baat voor de patiënten. Hierbij is ook kennis nodig over hoe het geneesmiddel in het land wordt gebruikt. Tegenwoordig is ook de 'communicatiewetenschap' van belang, om ervoor zorg te dragen dat de vaak ingewikkelde informatie over baat en schade van een geneesmiddel op de meest geschikte manier onder de aandacht wordt gebracht van artsen, apothekers en gebruiker, en meer en meer ook van andere geledingen. Naast overheid en zorgverzekeraars tonen tegenwoordig bijvoorbeeld ook de media, beroepsverenigingen, belangengroepen en juristen belangstelling voor de internationale ontwikkelingen op het gebied van de veiligheid van geneesmiddelen.

Hoofdstuk II – Van gegevensverzameling tot signaalanalyse

Aangezien de primaire uitdaging voor internationale farmacovigilantie het signaleren van nieuwe bijwerkingen is, is het verzamelen en analyseren van de internationaal gemelde ervaringen de centrale functie van het WHO-UMC. De karakteristieke functie van deze meldingen is dat zij een bron zijn van vermoedens, van hypothesen. Vervolgens is meestal aanvullende informatie en vaak ook verder onderzoek nodig voor een goed begrip van de aard en de omvang van het probleem en voor het vaststellen van de oorzakelijke betrokkenheid van het verdachte geneesmiddel.

Signaaldetectie doormiddel van meldingen van vermoede bijwerkingen is een inductief proces, waarbij men vanuit aan aantal praktijkervaringen en veronderstellingen via generalisaties tot een interpretatie en een voorlopige conclusie komt. Ervaringen kunnen echter onbetrouwbaar zijn en meldingen zijn vaak maar korte notities en als regel onvolledig. Of de feiten het rechtvaardigen om aan de hand van generalisaties dergelijke gevolgtrekken te maken is echter vaak onzeker. Door het combineren van de meldingen met gebruiksgegevens kan een beter zicht op de verdenking (hypothese) worden verkregen en een

indruk worden gevormd van de grootte van het probleem. In veel gevallen zal echter met behulp van voortgezet wetenschappelijk onderzoek de hypothese moeten worden getoetst en het antwoord op de vele nog openstaande vragen worden verkregen.

Voor bepaalde vraagstellingen kunnen 'Prescription Event Monitoring', een patiënt controle onderzoek of een speciaal cohort onderzoek meer exacte informatie opleveren dan het meldingssysteem, maar hier staat tegenover dat meer in het algemeen de mogelijkheden van deze methoden beperkter zijn en dat ook zij hun voor – en nadelen hebben.

De meldingen in de database van het WHO-UMC komen uit een groot aantal zeer verschillende landen. Tussen deze landen bestaan vaak karakteristieke verschillen. Daarnaast zijn er diverse factoren die per land het meldingspatroon kunnen beïnvloeden, bijvoorbeeld de tijd dat een geneesmiddel er al op de markt is. Sommige landen doen een oproep op de artsen om vooral ernstige bijwerkingen te melden, andere doen dat niet. Vanzelfsprekend heeft de bekendheid en waardering die het nationale centrum heeft verworven een grote invloed op het meldingsgedrag en indirect speelt ook het geneesmiddelgebruik in het land een rol.

Het is van begin af aan een grote uitdaging geweest om de gegevens zodanig de bewerken dat dit tot een zo effectief mogelijke signaaldetectie zou leiden. Oorspronkelijk had men het – achteraf gezien visionaire – idee om hierbij gebruik te maken van een geautomatiseerd systeem dat was gebaseerd op statistische disproportionaliteit, maar met de toenmalige computertechnologie bleek het niet goed mogelijk om dit te realiseren.

Gedurende decennia heeft het internationale systeem, per kwartaal en per jaar, een variëteit van documenten geproduceerd, waarin gegevens werden gepresenteerd die op verschillende manier een rol konden spelen bij signaaldetectie en signaalversterking. Door de sterke stijging van de aantallen meldingen is het gebruik van deze gegevens echter moeilijk en onpraktisch geworden. Enkele jaren geleden is het WHO-UMC er in geslaagd om toch een systeem voor geautomatiseerde kwantitatieve signaaldetectie te introduceren, waarbij gebruikt wordt gemaakt van een neuraal netwerk-architectuur en Bayesiaanse logica. Hiermee kan een uiterst groot en gecompliceerd gegevensmateriaal worden ontsloten dat tevoren maar moeilijk toegankelijk was, en kunnen verbanden worden gevonden die eerder niet zichtbaar konden worden gemaakt. Bij de beoordeling van de resultaten wordt de wetenschappelijke staf van het WHO-UMC bijgestaan door een internationaal panel van experts of het gebied van de bijwerkingen van geneesmiddelen.

Intussen wordt met behulp van meer ingewikkelde algoritmen de toepassing van de neurale netwerk-structuur verder ontwikkeld ten behoeve van een meer complexe patroonherkenning. Door een overeenkomst met IMS Health is het WHO-UMC in de gelegenheid om de signalen in de WHO-UMC database in het perspectief te plaatsen van internationale gebruiksgegevens en is

het mogelijk geworden de signaleringsstrategie verder te verfijnen. Het WHO-UMC zoekt in toenemende mate aansluiting van het internationale databasesysteem met andere centra en andere systemen, om te bevorderen dat het vinden en onderzoeken van signalen zo snel en zo deskundig mogelijk kan plaatsvinden.

Hoofdstuk III – Van signalen naar genuanceerde communicatie over geneesmiddelveiligheid

Wanneer er een signaal over een vermoede nieuwe bijwerking is gevonden heeft dat een cascade van activiteiten tot gevolg, bedoeld om de overtuigingskracht van de gegevens af te tasten, de mogelijke frequentie van de bijwerking te taxeren en de zaak van verschillende kanten en in overleg met de verschillende betrokkenen te bezien. De volgende stap is om een schatting van de betekenis van de nieuwe informatie te maken voor de balans van baat en schade van het geneesmiddel, ook in relatie tot die van andere geaccepteerde middelen voor dezelfde indicatie.

Het uiteindelijke doel is om patiënten en behandelaars behulpzaam te zijn bij het kiezen van de meest geschikte therapie. Bij dit proces is hoogkwalitatieve communicatie aangewezen. In geval van een ernstig signaal kan het nodig zijn om een bekendmaking of waarschuwing te doen uitgaan, zelfs als de verdenking nog onzeker is. Wanneer naderhand meer gegevens beschikbaar zijn gekomen, kan het nodig zijn om het standpunt te herzien. Aanvullende informatie kan niet alleen tot een standpuntswijziging leiden, maar ook de balans van baat en schade een andere kant doen uitslaan. Communicatie is dus een samengesteld proces, waarbij zowel de verstrekkers van de informatie als de ontvangers ervan een actieve rol spelen. Omdat er bij twijfel over veiligheid tegengestelde belangen op het spel kunnen staan, moet bij communicatie zowel wat betreft het formuleren van de boodschap als de keuze van het communicatiemiddel rekening houden met de doelgroep waar het om gaat. Bovendien is het nodig dat de verstrekker van de informatie zich ervoor inzet dat de boodschap daadwerkelijk zijn doel bereikt en daar ook begrepen wordt.

Een van de vereisten bij communicatie is dat de woorden en begrippen die worden gehanteerd eenduidig zijn. Met name bij grensoverschrijdende communicatie, waarbij de doelgroepen een verschillende maatschappelijke en professionele achtergrond kunnen hebben, moet het WHO-UMC gebruik maken van heldere en geaccepteerde begrippen en definities. Communicatie is pas goed geweest als de boodschap ook de juiste reactie heeft opgeroepen.

Het is bij communicatie in farmacovigilantie erg belangrijk stil te staan bij alle partijen die erbij een rol spelen en bij allen die op de een of andere manier betrokken zijn bij het tot stand komen van actie. In het ideale geval zou iedereen op dezelfde manier moeten denken over het beoordelen van baat en schade: bij de aanvankelijke afweging op nog beperkte gegevens ten tijde van de toelating,

bij de beleidsvorming daarna op verschillend niveau op geleide van overwegend farmaco-epidemiologische gegevens, en in de individuele behandelingssituatie waarbij ook persoonlijke voorkeur en ervaring meetellen.

Van alle activiteiten waarmee we ons in farmacovigilantie bezighouden heeft de beoordeling van de uitwerking van onze inspanningen, op de volksgezondheid en op de behandeling van de patiënten, nog de minste aandacht gekregen. Hierin zullen we juist veel moeten investeren, wat dit is de enige maat op geleide waarvan we farmacovigilantie – locaal, nationaal en internationaal – verder kunnen verbeteren.

Hoofdstuk IV – Een blik op de toekomst – discussie en conclusies

Erg belangrijk voor de toekomst is om na te denken over de verdere ontwikkeling. Tegen de achtergrond van alles wat aan ervaring en deskundigheid is opgebouwd zijn er goede redenen om farmacovigilantie te verwelkomen als een nieuwe, belangrijke en veelbelovende tak van wetenschap. Welke rol zal er zijn weggelegd voor Internationale Farmacovigilantie om datgene waar het allemaal om is begonnen - een verstandig en veilig geneesmiddelgebruik - zo goed mogelijk na te streven? In de eerste plaats moeten we er met zijn allen voor inzetten om de zwakke kanten van farmacovigilantie te verbeteren en er voor te zorgen dat onze inspanningen daadwerkelijk ten dienste staan van het bevorderen van de volksgezondheid zowel als van het welzijn van de individuele patiënten.

Farmacovigilantie begint en eindigt met patiënten die geneesmiddelen nodig hebben en hun behandelaars. Sinds de komst van de eerste systemen voor het melden van bijwerkingen en het tot stand komen van een breder georiënteerde farmacovigilantie, is de aandacht vooral gericht geweest op wetenschappelijke onderbouwing ervan, de toepassing van epidemiologische technieken en het belang van regelgeving. Vanaf nu zal de nadruk vooral moeten liggen op informatie, educatie en het ondersteunen van behandelaars en patiënten. Dit is nodig om een zo goed en veilig mogelijke farmacotherapie te stimuleren en effectief een ramp zoals destijds met thalidomide te voorkómen.

Educatie kan mensen leren dat geneesmiddelen niet altijd werken en nooit zonder risico van bijwerkingen zijn. Door al tijdens de opvoeding aandacht te schenken aan gezondheid en het voorkomen en behandelen van ziekten, kunnen mensen leren om over vraagstukken van baat en schade na te denken en er een beter begrip van te krijgen van wat met geneesmiddelen mogelijk is. De media bieden hiertoe grote mogelijkheden en hebben ook een verantwoordelijkheid met betrekking tot het geven van genuanceerde voorlichting.

Er is in de opleiding van artsen en apothekers en tijdens nascholing behoefte aan meer aandacht voor het herkennen en omgaan met bijwerkingen van geneesmiddelen en ook aan het melden daarvan. Bovendien kunnen artsen en verpleegkundigen door meer gebruik te maken van de specifieke

deskundigheid van apothekers tijd vrijmaken voor patiëntenzorg. Apothekers kunnen helpen om het doelmatig en veilig gebruik van geneesmiddelen te optimaliseren, erop toezien dat interacties tussen geneesmiddelen worden voorkomen en er voor zorgen dat bijwerkingen worden gemeld. Hoe meer artsen en andere zorgverleners bij het farmacovilantiesysteem worden betrokken en goede feedback krijgen, des te beter zullen zij daar hun medewerking aan verlenen. Artsen die gewend zijn om bijwerkingen te melden, gaan ook voorzichtiger om met geneesmiddelen en zodoende ook met hun patiënten.

De registratieautoriteiten en farmaceutische bedrijven spelen een sleutelrol bij het reageren naar aanleiding van signalen over problemen met de veiligheid van geneesmiddelen. Het is begrijpelijk dat men in eerste instantie vaak geneigd is om te proberen zekerheid te zoeken en uit te pluizen hoe groot het eventuele gevaar is. Het dilemma waar men hierbij tegen aan kan lopen is dat aan de ene kant moet worden voorkómen dat het nemen van maatregelen onnodig wordt vertraagd terwijl aan de andere kant te snelle of te ingrijpende beslissingen in het nadeel van betrokken partijen kunnen zijn.

Een kernprobleem van farmacovigilantie is dat vaak conclusies moeten worden getrokken en beslissingen worden genomen op een moment dat de beschikbare informatie nog onvolledig is en een voorlopig karakter heeft. Om hierin verder verbetering te brengen moeten alle betrokkenen bij farmacovigilantie er gezamenlijk voor ijveren dat:

- aantal en kwaliteit van de meldingen verbeteren en de onderrapportage tot redelijke proporties wordt teruggedrongen,
- de gemelde observaties worden beoordeeld in hun onderlinge samenhang en met zorgvuldigheid en verbeeldingskracht, voor wat betreft hun mogelijke medisch-biologische betekenis,
- er creatieve verbindingen tot stand worden gebracht tussen de meldingssystemen en de meer formele universitaire farmaco-epidemiologie, en er meer geïnvesteerd wordt in het verrichten van signaaltoetsend onderzoek, om die kennis te genereren die nodig is voor gefundeerde farmacotherapeutische keuzen en beleidsmatige beslissingen,
- stelselmatig wordt nagegaan of alle inspanningen die we ons getroosten ook daadwerkelijk tot het beoogde resultaat leiden, in de zin van een beter voorschrijfgedrag en een beter geneesmiddelgebruik.

Het is onvermijdelijk dat we ons ook in de toekomst zullen moeten baseren op heterogene en onvolledige gegevens. Het beoordelen en afwegen van de positieve en negatieve eigenschappen van een geneesmiddel zal daarom niet een eenvoudige en eenduidige zaak zijn. Toch kan er heel veel worden bereikt als er bij alle betrokken partijen bereidheid bestaat om gegevens en gedachten uit te wisselen en het gehele besluitvormende proces op een openlijke en inzichtelijke manier plaatsvindt.

De Wereldgezondheidsorganisatie heeft een cruciale taak bij het tot standbrengen van internationale standaardisatie en harmonisatie, gebaseerd op inspraak en eenstemmigheid van alle landen. Het WHO-UMC levert een bijdrage aan de leidende rol wat dit betreft van de Wereldgezondheids-organisatie op het gebied van farmacovigilantie en geneesmiddelenbeleid. Wat betreft de activiteiten in dit verband van de International Conference on Harmonisation is het territorium beperkt tot Europa, de Verenigde Staten en Japan. Deze landen tezamen vormen weliswaar het grootste economische blok in de wereld, maar de overgrote meerderheid van de wereldbevolking bevindt zich buiten deze grenzen. Het is echter maar de vraag of maatstaven en regelgeving die geëigend zijn voor de geïndustrialiseerde landen ook goed aansluiten bij de cultuur in andere delen van de wereld. Goede communicatie, samenwerking en consensusvorming bij het tot stand komen van internationale harmonisatie en standaardisering, in de regelgeving en op het gebied van geneesmiddelonderzoek, zijn daarom van het grootste belang. Alleen op deze manier kunnen conflicten en duplicatie van werk worden voorkomen.

De harde kern van het netwerk van het WHO-UMC in samenwerking met het WHO Department of Essential Drugs and Medicines (Geneve) wordt gevormd door de samenwerkende nationale farmacoviglantiecentra en een groep bijwerkingendeskundigen uit alle streken van de wereld. Dit netwerk zal ook in de toekomst samen met de andere hoofdrolspelers in farmacovigilantie het fundament blijven vormen. Voor de verder uitbouw en het ontwikkelen van nieuwe ideeën en mogelijkheden voor feedback zal het netwerk geleidelijk aan worden uitgebreid met andere partners in de gezondheidszorg. Een uitdaging voor het WHO-UMC is om in samenwerking met universiteiten opleidingsprogramma's op te zetten. Een meer directe communicatie tussen het WHO-UMC en de melders of nationaal niveau zal tot wederzijds voordeel strekken.

Een andere hoofdtaak van het WHO-UMC is het stimuleren van farmacovigilantie in de wereld in het bijzonder van landen waar farmacoviglantie nog in de kinderschoenen staat. Het WHO-UMC is behulpzaam bij de training en ondersteuning van participerende nationale centra in verschillende fasen van ontwikkeling, ook op gebieden zoals communicatie, crisis management en het omgaan met de media. Het WHO-UMC heeft, bijvoorbeeld, in samenwerking met het nationale centrum van Zwitserland een software pakket samengesteld waarmee het centrum kan voorzien in zowel alle behoeften van landelijke systeem als in de samenwerking met het WHO-UMC, waarbij via een beveiligde Internetverbinding gebruik gemaakt wordt van de computer in Uppsala. Dit opent aantrekkelijke mogelijkheden voor verbetering, zoals minder vertraging, betere kwaliteit van de gegevens en goede mogelijkheden voor het uitwisselen van informatie. Het is de verwachting dat meer nationale centra van dit uiterst moderne computersysteem gebruik zullen maken.

Zoals is betoogd in dit proefschrift is internationale signaaldetectie en analyse de hoofdfunctie van het WHO Programme for International Drug Monitoring. Het WHO-UMC zal derhalve in de frontlinie blijven van het experimenteren met en verder ontwikkelen en verbeteren van signaaldetectie. Zo is een onderzoek gestart naar samengestelde bijwerkingenpatronen en wordt aan een project gewerkt waarbij geprobeerd wordt om geautomatiseerde analyses te maken van verbanden tussen chemische structuur en werking. Dank zij de enorme ervaring en know-how – van het definiëren van de betekenis van ziektetermen die gebruikt worden in farmacovigilantie tot de creatie en verbetering van methoden en technieken – is het WHO-UMC er klaar voor om de uitdagingen van de toekomst aan te gaan.

In het proefschrift wordt geconcludeerd dat we in de jaren die voor ons liggen onze uiterste best moeten doen om zoveel mogelijk gegevens te krijgen over hoe geneesmiddelen in de praktijk worden verdragen, wat de ervaringen van artsen en patiënten zijn. Dit is nog steeds de enige snelle en effectieve manier om nieuwe kennis over zowel de positieve als de negatieve eigenschappen van geneesmiddelen op het spoor te komen. Iedereen die met geneesmiddelen te maken heeft moet zich hier veel meer bewust van worden, terwijl het vastleggen en ter beschikking stellen van gegevens uit de dagelijkse medische en farmaceutische praktijk met behulp van betere Informatie Technologie gemakkelijker moet worden gemaakt.

Het evalueren van farmacotherapie is een continue proces. Om tot een zinvolle vergelijkende beoordeling van geneesmiddelen te kunnen komen, moet gebruik worden gemaakt van alle relevante gegevens die betrekking hebben op de werkzaamheid en veiligheid ervan. Van ieder geneesmiddel moeten planmatig, vanaf de beperkte informatie ten tijde van de toelating, alle nieuwe gegevens worden vervolgd om stap voor stap een meer compleet beeld van de bijwerkingen en risico's te vormen. Wanneer er behoefte is aan meer informatie, zowel in relatie tot de volksgezondheid als de behandeling van individuele patiënten, moet daarvoor het nodige aanvullende onderzoek worden gedaan.

Wanneer nieuwe geneesmiddelen op deze manier worden vervolgd kan op een snelle en logische manier een op feiten berustende plaatsbepaling worden gemaakt ten opzichte van de stoffen die reeds langer in gebruik zijn. De huidige vorm van geneesmiddelbeoordeling, die is gebaseerd op onvolledige en vaak moeilijk te vergelijken gegevens en een onvoldoende geïntegreerde ('holistische') beeldvorming, is aan verbetering toe. Hierbij is ook van belang dat er goed op wordt toegezien of het uit farmacovigilantie voorvloeiende samenstel van informatieverstrekking en beleidsmaatregelen in voldoende mate de beoogde verbeteringen in het geneesmiddelgebruik tot gevolg heeft.

Epilogue

Having worked at the Uppsala Monitoring Centre for more than twenty years, I have been at the heart of an important international enterprise. From a modest start in 1978 when the International Drug Monitoring Programme moved its technical and scientific centre from WHO Headquarters in Geneva to Uppsala in Sweden, the range of activities carried out, and the number of staff, have expanded considerably.

Being the only independent international pharmacovigilance centre in the world the Centre has a unique contribution to make. Almost three million adverse reaction case reports from almost seventy countries all over the world are stored in the WHO database. This information source is the basis for the Centre's core operations; finding new international safety signals. Pharmacovigilance as a scientific discipline is a relatively new area. In many ways, therefore, my work, and that of the UMC, has been to tread into the unknown and break new ground.

There have been many challenges, and also great successes, although not always immediate. We have provided new tools, and new thinking, and, in doing so, have had a substantial impact. The UMC is now established, and recognised worldwide, as a competent and effective organisation that constantly pushes the boundaries. New challenges lie ahead, but I am looking forward with confidence to future contributions to global pharmacovigilance.

A final note to those who have been wondering about the title of this thesis. It refers to a quote from one of the Sherlock Holmes stories by Sir Arthur Conan Doyle, in which Holmes complains to his companion Dr Watson "you see, but you do not observe". I hope I have avoided making that mistake in my work!

Acknowledgement

January in Uppsala, Sweden. The task is finished. A gentle rain is falling; it is one of those winter days when the clouds hang so low in the sky that they do not permit enough light to even temporarily lift the dull curtain of compact greyness. As I reflect on the writing of these pages, my thoughts wander. Fragments from the past appear, disappear and reappear, like the threads of an intricately woven tapestry. These threads, linked together, intertwined, all adding to the form and shape and colour of the fabric, show a picture of events and people of significance for the making of my thesis.

How can I thank all of you who have contributed? How can I, in a few words, do justice to your input? When attempting to formulate my words of appreciation, the risk is obvious that I will leave someone out, which is the last thing I want to do. Although not always obvious when looking at a fabric from a distance, all threads are important! To start with, I would therefore like to convey my sincere thanks to all those who in one way or another have helped and inspired me over the years, in my work and privately, but who are not acknowledged in person.

Having said that, I specifically wish to thank

Professors Chiel Hekster and Frank Gribnau, for your willingness to take me on. I shall never forget our first meeting to discuss the thesis – that was when I first felt that it was really going to happen. My heartfelt thanks to you both for helpful comments and gentle guidance while the manuscript was prepared. A special thanks to Chiel for your kind support and assistance with all the practical matters, and for sharing your inspiring thoughts on the potentials for pharmacists in the health care team

The members of the Doctoral Thesis Committee, for accepting to examine my thesis, especially since the work had to be done in connection with the Christmas holidays! The constructive comments I received, particularly from Professors Toine Egberts and Vladimir Lepakhin, helped me in the final editing of the text.

Ralph Edwards, my mentor, who has stood by me always, leading me forward with empathy, patience and humour, making sure I do not loose track of the vision and get lost in detail. You have helped me grow as a scientist and as a person. Neither the UMC nor I could possibly have been where we are now if it weren't for you!

Ron Meyboom, for being the facilitator of this thesis project, and for helping me with both practical and scientific issues throughout the writing process. Ever since we first met in 1979 I have much enjoyed our stimulating work discussions about scientific matters, and discussions about life in general,

and our debates on whether classical music must be played on original instruments!

I also wish to express my gratitude to co-workers, professional colleagues and friends; in particular

The experts in the signal review panel, for your tireless contribution over the years to keep the vision of "never miss a signal" alive

All the people working in national centres, for sending your reports and for your active collaboration; and Bill Inman, Barbro Westerholm, David Finney, Jan Venulet and others, who were instrumental in making the WHO Programme work in the early years. Without all of your efforts, pharmacovigilance as we know it today might not exist. On the personal level, I would not have had the same job – and I would undoubtedly have had much less fun, too!

Monica Pettersson, for your keenness to take on new challenges, and patience with me as your guide into the wonderful worlds of ASAP and Paradox! By your own accord and with catching enthusiasm you have developed into a fully fledged scientist and manager. Knowing I can always rely on you is a great relief and a source of joy.

Andrew Bate, for ambitious and dedicated work from the moment you set your foot in Sweden. Your skills in pushing the BCPNN project forward have been instrumental for the success of our approach for automated signalling. Your zeal in understanding, and explaining to outsiders, the intricacies of formulae and theories is inspiring!

Roland Orre, BCPNN guru and co-author, for opening my eyes to what the combination of Bayesian statistics and neural networks can do, and for showing me that mathematics and spiritualism can be integrated into a philosophy of life. Where would our ideas of an automated signalling system have been if it weren't for you?!

Helena Fucik, for taking on the difficult task of managing the UMC database development, so that I could concentrate more on my other work, including writing this thesis. I am full of admiration for your continuous efforts in inspiring your co-workers to do that little bit extra!

Bruce Hugman, for making me fully realise the scientific importance of good communication practices, and for helpful comments and discussions on the thesis content. Dynamic and energetic, and a wonderful host, you have helped me feel enthusiastic about difficult challenges, and brought lots of joy and charm to numerous work situations, and in private.

Cecilia Biriell and Sten Olsson, for guiding me when I took my first stumbling steps into the world of pharmacovigilance, and for allowing me space to develop my particular interests.

Gunnar Boman, for your gentle but firm insistence that I could, and should, write a thesis. You have been an inspiring friend, and supporter of my

professional endeavours for many years. Also, "Carpe diem" has a special meaning thanks to you.

Beje Wiholm, for your passionate belief that science has a place in the regulatory world, and for giving me the freedom and responsibility to develop while I worked under your leadership at the Swedish national pharmacovigilance centre.

Norman Taylor, for your foresight and willingness to go into what became the ASAP project, and for your leadership throughout the project work.

Joel Sanderson, Peter Fletcher, and Jens Schou, for stimulating, and sometimes challenging, discussions on how to best use the combined resources of IMS and WHO data.

Ruth Savage, for your dedication and hard work on one of the more difficult analyses during the ASAP project, and many others to follow. It is a joy to work with someone who manages to combine gentleness with stubbornness!

Cecilia Bernsten, my friend and fellow pharmacist, for showing, by your own example, that dedication and hard work gives results. You have in many ways served as a role model for me as a mature PhD candidate. For years, your house was my second home, and, always ready to listen, and to share both happy and sad moments, you have a special place in my heart.

Ken Hartigan-Go and many others in the newer generation of national centres, for helping me see pharmacovigilance from a different perspective than that of the dominating industrialised western world.

Charles Medawar, for being challenging and inspiring in your fight for patients and consumers right to be partners in pharmacovigilance.

David Coulter, for always putting the patient in the foreground in inspiring presentations at national centre meetings.

All the staff of the UMC, for your understanding and support throughout this endeavour!

Finally, my deepest thanks to my parents and daugther

Björg and Herman Lindquist, for raising me with the notion that I can do anything if I put my mind and heart into it, and for your encouragement and support throughout my life. "Everything will be allright in the end", and "Never give up" are two expressions that you have, by your example, made me take to my heart, and remind myself of in my daily life.

Anna Lindquist, for having shared so much of my life's good, and bad moments, always supportive, and with a wonderful eye for the absurdity of some situations in which I have found myself on occasions (for instance when the video recording I had made had stopped ten minutes before the end of a particularly exciting thriller). I so admire your honesty, integrity and mind. You are indeed one of my wisest critics!

Curriculum vitae

A Master of Science in Pharmacy, graduated from Uppsala University, Sweden, in 1979, Marie Lindquist has worked for the World Health Organisation 1979-1985, and from 1986 to now. She has also worked at the Swedish Medical Products Agency in 1979 and 1985-1986.

At present she is the General Manager and Head, Data Management & Research at the WHO Collaborating Centre for International Drug Monitoring (the Uppsala Monitoring Centre).

She is responsible for the UMC's signalling process and research projects in the pharmaco-vigilance and clinical toxicology areas. She is also in charge of database developments, improvements of information retrieval facilities, and represents the Centre in standardisation and classification efforts. In her role as General Manager she oversees the operations of the UMC's programmes and projects.

Other assignments include:

- observer in the Nordic Working Group on ATC classification 1982-91
- member of the Advisory Board to the WHO Collaborating Centre for Drug Statistics Methodology, Oslo, Norway 1987-1997
- consultant to the WHO Division of Epidemiological Surveillance and Health Situation and Trend Assessment on International Classification of Diseases, Medicinal Substances part of the ICD-9 & ICD-10, 1990-91
- consultant systems analyst and designer of software to collect toxicological information within the International Programme on Chemical Safety.
- Core Project Team member of the European Committee for Standardisation (CEN) Technical Committe 251, Working Group 2, Project Team 14: Terminology and Coding Systems of Drugs. The Project Team, mandated and funded by the Commission of the European Union, has in 1996 produced a draft European preStandard "Medicinal Product Identification Standard" .

Publications include work on international drug safety, the methodology for the early recognition of adverse reaction signals, analysis of ADR signals and new signal developments, including the use of a Bayesian data mining tool.

APPENDIX I. Thesis based papers

List of papers

This thesis is based on the following publications, which are referred to in the text by their Roman numerals, I-XI.

All reprints were made with the kind permission of the publishers.

Paper I. Lindquist, M., Edwards I.R. Adverse drug reaction reporting in Europe: some problems of comparison. *International Journal of Risk & Safety in Medicine* 1993;**4:**35-46.

Paper II. Lindquist, M. The WHO Programme for International Drug Monitoring: The Present and Future. In: Mitchard, M., ed. Electronic Communication Technologies, 1998: 527-549.

Paper III. Edwards, I.R., Lindquist M., Wiholm B.-E., Napke E. Quality criteria for early signals of possible adverse drug reactions. *Lancet* 1990;**336:**156-158.

Paper IV. Lindquist, M., Edwards I.R. Endocrine adverse effects of omeprazole. *BMJ* 1992;**305:**451-452.

Paper V. Lindquist, M., Edwards I.R., Bate A., Fucik H., Nunes A.M., Ståhl M. From Association to Alert – a revised approach to International Signal Analysis. *Pharmacoepidemiology and Drug Safety* 1999;**8:**S15-S25.

Paper VI. Bate, A., Lindquist M., Edwards I.R., et al. A Bayesian neural network method for adverse drug reaction signal generation. *European Journal of Clinical Pharmacology* 1998;**54:**315-321.

Paper VII. Lindquist, M., Ståhl, M., Bate, A., Edwards, I. R., Meyboom, R. H.B. A retrospective evaluation of a data mining approach to aid finding new adverse drug reaction signals in the WHO international database. *Drug Safety* 2000;**23**(6)**:**533-542.

Paper VIII. Coulter, D.M., Bate A., Meyboom R.H., Lindquist M., Edwards I.R. Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: data mining study. *BMJ* 2001;**322**(7296)**:**1207-9.

Paper IX. Lindquist, M., Sanderson J., Claesson C., Imbs J.L., Rohan A., Edwards I.R. New Pharmacovigilance Information on an Old Drug – an International Study of Spontaneous Reports on Digoxin. *Drug Investigation* 1994;**8:**73-80.

Paper X. Lindquist, M., Pettersson M., Edwards I.R., et al. How does cystitis affect a comparative risk profile of tiaprofenic acid with other non-steroidal antiinflammatory drugs? An international study based on spontaneous reports and drug usage data. *Pharmacology and Toxicology* 1997b;**80:**211-217.

Paper XI. Lindquist, M., Edwards I.R. Risks of non-sedating antihistamines. *Lancet* 1997a;**349:**1322.

I

International Journal of Risk & Safety in Medicine, 4 (1993) 35–46

RISMED 00170

Adverse drug reaction reporting in Europe: some problems of comparison

Marie Lindquist and I. Ralph Edwards

W.H.O. Centre for International Drug Monitoring, Uppsala, Sweden

(Accepted 3 November 1992)

Key words: Adverse drug reactions; International comparisons; Monitoring

The reasons for differences in adverse reaction reporting rates between countries are partly methodological, partly due to the ways in which drugs are used and partly due to factors affecting the populations within countries such as disease prevalence, age distribution, genetic differences amongst others. Whilst these factors make international comparisons difficult to interpret, there can be some advantages in the global approach since some of the differences (e.g. a drug used in a special way for a disease seen only in some countries) may provide situations where early signals of drug problems are accentuated. Also the systems used to detect ADR's in one country may have advantages over others though this has yet to be agreed. On the other hand methodological problems arising out of discrepancies in definitions and terminology can give rise to apparent differences between countries and should be obviated by international agreement. There is very little published information on international differences but a careful analysis of the data may give new insights into drug safety and lead to a general improvement in pharmacovigilance methodology.

Introduction

The reason for devoting attention to international differences in adverse drug reaction (ADR) monitoring is the need both to pool and compare data emerging from national and regional centres for "pharmacovigilance", as the process is commonly termed. Many people are still concerned about differences between country data because they fear that these differences reflect primarily the incompatibility of the monitoring methods used in the various countries. So indeed they

Correspondence to: Marie Lindquist, WHO Collaborating Centre for International Drug Monitoring, Box 26, S-751 03 Uppsala, Sweden.

The present paper is based on two presentations by the authors to the IBC Conference on "How to Cope with Different Medical Cultures in Europe", held in London, 24 and 25 September 1992. Tables 3, 5–8 originally published in Drug Information J 1992;26:481–486.

TABLE 1

Indication for propranolol

Indication	Country		
	UK	Germany	France
Hypertension	+	+	+
Portal hypertension	+		
Phaeochromocytoma	+		
Angina	+	+	+
Arrhythmia	+	+	+
sympathetic driver			+
sino/atrial/junctional			+
atrial fibrillation			+
ventricular			+
Anxiety + tachycardia	+		
Anxiety + sweating and tremor	+	+	
Hypertrophic obstructive cardiomyopathy	+		+
Post infarct prophylaxis	+		+
Migraine prophylaxis	+	+	+
Thyrotoxicosis	+	+	+
Essential tremor	+	+	

reactions. Similar comments may be made as to the role of nurses. The more they are involved in managing the treatment of patients the more adverse reactions they are likely to observe for themselves; in some countries direct reporting by nurses is encouraged. Corresponding factors apply to other health professionals, such as opticians, who may be well placed to observe ocular adverse reactions yet who for one reason or another may not have been recruited into the adverse drug reaction reporting system.

Approved *indications* for the use of drugs are different in different countries; this will clearly affect the situations in which drugs are used and the problems which they are likely to elicit. To take a single example (Table 1): the indications for propranolol listed in the United Kingdom's *British National Formulary*, Germany's *Rote Liste* and France's *Vidal* show important differences. As will be seen, portal hypertension is an indication only in the United Kingdom and it is conceivable therefore that there will be relatively more adverse events (including true adverse reactions) reported which are related to the hepatic handling of propranolol or to other hepatic events. Other differences are very evident from the table, such as the use of the drug in phaeochromocytoma, France's particularly detailed indications in the area of arrhythmia, and variations in the acceptance of the drug for anxiety, hypertrophic obstructive cardiomyopathy, post-infarct prophylaxis and essential tremor. Considering that propranolol has been available for a long time and that there has been much investigation into its use, the extent to which indications for the drug still differ in 1992 is surprising. With newer drugs which have yet to find their therapeutic niche, differences in the field of indication from country to country are even more likely.

Variations in monitoring rules and practice

Even where the incidence of a particular adverse reaction is the same across the world, one might expect some differences in the figures actually reported. Drug monitoring practices vary very considerably from country to country, particularly as regards the existence of a legal requirement to report and the question as to whether the monitoring system is centralized or decentralized. France has a very strongly decentralized system but it applies a standardized method for assessing the attributability of reported adverse events to the drug in question. The sources of adverse reaction reports can vary considerably with official policy. Many countries have imposed an obligation on drug licence holders (i.e. manufacturers and importers) to pass on reports on adverse reactions which they receive, but these same countries may not have imposed such stringent conditions on health professionals (see Table 2). This may result in biased reporting, depending on the capacity which individual manufacturers within the countries have for "toxicovigilance" and their attitude towards it. It has been pointed out above that certain countries accept adverse reaction reports from a wider range of health professionals than others, and it is clear that the differing background and experience of the professionals involved in the process will result in different spectra of adverse reactions being reported.

Standardization of ADR monitoring?

The above are some of the many possible diverse influences which exist even within the European Community but indeed also in countries around the world, and one needs to consider carefully what direction pharmacovigilance should take in the future. The point was made above that international differences in approach are not necessarily harmful or troublesome, and the existence of differing systems alongside one another may indeed potentiate the development of pharmacovigi-

TABLE 2

Source of reports: mandatory/voluntary reporting (M/V)

	Doctors	Dentists	MA holders
Belgium	V		M/V
Denmark	V	V	
France	M/V	M/V	M
Germany	M		M
Greece	V		M
Ireland	V	V	M
Italy	V	V	M
Netherlands	V	V	M/V
Spain	V	V	V
UK	V	V	M

lance by providing a greater opportunity for testing different techniques simultaneously. On the other hand, it does seem sensible to harmonize some basic elements essential to provide a degree of compatibility between systems, such as defining clearly what we really mean by the terms "adverse reaction" and "adverse event". We also need to be consistent in the use of terms indicating the degree of causality such as "certain" or "possible". The World Health Organization's Collaborative Programme for International Drug Monitoring has now adopted several definitions of this sort which have been agreed between the 35 participating countries [2]. Similar considerations apply to the use of terms used to describe and define an adverse drug reaction; we need to be sure that the diagnosis of "polyneuropathy" is as consistent as possible in the countries involved; we similarly need to know whether the condition alluded to as "deep vein thrombosis" can be reliably distinguished from "thrombophlebitis" and was so distinguished when cases were reported. The WHO programme, in collaboration with the Council for International Organizations of Medical Sciences (CIOMS) is working towards agreement for the standards of diagnosis for many more WHO "preferred terms" used in the collaborative venture. It should however be noted that the WHO Adverse Drug Reaction Terminology [4] which is used in all the European countries does make allowance for the degree of uncertainty which is often unavoidably present in the diagnosis of adverse reactions by the use of "included terms" which, while falling outside the galaxy of "preferred terms" do fit into a recognized diagnostic hierarchy.

It might be possible to develop other initiatives to promote the harmonization of systems, but areas such as the attribution of causality remain very controversial and it is extremely important to investigate differences between national methods rather than to attempt harmonization too early, perhaps imposing a system which is not the best and most complete.

Differences in national reporting: quantity and quality

Table 3 provides a compact summary of the volume of adverse drug reaction reporting from the various EC countries and from Sweden from 1985 to 1989, expressed as numbers of reports per million inhabitants per year. Three Community countries are not listed in the table. Greece joined the programme only last year. Luxemburg and Portugal have yet to join the programme as official national centres. However, all three countries are involved in pharmacovigilance, and Luxemburg actually sends its adverse reaction reports at present to France.

It will be seen from Table 3 that Denmark has a very high reporting rate, which might be explained in terms of its being part of the medical tradition to report adverse reactions. The same applies to the Netherlands, yet as will be noted below there is a difference between these countries as regards the kind of reactions reported. France has from 1985 onwards shown a steady increase in reporting, demonstrating that its regionalized programme works well.

Germany in fact received during these years many more reports than indicated in the table; software problems for a while prevented satisfactory data transfer, but

TABLE 3

Adverse reaction reports in WHO data base from EC countries 1985–1989 *: number of reports per million inhabitants and year

Country	Year					Mean	Total
	1985	1986	1987	1988	1989		
Belgium	54	52	53	47	36	48	2393
Denmark	213	379	372	346	160	294	7501
France	5	44	95	108	53	61	16626
Germany, FRG	38	41	48	23	1	30	9259
Ireland	293	336	227	147	74	215	3770
Italy	17	21	21	17	3	16	4452
Netherlands	69	68	65	24	6	46	3302
Spain	30	42	58	57	28	43	8203
United Kingdom	217	273	301	314	254	272	76135
Sweden	304	296	295	319	290	300	12503

* The search was made in June 1990. The figures are based on the year of onset of reaction, or, if onset date is not stated, on the year of storage in the WHO data base.
Greece joined the programme 1990, Luxembourg and Portugal are not yet participating.

these difficulties have been solved. The number of reports from Ireland has declined over the years, possibly because of a decrease in the resources available to the national centre. Italy has shown a steady but comparatively low level of reporting; the recent introduction of a new computerized system should facilitate the handling of reports. Spain received a low number of reports during the period analyzed here, since at the time it was dependent largely on a single regional centre; since that time a network has been developed which covers the whole country. The United Kingdom has been operating for the longest period; this, and the success of its "yellow card" system explains the high level of reporting from Britain.

Reports submitted to the international data base are expected to contain certain basic elements, but the extent to which this standard is attained varies between countries. Using appropriate criteria for grading the amount of data in reports (Table 4) one finds that some countries have a large proportion of well-documented reports, whereas others provide a substantial number of reports containing only a minimum of information, rendering them less useful than they could be for the immediate assessment of the validity of the information and thus lessening their usefulness for direct inter-country comparisons without further elaboration of nationally held data.

Apparent national differences in outcome

A more detailed analysis of the reports received and their distribution by therapeutic group and body system/organ class, presented in Table 5, shows that there are variations both in the types of drugs to which the reports relate and body

TABLE 4

Documentation grading

Criteria *In addition to the minimum information required*:

Grade 3
- rechallenge positive
- dates of onset and treatment
- outcome of the reaction
- indication for treatment

Grade 2
- dates of onset and treatment
- outcome of the reaction
- indication for treatment

Grade 1
- dates of onset and treatment

Grade 0
- none of the above

systems involved in the adverse effects attributed to them. The difference in reporting is particularly prominent with the cardiovascular and musculo-skeletal drugs; Germany and Italy had relatively fewer reactions reported to cardiovascular drugs than did most of the other European countries, while the United Kingdom submitted more reports on musculo-skeletal agents. As regards the body systems affected, Table 5 shows that Denmark had a much higher reporting rate than average for skin reactions, whereas liver reactions were most common in France. There were also differences between countries in the reporting of adverse effects involving the gastrointestinal tract.

TABLE 5

Adverse reaction reports in WHO data base from EC countries 1985–1989 *: distribution of reports per body system organ class (as percentage of total number of reports)

Country	Body system organ class			
	Skin	CNS	G-I	Liver
Belgium	19.2	11.0	10.8	4.5
Denmark	30.3	7.7	8.9	4.3
France	17.6	9.1	8.0	8.4
Germany, FRG	12.4	10.1	15.0	2.5
Ireland	13.9	13.1	15.4	1.6
Italy	17.7	8.0	18.2	1.9
Netherlands	17.5	10.6	9.3	5.4
Spain	18.6	11.9	17.2	1.7
United Kingdom	20.7	11.1	12.9	2.4

* The search was made in June 1990. The figures are based on the year of onset of reaction, or, if onset date is not stated, on the year of storage in the WHO data base.
Greece joined the programme 1990, Luxembourg and Portugal are not yet participating.

TABLE 6

Adverse reaction reports in WHO data base from EC countries 1985–1989 *: skin reactions

Country	Rash	SJS	Total	R/T (%)	S/T (%)
Belgium	257	4	642	40.0	0.6
Denmark	2086	0	3241	64.4	0
France	2290	69	4778	47.9	1.4
Germany, FRG	1872	22	4348	43.1	0.5
Ireland	549	9	956	57.4	0.9
Italy	578	8	1207	47.9	0.7
Netherlands	468	4	969	48.3	0.4
Spain	1445	20	2757	52.4	0.7
United Kingdom	12645	203	24382	51.9	0.8

* The search was made in October 1991 and covers total number of reactions reported up to and including June 1991. The figures are based on the year of onset of reaction, or, if onset date is not stated, on the year of storage in the WHO data base.
Greece joined the programme 1990, Luxembourg and Portugal are not yet participating.

Within a particular field of adverse effects, the proportion of serious as opposed to trivial reactions can differ considerably from country to country. This emerges clearly from Tables 6 and 7 in which the phenomenon is illustrated with respect to dermatological and hepatic reactions. For each of these fields, the level of reporting of an apparently mild reaction ("rash" and "hepatic function abnormal" respectively) was compared with that of a more severe reaction ("Stevens Johnson syndrome" and "hepatic cirrhosis"). Denmark, where the overall reporting of skin reactions was high, as noted above, also had the highest reporting rate for rash yet relatively few reports of Stevens Johnson syndrome. France on the other hand, with the highest reporting level for liver reactions, had very few reports of hepatic

TABLE 7

Adverse reaction reports in WHO data base from EC countries 1985–1989 *: Liver reactions

Country	Hep. fnct. abn.	Hep. cirrh.	Total	HF/T (%)	HC/T (%)
Belgium	19	0	152	12.5	0
Denmark	144	4	483	29.8	0.8
France	65	33	2253	2.9	1.5
Germany, FRG	311	4	965	32.2	0.4
Ireland	45	0	115	39.1	0
Italy	8	0	128	6.3	0
Netherlands	95	5	287	33.1	1.7
Spain	9	2	269	3.3	0.7
United Kingdom	1012	14	2994	33.8	0.7

* The search was made in October 1991 and covers total number of reactions reported up to and including June 1991. The figures are based on the year of onset of reaction, or, if onset date is not stated, on the year of storage in the WHO data base.
Greece joined the programme 1990, Luxembourg and Portugal are not yet participating.

TABLE 8

Adverse reaction reports in WHO data base from EC countries *: Liver reactions reported to ketoconazole

Country	Ketoconazole reactions		
	Liver	Total	L/T (%)
Belgium	18	59	30.5
Denmark	12	44	27.2
France	39	115	33.9
Germany, FRG	125	223	56.0
Ireland	8	51	15.6
Italy	4	19	21.0
Netherlands	81	223	36.3
Spain	43	191	22.5
United Kingdom	174	929	18.7
Total data base	1132	3765	30.0

* The search was made in October 1991 and covers total number of reactions reported up to and including June 1991. The figures are based on the year of onset of reaction, or, if onset date is not stated, on the year of storage in the WHO data base.
Greece joined the programme 1990, Luxembourg and Portugal are not yet participating.

reaction abnormal but produced a reporting rate for hepatic cirrhosis which far exceeded that in other countries.

Finally, it is remarkable that the pattern of adverse reactions produced by a particular drug appears to differ from country to country. Table 8 shows that of the reactions to ketoconazole reported to the WHO Centre up to June 1991, the proportion relating to the liver varied from a mere 15.6% in Ireland to 56% in Germany.

Discussion and Conclusion

The above are only a few examples of the differences in reporting patterns between countries associated with the WHO International Monitoring Programme. For some of the differences in reporting we have valid – or at least speculative – explanations. For many others we clearly do not. If one must conclude that some of the apparent differences in adverse reaction incidence which we detect are not clinically genuine, so we must also be prepared to accept the corollary: apparently similar levels of adverse reactions in different countries may in reality be different because of as yet undetected distortions. For such reasons a great deal of caution is still called for when any attempt is made to compare and collate side effects data from the different national ADR reporting systems. An aim for the near future is to study these and other differences in more detail and to investigate the nature and the scope of the influences responsible for whatever genuine differences in incidence may prove to exist. The WHO data base, with its million adverse

reaction case reports from 35 countries, is a unique information source, offering ample opportunity for finding facts and generating new hypotheses in the important and fascinating field of inter-country differences.

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The WHO Programme for International Drug Monitoring: The Present and Future

Marie Lindquist
The Uppsala Monitoring Centre
WHO Collaborating Centre for International Drug Monitoring
Uppsala, Sweden

In a time when technical developments have enabled people from all parts of the world to communicate with unprecedented ease, and at a reasonable cost, is there a place for a centralised drug safety system? The WHO (World Health Organization) Programme for International Drug Monitoring was established in 1968. Its aim is to detect international drug safety problems and bring spontaneous adverse drug reaction (ADR) reports from national ADR centres together into one database, with the hope that signals of potential drug hazards could be generated–and dealt with–at an earlier stage than via national monitoring systems only. The rationale was that reactions occurring

in low numbers at a national level would become visible when data from many countries was put together and could be retrieved from a single source.

But is this idea still valid? It has been argued that the exchange of data between different systems would be more efficient than pooling data in a central database. There is no doubt that modern technology has made data transfer easier and more effective, but it does not provide an answer to the fundamental issues of signal detection and evaluation. The international community needs an independent supranational body that will work in the interest of patients and doctors around the world, providing information to those with a genuine interest in drug safety. The cooperation within the WHO programme, and the existence of the Uppsala Monitoring Centre (UMC), which was set up as a dedicated WHO Collaborating Centre responsible for maintaining and developing the system, ensures that global data can be used to identify early signals of drug problems. The collection and examination of pooled data have the following spin-off advantages:

- Worldwide drug safety and risk/benefit data are collected in a consistent and internationally agreed-on way.
- The global health community is served with information, services, and useful and efficient tools.
- Harmonisation efforts will be undertaken in order to develop, and comply with, internationally agreed-on standards in the drug safety area.

Information technology (IT) solutions will not replace human minds and efforts; both are necessary for the assessment and interpretation of drug safety information. The use of new technology will, however, improve the speed and ease with which communication can take place, and it will provide the tools needed to create efficient and user-friendly systems for data storage, retrieval, exchange, and security. Once a drug safety signal has been raised, the decision-making process will also be aided by quick and easy access to relevant information. It is the aim of the UMC to meet these needs and to provide a single source for a wide range of services in the international drug safety area–now and in the future.

The Present System

At the start of the programme in 1968, a common case report format was agreed-on, and guidelines for entering information were formulated. To ensure that the information would be recorded in a harmonised and structured way, the term adverse reaction was defined. A terminology for adverse reactions and a drug classification system, both hierarchical, were elaborated.

With these basic elements in place, a system for transmitting, storing, retrieving, and disseminating data was created.

> *Adverse Reaction:* a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. (Edwards and Biriell 1994)

In 1978, the operations of the programme were transferred to the WHO Collaborating Centre in Uppsala, Sweden. The present WHO database was one of the first operational, large-scale relational databases in the world. With today's nearly two million case reports from 47 countries, the database is a unique drug safety information source.

Data Input

To participate in the programme, a nationally recognised centre needs to be established, having the necessary resources to collect, evaluate, and transfer case reports received within a national, spontaneous reporting scheme. The national centres should submit their case data regularly and at least four times per year to the UMC, where the reports are processed and stored in the common database. Instructions for coding individual items in the reports and technical specifications for submitting reports by computerised media are distributed to all national centres. Today, most centres use diskettes as the means of transfer, but a system for electronic transfer of case data using FTP (File Transfer Protocol) has been in place for some time and is expected to be more widely used in the near future. For those countries that do not have a computerised adverse reactions management system the UMC has developed a software application that allows for entry of ADR reports according to the WHO format. A built-in error check and help information enables user-friendly and accurate data entry. This procedure has almost completely replaced paper forms, and thus facilitates the work for both national centres and the UMC.

Before being stored in the database, all reports are checked by a computer programme for technical completeness and correctness, and drug names and adverse reaction terms that are not found in the terminologies are identified. Information on new drugs is entered by the UMC staff, and the adverse reaction terminology is regularly updated with synonyms and new terms to accommodate the entry of all incoming reports.

The ability to generate early warning signals of potential drug problems is one of the fundamental functions of the WHO Programme. To meet this need, it is essential to reduce the reporting delay to a minimum. Previously, the database was updated quarterly; however, in the early 1990s, the procedure was changed to allow updating as soon as the reports are received.

Data Output

Various output documents have been proposed and agreed-on by WHO Programme member countries as being useful for data presentation and analysis. These regular documents are produced quarterly, and include the following document categories: New drug/adverse reaction combinations; reports on potentially serious reactions (so-called "critical terms"); reports on new drugs; reports of foetal malformations, deaths, and neoplasms; and a follow-up list of selected drug/adverse reaction combinations. The documents are distributed to the national centres and to specially designated reviewers. In addition, a cumulative report of all adverse reaction associations and the Drug Reference List, which is a compilation of the contents of the drug dictionary, are issued once a year.

As a complement to the standard output formats, data can be retrieved at any time using on-line data retrieval programmes. These programmes were developed to provide quick and comprehensive answers to the most common type of questions; they were made available to national centres in the early 1980s. In 1993, the first client-server software for on-line data retrieval was introduced. Thirty-seven national monitoring centres now have access to this programme.

Although the standard programmes cater to a majority of the requests for information from the WHO database, there are situations where none of the existing applications can be used. In these instances, specific data retrieval query statements are formulated by the UMC staff using SQL (Structured Query Language). The queries are run directly on the mainframe computer or are generated and run using a client/server solution, with a PC (personal computer) software as the interface. The advantage with this search strategy is that it is flexible and permits the user to extract just the information that is needed. Any data field can be searched, and the query can be fine-tuned by use of query operators and calculation statements. The resulting answer tables can be printed, or manipulated further by using PC tools, such as report generators, spreadsheet programmes, and software for graphical representation.

Data Analysis

With the motto "never miss a signal" in mind, the system for signal generation and data analysis has been continuously revised and expanded. At the start of the Programme, much effort was needed to create a functioning system: establishing working procedures for data transfer and communication between national centres and the UMC and creating routine operations for data processing, storage, coding, and retrieval. Once in place and operating well, the next major task was to build a structure that would allow identification

and follow up on drug safety signals. Although still appreciated by the participating centres as a source of information and feedback, the regular screenings and production of output documents were soon found to be insufficient as the sole instruments for signal generation. It was clear that more focussed strategies had to be adopted to fulfill the aim of an early warning system. International experts covering a broad range of clinical disciplines were invited to form a panel of reviewers to go through the output documents and identify possible new signals. The panel now has members from national centres as well as from outside the programme. The UMC serves as the focal point for the process. UMC staff provides the expert panel with detailed case information on request, handles the administration, and produces the "Signal" publication that contains summarised reports of the findings. Signal is also a forum for the publication of results of investigations initiated and undertaken within the UMC.

> *Signal:* Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information. (Edwards and Biriell 1994)

Data Access

The WHO Programme has been criticised in the past for not making data readily available to outside parties with a legitimate interest in drug safety issues. Indeed, for many years, the programme had the character of a "members only club"; access to data held in the WHO database was restricted to the participating national centres or the competent national authorities. The degree of confidentiality to be applied to data held by WHO was, and is, determined by WHO policy. With the existence, or introduction, of national laws requiring national centres to make their data available to the public, a debate was initiated in the early 1980s when several member countries requested a change in the policy toward greater openness. Following this debate, it was agreed on that data from those centres that authorised such release could be made available directly from the WHO database to external enquirers, provided that the information is accompanied by a statement explaining the nature of the data and the limitations that apply to its use. A majority of the countries in the programme now allow direct external access, whereas some national centres have set up certain qualifications for information that can be provided from the international database. The remaining centres have chosen to decide on a case-by-case basis whether data may or may not be released.

THE FUTURE

It is clear that the WHO Programme for International Drug Monitoring depends on a continuously developing, efficient, and up-to-date system for data collection, storage, retrieval, and analysis. The ability of the UMC to provide the necessary services and tools for international drug safety work will determine its success in the future. Some of the recent projects and developments initiated and undertaken by the UMC will be discussed below, with an emphasis on technical advances. Before describing the development and functions of the new WHO surveillance system, it would seem appropriate to discuss some essential prerequisites.

Consistency and Compatibility

In order to be widely accepted, a global drug surveillance system must reflect an international consensus as to what information it contains, the way in which the information is recorded, and how the information is communicated. There also must be a mechanism for achieving a correct understanding and interpretation of the information. Furthermore, the pharmacovigilance area is highly regulated, and there are a number of existing standards and conventions–all need to be considered when designing a computerised information system.

An international system should be able to build on and link together the knowledge, experience, and information systems that have been developed over time and in different settings. Thus, there are a number of technical, linguistic, and cultural issues that need to be addressed. There are two possible methods of achieving working solutions: standardisation or harmonisation.

Standardisation can achieve a high level of consistency, accuracy, and transparency, which is particularly important in those areas where uniformity is required. This applies to the data elements recorded, the terminologies and classifications used, and the electronic transfer of data. However, the development of standards that cover everything is not usually possible, or even desirable, because of real differences in attitude, language, culture, and so on. Standards also introduce a rigidity that should be avoided when it is not absolutely necessary.

The aim of harmonisation is to bridge the differences between systems that are conceptually and structurally related. By understanding the differences and the development of systems that can accommodate them, it is possible to build a coherent system in which the integral parts can communicate. Instead of enforcing changes in existing systems, which need to communicate with each other, compatibility can be achieved through harmonisation.

Definitions

Both in the pharmacovigilance area and in computer science, there are a large number of established expressions and terms. Within a given setting, these might be understood and applied consistently, but when it comes to communicating between and outside certain confined areas, there is a possible risk of misunderstanding. One reason is that many terms are expressions of existing knowledge, or jargon, that is particular to certain groups or areas. Moreover, terms might not have the same meaning in different settings or cannot easily be translated between different linguistic and societal groups. To avoid confusion, it is essential to establish agreed-on definitions of terms and concepts used and referred to. A definition should be easy to understand and provide a concise and unambiguous description of a word or an expression. Any additional information or examples should not be part of the definition but be placed in a separate note. Accurate and clear definitions also facilitate translation and interpretation, which is particularly important in an international setting.

Data Representation

Terminologies, Classifications, and Controlled Vocabulary

In a computerised pharmacovigilance system, information must be recorded in a structured way to allow for easy and flexible retrieval and analysis of the data. The information that goes into a database can be divided into two main categories: numerical data and alphabetical data (text or codes).

Numerical data is typically the result of counts or measurements and is recorded as the number of what is counted or the amount of what is measured. The unit of measurement should be added to the value. If a decision is made to only use a specific unit, the unit is not recorded.

Alphabetical data poses more of a problem, in that it is usually more complex and difficult to record in a systematic way. Some textual data falls into natural categories with clear divisions and a limited number of possible entries. Consistency is, however, not automatically achieved, in that there are many ways of expressing the same thing. Therefore, data entry must be restricted to a selection from a list containing only predefined, allowed terms, expressed as formatted text or codes.

A terminology is defined as "a set of terms representing the system of concepts of a particular subject field" (ISO 1087:1990). The simplest form of a terminology is a straightforward enumeration of terms, commonly listed alphabetically (e.g., a list of countries or pharmaceutical dosage forms).

When a larger number of terms is involved, it should be considered whether the list could be organised in a more structured way. By grouping the terms and assigning them to classes or categories, a logical classification

can be formed. If the classes can be ranked one above the other, the classification can be structured in a hierarchical way.

The advantage with a hierarchical classification is that it enables the use of different levels of precision and detail, both at data entry and retrieval. A complication occurs when a term belongs to more than one class. There are two ways of dealing with this: allowing polyhierarchy (i.e., assigning or linking terms to more than one class) or choosing one "preferred class" for each term. The former structure can be useful for retrieval purposes (less chance of "missing" a term); however, in the presentation of results of calculations, one must be aware of the risk of the same term being included under several headings and, therefore, counted more than once. Using the second option, this risk is eliminated. Yet, this method is more restricting, and there must be clear guidelines as to what goes where in the system.

It is not always feasible to use a controlled vocabulary approach—sometimes the use of free text fields is the preferred option. Free text fields are not limited in terms of how the information is expressed, and a large number of characters may be used. They allow storage of useful and detailed information in the form of comments and narrative descriptions. Free text fields are, however, less suitable for retrieval purposes or for the presentation of information and should be used as a complement to, not the replacement of, formatted fields.

The New WHO Drug Surveillance System

The existing WHO system was developed at a time when reporting on paper forms was the norm, the cost of computer disks was high, and the supply of sufficient storage capacity limited. With access to new technology a modern, comprehensive system has been designed that will meet the requirements of the international pharmacovigilance community, now and in the foreseeable future.

The design of the new system was driven by the needs of existing and prospective users, in terms of data fields and functionality. The data set required in the original WHO case reports form was the lowest common denominator consistent with being useful for signal generation and evaluation. Although the data fields are still valid, they are needlessly restricting in view of today's demands and possibilities for storage and electronic transfer of information. The new database builds on another philosophy: instead of a limited amount of data fields, the data model is exhaustive. It is up to the international community to define to what extent, and during which circumstances, the fields should be filled in.

In addition to the ADR database, the system includes the following core parts:

- A user interface for the ADR database
- A document generator
- A medicinal products database (MPD)
- A user interface for the product database
- A work-flow system to monitor and control processing of ADR reports
- System tools to maintain and update the database and to produce output documents
- An exchange server for the transfer of data and documents.

These modules will now be described in more detail.

The ADR Database

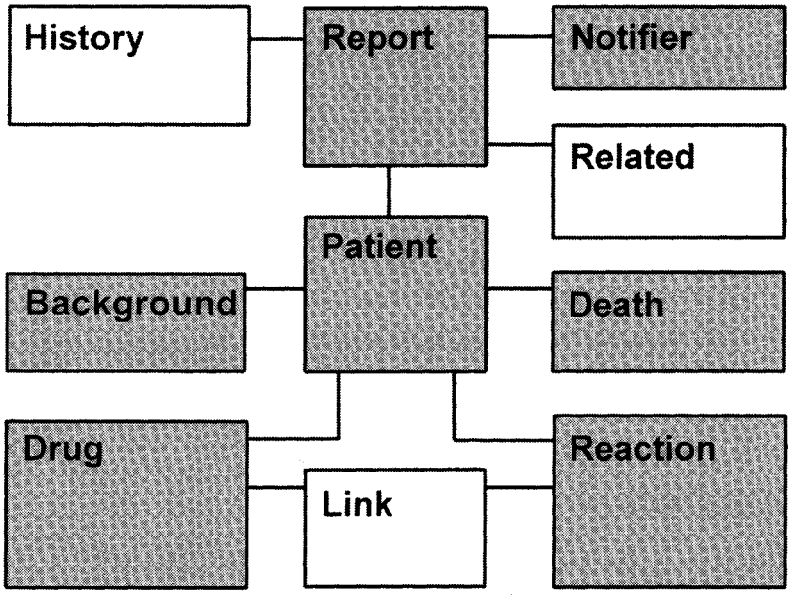
When the data model for the new ADR database was elaborated, it was based on the proposals made by the Council for International Organizations of Medical Sciences (CIOMS) 1A working group (1995) and the recommendations by the ICH (International Conference on Harmonisation) (ICH E2B EWG). This ensures that regulatory demands are taken into account and that the database structure and content complies with internationally agreed-on standards and definitions.

The database model (see Figure 27.1) can be run on all SQL-based relational database management systems (DBMSs). SQL is a standard language used to retrieve information and to request the relational DBMS to perform various actions. The WHO system will run on a server using the operating system UNIX (Uniplexed Information and Computing Service), and the relational DBMS Mimer. It is ODBC (Open Database Connectivity) compatible, and uses SQL for the database communication. This means that the database can be accessed and information retrieved using various mainframe or PC software systems.

The main tables are as follows:

- *Report:* case identification, dates, classification
- *Patient:* identification, age, gender, outcome, causality
- *Background:* information on patient's previous illnesses/predisposing conditions
- *Death:* cause of death, causality, and postmortem information
- *Related:* link to and information on a related case

Figure 27.1. Schematic Illustration of the ADR Database



- *History:* information related to re-evaluation of a case
- *Notifier:* identification of the reporter
- *Drug:* medication information, including dosage, treatment dates, indication
- *Reaction:* information on the adverse reaction, including onset date, date of resolution, seriousness
- *Link:* causality assessment and information on de/re-challenge.

Some of these tables also exist in the current system (chequered in Figure 27.1), although the amount of available fields has been expanded considerably. The remaining tables are completely new and have no equivalent today. Detailed table descriptions are available, including definitions for those fields where an internationally agreed-on definition exists. Some new concepts that have been introduced warrant special mention, since they lead to major improvements compared with today's system.

Any modification of a report is registered in an audit trail process, and the details of changes made are stored in the history table. Thus, previous versions of a report can be retrieved, and there is no loss of information.

An additional audit trail will also be implemented for the registration of external database accesses. This log will contain a full record of what information has been retrieved, by whom, and when.

The possibility to create a link between each adverse reaction and drug mentioned in a report is also new. This enables the reporter to make a causality assessment for any combination of drugs–reactions, and to record the outcome of each event. The result of de- and re-challenge is also recorded for each drug/reaction pair.

Finally, there is a table pointing to another case, designated as "related". This is used for example when a mother who has taken a drug during pregnancy bears a child who suffers an adverse reaction. In the table, data on exposure and pregnancy can be recorded.

Adverse Reaction Terminology

The WHO Adverse Reaction Terminology (WHO-ART) has been developed and maintained within the WHO Programme for International Drug Monitoring to provide a tool for the rational coding of adverse reaction signs and symptoms. The terminology forms an integral part of the ADR database, but it is also an independent database in its own right. This means that regulatory authorities and pharmaceutical companies may implement and use WHO-ART as part of their own drug surveillance system.

The basic logic of the terminology is a hierarchical structure starting at the body system organ level, within which there are grouping terms (general/high-level terms) that are useful for the broadest view of drug problems. The next level, consisting of specific "preferred" terms, allows for a precise identification of a reaction. Finally, WHO-ART includes a large number of "included" terms, which point to the closest preferred term available.

In recent years, an ICH initiative has been undertaken to develop a new international, multipurpose medical terminology. Because of the modular structure of the WHO ADR database, it will not be a problem to replace the existing terminology with a new one when it is available and provided that it has been adopted for use within the WHO Programme.

The ICD Classification

The reason for drug treatment (indication), cause of death, and the patient's underlying diseases/predisposing conditions are all stored in the ADR database as ICD (International Classification of Diseases) codes. The ICD is maintained by the World Health Organization in Geneva and is an international standard disease classification for general statistical use.

Tables for Codes and Text Values

Many of the data fields in the ADR database are populated with code values rather than texts. Examples of these are "country", "route of administration",

"dosage form". The codes and their corresponding text values are stored in separate tables. These "lexicon" tables provide language independence and are easy to maintain.

Interface with the ADR database

In order to communicate with the database, an interface is needed between the user and the computer. Running in a Windows™ environment, the interface created for the ADR database provides a flexible instrument to update and retrieve information. The software can be configured to suit different users' needs, and it contains extensive search capabilities and graphical presentations of search results. The basic version is a client-server programme installed in the user's PC (the client), which communicates with the mainframe computer (the server). The communication uses the TCP/IP protocol (Transmission Control Protocol over the Internet Protocol), which is an industry-standard set of rules allowing different types of computers to communicate with each other over the Internet. Access is made from a PC with a permanent IP connection (e.g., using a local area network [LAN]) or via direct dial-up connection using a modem. The application will run under any software that supports the standard for Windows™ TCP/IP applications, Windows Sockets.

Future developments include a planned conversion of the interface from the programming language Visual Basic to Java script. This means that the programme will be available directly from the Internet, accessed through Internet browsers such as Netscape Navigator and Internet Explorer. The advantages are that there is no need for the user to install the client software and the latest version is automatically used.

The interface consists of an entry/update module and a search module.

The Entry Module

The entry module allows the user to edit information in a case report. It will be used by the UMC staff to edit received reports by correcting incoming reports that have not passed the syntax checks or when asked by the report custodian to modify the case information. When a report is modified, all changes made are monitored by the audit trail process, which allows any previous version of a report to be recreated. Every report update must be signed off by the responsible person. The changes made and the sign-off signature will be displayed in the audit trail window. It will also be possible to lock any version of a report so that no changes can be made to it.

The right to makes changes is determined by the user's predefined access level. This is part of the security system, which makes sure that no unauthorised person can access the database and that only certain users can act as supervisors, with a right not only to read but also update and delete information.

It is also intended to make a stand-alone version of the report entry module available to those reporting centres that do not have the facilities to submit reports by computerised media.

The Search Module

The search module provides a user-friendly and flexible way of querying the database. The search results can be presented in a number of formats, including graphical data representation.

All data fields in the ADR database are searchable. The standard search window displays the most commonly queried field. A query is composed by selecting fields and entering search criteria. Instead of typing the whole field value, it is possible to use wildcard operators to replace characters. For some fields, there is a browse function, which displays the contents of the field and allows the user to select a value from the list. The search will be performed on cases that fulfil all of the specified search conditions (logical operator AND).

In the advanced search window, any field can be selected for querying. With the help of relational operators and the possibility to connect several search criteria with the logical operators AND/OR, complex search criteria can be created and saved.

The *logical operator* (LOP) AND/OR connects the different subconditions of a database query. *Relational operators* (ROPs) define the comparison between the values that the expressions on either side of the ROP represent. Examples of relational operators are: begins with, less than, and equal to.

When a search is run, a summary of the search result is displayed in the search result list window. The following information is displayed:

- Year when first/last report was received
- Number of reports
- Gender distribution
- Number of reactions per causality assessment level
- Number of reports per documentation grade
- Number of fatalities

Documentation grades:

1. Report contains date of onset of reaction and dates of treatment
2. (1) plus indication for treatment and outcome
3. (2) plus a positive re-challenge

A list of the reports is displayed, showing the case identity numbers, country, gender, and age of the patient (the user may choose different

attributes). From this list, one or more individual case reports may be selected for viewing. The selected reports can also be displayed graphically as a bar graph, showing the distribution of reports by main ADR groups (body system organ classes) or by drug groups (ATC classification).

Alternative displays include distribution of selected reports by

- Year
- Gender and age
- Outcome
- Seriousness
- Country

Graphs and screen displays can be printed, or the data can be sent to a file.

Document Generator

The document generator can create a number of reports in different file formats, including ASCII (American Standard Code for Information Interchange) text files ("flat files") and SGML (Standard Generalised Markup Language, ISO 8879) documents.

The reports produced include:

- *ADR number per country:* The number of reported cases of specified reactions or a whole body system organ class are listed for individual drugs or salts/esters of a drug. The information is grouped by reporting country.
- *Comparison of ADRs to different drugs:* The total number of adverse reactions reported to each drug is given, together with number of reactions in the selected reports, and the proportion of these as a percentage of the total.
- *CIOMS line listing:* This report contains some fundamental case data fields, as indicated in the CIOMS II report (1992). The data are presented in body system organ class order for the most serious reaction reported.
- *Complete case report:* All case details forwarded to the WHO database are presented, case by case.
- *Type A report:* The selected drug/adverse reaction associations are presented by body system organ class and year.

- *Reaction by drug report frequency:* This report is a list, in descending order, of the drugs that are reported to have caused a specified reaction.

The Medicinal Products Database

Information on drugs has been entered into the WHO drug database since the start of the international programme. All registered products from the participating countries are, however, not included, since the drugs entered routinely by the UMC staff are those that have been mentioned in ADR reports. For each case report, though, information on all drugs is recorded, whether or not the drugs are suspected of having caused the reaction. Thus, the register covers a majority of the drugs used in the programme countries.

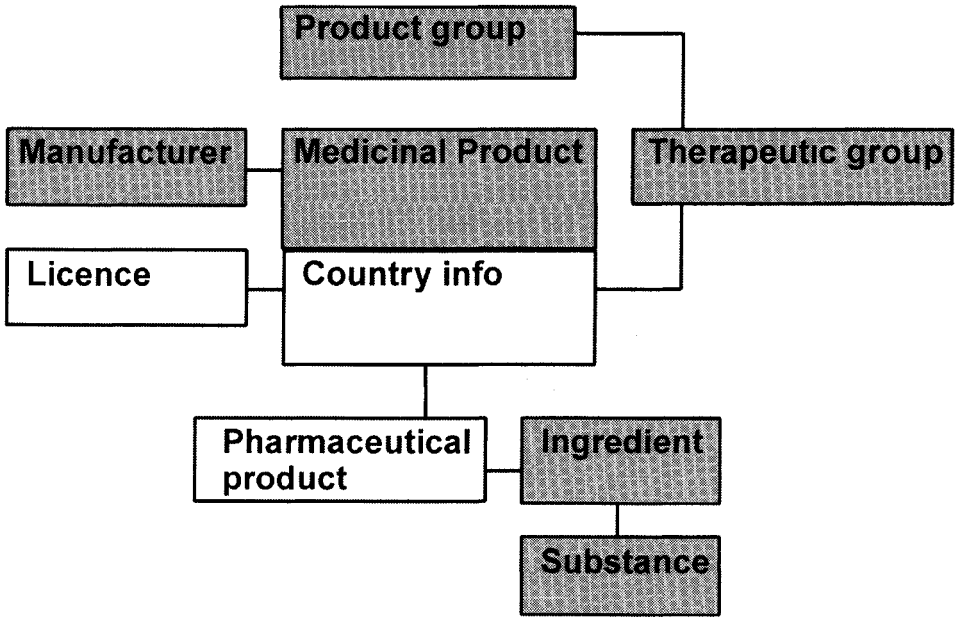
Again, the need for expansion has been recognised over the last several years. In connection with a general overhaul of the system, an extended medicinal products database (MPD)will be introduced, replacing the existing one. The data model complies with the CEN preStandard for medicinal product identification (1995), which contains definitions of the concepts and descriptions of the characteristics and the relationships needed to identify each of these unambiguously, particularly for exchanging information between information systems. The advantages with adhering to this standard are that the naming of the data fields follows a standardised nomenclature, and the concepts and terms included in the database are defined.

The MPD model (Figure 27.2) that will be used for the WHO system is the core part of a general drug database model, which has been jointly developed with the UMC software supplier, PharmaSoft. The general model contains some tables for drug-related information that is relevant only at a national or pharmaceutical manufacturer level. Compared with the existing database, the new MPD will provide a vast increase to the amount of information that can be stored on each product.

The main tables in the database are as follows:

- *Medicinal Product:* proprietary product and territory/country specific information
- *Product Group:* information on the generic level, or on a group of medicinal products
- *Manufacturer:* information on the product manufacturer
- *Product Licence:* information on the market authorisation holder
- *Therapeutic Group:* therapeutic classification

Figure 27.2. Schematic Illustration of Medicinal Products Database



- *Pharmaceutical Product:* pharmaceutical forms available for the product
- *Ingredient:* quantity and identification of active ingredients
- *Substance:* substance names and Chemical Abstracts Service (CAS) numbers

The main difference between the existing database (the WHO Drug Dictionary) and the new MPD is the level of detail. For each product, the register will contain country-specific information, including the name of the market authorisation holder (licence holder) and the pharmaceutical forms and strengths available in each country. The current drug record number system, which allows a hierarchical grouping of drugs, will be retained in the new database structure.

The ATC Classification

The therapeutic group will be designated using the ATC (Anatomical Therapeutic Chemical) classification, as in the existing database. The ATC system is a hierarchical classification, dividing drugs into different groups according to the main target body organ/system and their therapeutic, pharmacological,

and chemical characteristics. It is maintained and updated by the WHO Collaborating Centre for Drug Statistics Methodology (1996), Oslo, Norway. Since 1996, there is an agreement between the Norwegian government and WHO headquarters in Geneva stating that WHO is responsible for the co-ordination of the activities and for publications. As one of the main users of the ATC system, the UMC takes an active interest in the development of the classification, and it is represented in the international ATC/DDD (Defined Daily Doses) working group.

The ATC codes are assigned on a generic level (products containing the same ingredient/combination of ingredients will have the same ATC code/s), but, which is not the case today, also on the proprietary product level which allows for different ATC codes depending on the form or the strength of a product. For example, there are several possible ATC codes for prednisolone products; the form and indication will determine the ATC code for a particular product. Thus, a prednisolone cream indicated for topical use will have a "dermatological" code, a suspension for use in the eye will have an "ophthalmological" code, and so on.

Interface with the MPD

The interface for the MPD is similar to that for the ADR database. It is a graphical, Windows™ application that allows the user to update the information in the database and to make searches.

One of the major challenges is to populate the MPD with correct and up-to-date information on medicines registered world-wide. To improve the speed and accuracy of data entry, the centre encourages companies to assist in providing the necessary information on their own products. This process will be aided by user-friendly software made available for external use, thus allowing distributed data entry. Advanced security features are necessary with this approach, and any information entered from outside the UMC will be labelled as provisional until checked and approved.

Work Flow

Every organisation has a work flow–the sequence of activities and tasks that are necessary to produce a desired result or output. To monitor and manage these processes, a systematic approach is needed. With the help of computer technology, the work flow can be managed effectively and accurately via the automation of procedures. It was decided to use a newly developed workflow software to support the organisational aspects of updating and maintaining the WHO databases.

The software is designed to model, execute and monitor any process. The design phase starts with modelling the information flow and the tasks to

be performed. The specified tasks are then assigned to actors (individuals) who fulfil different roles. A role is typically populated with several actors, and a particular person can have different roles. The software links specific tasks to tools needed to support the task, and it brings the right information to the right person at the right time. If a task is close to its deadline, the system generates a warning, and the appropriate action can be taken. The software can also perform a number of statistical functions, such as identifying bottlenecks in the information flow and measuring the time spent on different tasks.

The system can handle manual as well as automated tasks; it has a logging function that generates an audit trail of each process. When a task has been completed, information is stored on what actions have been taken and by whom.

Below is a list of some of the tasks supported and monitored by the work-flow system:

- Processing of batches of incoming ADR reports
- Acknowledgement of receipt to reporting centre
- Production of reporting statistics
- Syntax checks of incoming reports
- Checks for duplication
- Production of regular output documents
- Signal review

For every process, the system can ascertain that it is handled according to the applicable SOP (Standard Operating Procedure). The signal review process involves, in addition to the UMC staff, a panel of international expert reviewers. When a new signal of an drug/adverse reaction problem has been generated, and subsequently selected for follow-up, the work-flow software can support the signal review process because it allows for a virtual expert network, with functions for secure Internet communication.

System Tools

A number of programmes are needed for routine database operations and maintenance. These programmes–system tools–are only for internal use at the UMC and are run by authorised persons at the centre. Special security categories are implemented on the programme levels. All of the activities are defined in the work-flow package.

Batch Data Entry

To allow processing, ADR reports sent to the UMC must be in a predefined file format. In addition to ASCII text files, which currently is the only accepted electronic format, the new system will also handle data transfer using EDIFACT (Electronic Data Interchange for Administration, Commerce and Transportation) and SGML (Standard Generalised Markup Language). EDIFACT (ISO 9735, EN 29735) is an electronic messaging format standard, and SGML (ISO 8879), which is a generic language for the representation of documents, is an international standard that has become the norm for the exchange of formatted information within and between systems. EDIFACT and SGML are the standards recommended by the ICH for Electronic Data Interchange (EDI). The advantage with EDI transfer of reports is that the format and quality of the reports can be checked at the point of submission. Reports in incorrect format will be rejected at the sender's side. Also, the submitter can receive acknowledgment reports on the status of the transmission.

All incoming reports that have not yet been approved for entry into the ADR database are stored in a temporary buffer database. For a report to be accepted into the ADR database, it has to pass an extensive, error-checking procedure involving the following:

- Syntax check
- Inter-field coherence check
- Check for duplication
- Check of drug names and adverse reaction terms

In the syntax check, the technical correctness of each field is controlled against predefined validity checks (e.g., the field "amount" must not contain letters), and lexicon tables containing all approved codes.

The coherence check compares the values in certain fields against those in related fields. For instance, the date of starting drug treatment should be less than or equal to the date of stopping treatment, and the outcome on the case level cannot be less than the worst outcome of any of the adverse reactions mentioned. Some values are calculated automatically (e.g., if the date of birth of the patient is stated, "age" is calculated from this date and the date of onset of the first reaction).

The duplicate control checks the reporter's case ID number against case IDs of reports already stored in the database. This check might be extended in the future to include a check of a number of significant fields. Before such a check is introduced, criteria for what should be considered a "suspected duplicate" must be developed and tested.

All drug names and ADR terms given in a report are tested against those already stored in the MPD and in WHO-ART. Any name or term that is not recognised is rejected by the system.

A modified version of the ADR interface will be used for correcting of reports that have not passed the checks. Each report will be shown in a window, and technical errors detected in the syntax check will be highlighted. The programme will notify the user if the same incorrect field value occurs in more than one report in the checked batch. In this case, all reports with the same error can be corrected in one operation.

Any rejected product name must be checked and corrected and/or entered into the MPD, and any ADR term not included in WHO-ART is likewise corrected/entered into the WHO-ART. When all of the above checks/corrections are completed, the reports are cleared by the system. When signed off by an authorised person at the UMC, they are transferred from the buffer database to the ADR database.

Conversion Programme

Considering the extensive changes being made to the ADR database, it will take quite a long time before all reporting centres are able to provide data according to the new specification. Therefore, during a transitional period, a translation programme will convert incoming data in the old format into the new format. The same programme will also be used to convert the existing database, in a one-off operation.

Buffer Database Search Programme

There is always going to be a certain lag time between the receipt of a report and its entry into the ADR database. However, all reports are stored immediately on receipt in a temporary database, which holds the information as entered/transmitted by the reporting centre. This buffer database is transparent in that it allows data retrieval using free text searches.

Report Counting

An automatic report count throughout the whole data entry procedure keeps track of reports. The purpose is to prevent reports becoming lost somewhere between receipt and entry into the database.

Consistency Check

It is important that links within reports are not lost if data are changed. Therefore, a consistency check tool is developed that will notify the user if a change leads to any conflicts.

New Methods for Data Screening and Analysis

Two new developments for the improvement of ADR signal detection and analysis, undertaken by the UMC, deserve a special mention.

The ASAP Methodology

The main purpose of the ADR Signal Analysis Project (ASAP), funded by the European Union (EU) Biomedical and Health Research (BIOMED) concerted action, was to examine the use of the WHO ADR database, the IMS drug utilisation databases, and international demographics for the investigation of drug safety signals. The objective was to develop a methodology that would provide a set of relevant denominators for spontaneously reported ADR data to meet a wide range of ADR issues and to permit the analysis of subsets of a drug product's total use to isolate higher risk situations.

Although no definitive algorithms could be applied to every analysis, a number of standard tabulations were developed, together with methods to concatenate the data and recalculate sales and prescription figures into internationally comparable measurements. Some of the results have been published in medical journals (Lindquist et al. 1994; ASAP Team and Fraunfelder 1996; ASAP team and Savage 1997; Lindquist and Edwards 1997). The analyses made showed that the methodology can be used for a wide range of drug safety problems and that it is a cheap and quick way of analysing international ADR signals.

The Bayesian Neural Network

Bayesian logic seems to be intuitively correct for clinical diagnosis. Starting with a limited proposition and then adding information, one can proceed in a transparent fashion to determine for example probabilities for a diagnosis. Each additional piece of information will alter the probability. For example, a patient has a skin rash when taking penicillin. If the incidence in the population is known, a probability of a causal relationship can be assigned to that event. Another fact is gained–the patient has had penicillin before. This enhances the probability. We then find that the patient had a rash when the last antibiotic course was given, which was a cephalosporin. Again, this alters the probability of a causal relationship. With each additional piece of information, the posterior probability from one consideration becomes the prior probability before adding the new information. It is necessary to be cautious of including dependent variables, though this effect may be corrected (Fryback 1978). It is clear that a piece of information that has overlapping significance with another can falsely alter the probability by being counted twice.

Neural networks based on Bayesian logic are robust for missing information and can be made to manage large amounts of data. Of the nearly 2 million case reports in the WHO database examined in a pilot study,

various criteria for establishing a new signal have been tested. The current criteria are as follows:

- The Logarithmic Mutual Information Component (LMIC; similar to correlation) between two or more fields, which will primarily be drug and adverse reaction, exceeds zero.
- The LMIC is more than 2 standard deviations from zero.
- The LMIC after the addition of new cases in an update is more than two standard deviations from the previous level.

Mutual information may be treated as a correlation, and the network assigns a probability to all associations possible between each field of information. Clearly, just exceeding zero, on a log scale, is a very tentative, early signal. On the other hand, two standard deviations from the baseline gives a very strong probability for a true association, and a similar increase when adding new information indicates significant change that must be watched for development or analysed further.

Essentially, the probabilities derived are the probabilities that a given association is different from the generality of associations in the database. For example, the captopril/cough association is significantly stronger than the average drug association with cough. This is a new way of looking at ADR signals.

Once a primary signal is seen, it is possible to perform multiple associations to see whether the drug/ADR combination is associated with patients of a particular age group, gender, disease indication, taking other particular drugs, and so on. It is also possible to examine a particular drug group for comparisons.

The pilot study has clearly shown that statistically significant signals can be determined even before single case reports appear in the literature. The operational version of the network will be put into regular use during 1998 for work at the UMC.

Exchange of Information

The WHO system relies on information being transferred, stored, and retrieved in a timely and secure way. Through the use of a sophisticated, exchange server technology, the Internet can be used as a transport medium for data and document transfer with guaranteed security, authenticity, and client authentication. All data that is transferred is encrypted, and so-called smart cards can be used for client authentication and key management. Only authorised users (clients) are permitted access to the server.

A gateway that complies with the ICH ESTRI (Electronic Standards for Transmission of Regulatory Information) gateway will be installed. The

gateway is described in Chapter 23. This technology can, for example, be used for the secure transfer of ADR reports from the reporting centre to the UMC, with an acknowledgement of receipt and a notification to the report sender that the reports have been accepted into the database. Perhaps even more importantly, the exchange server methodology facilitates secure transfer of information from the UMC to clients all over the world. An audit trail of all external accesses can be made available to authorised providers of data.

Internet technology is also used for the exchange of information through E-mail discussion groups. Recently, a dedicated discussion group for pharmacovigilance issues, VigiMed, was set up by the UMC. It is open to all participating centres and serves as a forum for the communication of current drug safety issues.

Conclusion

The ultimate aim of all work done at the UMC is to improve global drug safety. With an effective communication of information, the awareness and knowledge of drug problems will increase, and appropriate actions may be taken.

Acknowledgments

The author would like to thank Ralph Edwards and Cecilia Biriell at the UMC for their support, and PharmaSoft, Uppsala, for invaluable technical advice.

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III

Quality criteria for early signals of possible adverse drug reactions

I. RALPH EDWARDS MARIE LINDQUIST BENGT-ERIK WIHOLM
ED NAPKE

The main function of the World Health Organisation's International Collaborative Programme on Drug Monitoring is to provide a reliable early warning of possible health hazards caused by medicines. Described here is an attempt to devise criteria that would produce a well-founded early signal of an adverse reaction on the basis of reports sent in by national collaborating centres and combined in the WHO database. To reduce the frequency of spurious associations (false-positive signals) it is suggested that publication be delayed until a few case-histories meeting the suggested criteria have been sent in. The criteria were tested retrospectively against early published case-reports on drug-associated agranulocytosis. 19 suspected associations were examined and a signal in the database was defined by there being three or more cases containing stipulated information about the patient and the treatment. The WHO database had reports on all the associations, suggested criteria for a signal being met in 15 instances. This signal was present when the first case was published in 7 instances and within three months of first publication in 1. Moreover, in 3 instances where publication came first the cases presented had been collected by a national drug monitoring centre. The WHO databank has the potential to provide doctors and scientists with signals which then should be evaluated in detail.

Lancet 1990; 336: 156–58.

Introduction

In an analysis of how serious new adverse drug reactions (ADR) were detected, Venning found that the first suspicions for 13 of 18 reactions were generated by observations made by single physicians who had submitted them as case-reports.[1,2] These reports were usually published in journals. Thus, observations made by astute physicians have a high sensitivity in detecting new associations. Venning also analysed the proportion of similar first reports of suspected ADR that were subsequently verified.[3] 35 of 47 (74%) were verified within 18 years. However, only 7 of the 19 reactions that were less well

ADDRESSES: National Toxicology Group, University of Otago Medical School, Dunedin, New Zealand (I. R. Edwards, FRCP); Drug Epidemiology and Information Branch, Department of Drugs, National Board of Health and Welfare, Uppsala, Sweden (M. Lindquist, MSc; B.-E. Wiholm, MD); and Health Protection Branch, Ottawa, Canada. (E. Napke, MD). Correspondence to Dr I. R. Edwards.

documented at the time of publication were later verified, a finding which prompted Venning to suggest criteria on the information that ought to be provided to make an ADR case-report publishable.

Serious ADRs are usually rare and to expect any one physician to wait for two or three cases might delay the detection process unnecessarily. Moreover, single cases tend to be published in a variety of journals, making it very difficult for any one person to cover all potential sources of information. In the 1960s these and others reasons led to the formation of national centres for the systematic collection of suspected ADRs via spontaneous reports. National data were later pooled in the WHO International Collaborative Drug Monitoring Programme, which has been in formal operation since 1971.

The WHO Collaborating Centre database on potential new ADRs has been used to generate publications such as those by Stricker and colleagues on terfenadine, indapamide, and cinoxacin.[4-6] In 1987 this database contained case-reports from twenty-seven countries, reflecting different prescribing practices in different populations with varying disease patterns, and sometimes different preparations of the same generic medicine. Moreover, the recognition of ADRs will probably vary from country to country depending on the pattern of medical practice and on the information available to doctors. Publications therefore had to be based on a thorough analysis of the primary material and it was a formidable task to collect and analyse case-reports originating in several different countries.

On the initiative of the Netherlands centre the collaborating national centres have agreed on a continuous review of the central database looking for new signals—ie, several suspected associations that can lead to publication. Even though the work has been shared out between eight countries the number of reports of possible drug/event associations makes this a tedious and time-consuming task.

Preliminary analysis suggested that the very first reports of drug-associated agranulocytosis had, in most instances, been received by the WHO centre more than 6 months before publication.[7] One way of speeding up the process might be to devise criteria for a consensus on whether enough information is available from single case-reports—which may be sent in from very different national backgrounds—for a warning of a suspected ADR to be published.

Material and methods

Reports sent in by national monitoring centres for entry into the WHO database are expected to contain certain basic information, which, with the criteria proposed for grading the value of the report, are shown in table I. Case-reports containing information on all eleven major items were designated "substantial" and, in the absence of any available confounding variables, constitute an "index case", warning of a possible problem with that medication. (Rarely, substantial cases will include a positive rechallenge, which is generally accepted as strong evidence for causality; such cases could be regarded as "presumptive".) Cases with less documentation are labelled either "feasible" or, if the missing information does not permit a judgment, "unassessable".

It is suggested that publication normally be deferred until three index cases or their equivalent have been collected. Here, an index case is equivalent to two "substantial" or four "feasible" cases. However, any reported collection of cases should include at least one index case, otherwise there will be little defence against a coincidence or confounding factors being responsible for a reaction ascribed to a medicine. The level of documentation needed for publication is, we suggest, three index cases; two index cases plus two substantial or four feasible; or one index case plus four substantial or eight feasible—or any other combination making equivalents of three index cases.

TABLE I—CASE INFORMATION ITEMS AND CRITERIA FOR INDEX CASES

Essential information: case-report "unassessable" if any item missing
Identification of source of case (eg, reporting doctor)
Identification of case
Description of reaction
Name of drug
Treatment dates
Reaction date
"Feasible" cases: all of the above items
Sex
Age
All drugs (product names specified) with doses and dates
Indication for treatment/underlying diagnosis
Outcome
"Substantial" cases: all of the above
Positive rechallenge = "presumptive" → "index case"
Negative rechallenge or no rechallenge and no confounding variables → "index case"

Each information heading should be completed with a negative statement where it does not apply rather than leaving a blank. The decision to make a "substantial" case an "index case" should be fully documented with reasons—eg, no confounding variables relevant and pharmacological support for the hypothesis.

The method described above has been tested using reports to the WHO Collaborating Programme of agranulocytosis with 20 randomly selected medicines alleged to cause that adverse effect. The drugs were selected from major therapeutic groups, mainly analgesics and cardiovascular, and psychotropic medicines. 1 drug marketed before the start of the WHO database was excluded.

First publications were sought in the MEDLARS database and in the serial books *Reactions* (ADIS Press) and *Meyler's Side Effects of Drugs* (Elsevier), and the original dates of publication were traced back from those secondary sources. Manufacturers were also asked to comment by letter on their first knowledge of agranulocytosis reported in association with their drug. The search extended to the end of 1987. Time differences were measured to the nearest three months because the WHO centre updates its information base quarterly. A report published more than one quarter before a similar report was received at the WHO Collaborating Centre was judged to have been the first producer of the suspicion. No quality criteria were applied to published reports.

Results

For all 19 medicines there were reports in the WHO database, and for 15 medicines at least one index case was identified. With all these 15 medicines the number and quality of reported cases constituted a signal on the suggested criteria. The median delay between the first index case and a signal accumulating was 1·5 years; with 5 drugs the delay was less than one quarter. First reports on these 19 suspected associations emanated from ten countries; a full signal was created by reports from a single country in only 3 instances and for 2 drugs reports from five countries were necessary to create a signal (table II).

A published report was found in 16 instances. These appeared in eleven journals published in four languages. Table II shows that the very first report was in 14 instances received by WHO before it was published in a journal. An index case was received by WHO before publication in 7 instances and it was also possible to produce a strong signal of agranulocytosis from the WHO data base, equivalent to three index cases, on 7 occasions before there were case-reports in the journal. In 1 additional instance this was possible within 3 months of publication. Moreover, on 3

TABLE II—DRUG-ASSOCIATED AGRANULOCYTOSIS: FIRST PUBLISHED REPORTS AND APPEARANCE OF FIRST INDEX CASES, AND SIGNALS, IN WHO DATABASE

Drug	Date (as year: quarter) of:				No of countries
		WHO cases			
	Publication*	First	Index	Signal	
Amoxapine	83:2	83:3	..	..	..
Aprindine	76:3	75:4	76:3	76:4	1
Benoxaprofen	..	81:2	..	..	..
Captopril	80:4	81:1	83:3	83:3	4
Clozapine	75:3	75:1	75:2	75:2	1
Diclofenac	79	78:2	85:1	86:2	3
Ibuprofen	76:2	72:1	76:4	78:4	5
Mebhydrolin	81	71:2	73:3	79:1	4
Mefenamic acid	..†	73:1	73:1	84:4	2
Mianserin	79:1	79:2	79:2	80:4	2
Naproxen	84†	78:3	78:4	81:4	2
Piperacillin	79:2	81:1	86:1	86:1	4
Piroxicam	(88)	83:1	87:2	87:2	5
Sulindac	81:2	82:3	82:2	85:1	4
Thenalidine	—	72:1	73:3	75:3	1
Ticlopidine	82:2‡	82:1	83:4	83:4	3
Tocainide	85:2	82:1	82:1	84:2	4
Tolmetin	78:2‡	77:1	..	..	..
Zomepirac	84:1‡	83:2	..	..	..

*References (sixteen publications) available from authors.
†Before 1978 in the US Physicians Desk Reference.
‡Publication based on cases collected by National Drug Monitoring Centres.

occasions where a published report came first the cases had been collected by national monitoring centres but published before they had all been received by the WHO Collaborating Centre.

Discussion

Agranulocytosis was chosen to test the method because the reaction is often recognised as drug-related and results in early case-reports in journals. This allowed us to see whether the accumulation of sufficient cases (index, substantial, or feasible) in the WHO database to satisfy the suggested criteria for publication would have unduly delayed the production of a signal worthy of serious consideration by health-workers. We found that the WHO database can provide information for strong signals according to the described logic; that the delay caused by the collection of three index cases (or equivalent) was not unduly long when set beside the confidence that a series of cases rather than single case-reports provide; and that well-described cases of agranulocytosis, meeting the criteria for a signal, were available from the WHO database before they had been published in one-third of the drugs reviewed (in 2 instances no publication had appeared by the end of 1987).

For benoxaprofen and piroxicam there was by the end of 1987 no report in the sources used for this study, and in a large multinational case-control study on the risk of agranulocytosis by analgesics none of the 221 published cases was exposed to benoxaprofen and only 1 had been exposed to piroxicam.[8] The antihistamine thenalidine provides an interesting example of how old information can disappear. In Sweden 9 cases were reported between 1971 and 1974 and the problem was mentioned in local publications in 1973 and 1974[9,10] and led to the withdrawal of thenalidine in 1974. At that time there were published reports on another 9 cases,[11] the first appearing in 1958.[12,13] This medicine was withdrawn by the manufacturer from the market in the UK and USA in 1960, but was later reintroduced in the UK and is still available in some countries. However, the early publications are not retrievable in MEDLARS; in *Meyler's Side Effects of Drugs* thenalidine is mentioned as a drug associated with agranulocytosis in the 1960–68 editions but not in 1975.

The detection of new ADRs needs a system with high sensitivity and thus some loss of specificity. The production of some false signals is the price to be paid for early warnings of important health hazards. The sensitivity and the specificity of the criteria we suggest can be varied by increasing or decreasing the number of index cases needed to define a signal. The criteria do ensure that index cases are properly described and that substantial and feasible cases have any confounding variables clearly indicated.

Once index cases have been found the observer has to decide what to do. A single index case in itself seems poor grounds for any action, including publication. Presumptive cases or other index cases in which the reaction is unlikely to be due to coincidental underlying disease or is previously unsuspected or severe may suggest the need for immediate publication but it seems much safer to wait for perhaps three index cases (or equivalent). Only rarely can three index cases be seen as anything more than a publishable warning of a possible hazard. The most important reason for publishing such information is to allow other studies to be started, to strengthen the signal or refute it. Concurrent epidemiological investigation, preferably as controlled studies, will show how serious the ADR is quantitatively. In publishing such early warnings from the WHO database index cases should be described in full; other substantial cases can be tabulated with confounding variables clearly shown; and feasible cases may simply be counted. An important step is to decide which substantial cases provoke enough suspicion to become index cases. Almost certainly those that are presumptive will, and we suggest that those cases where neither other medicines nor the underlying disease are likely to be confounding variables should also be regarded as index cases. This decision requires clinical judgment, and the grounds for that judgment should be clearly stated.

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IV

Endocrine adverse effects of omeprazole

Marie Lindquist, I Ralph Edwards

WHO Collaborating Centre for International Drug Monitoring, Box 26, S-751 03 Uppsala, Sweden
Marie Lindquist, *senior pharmaceutical officer*
I Ralph Edwards, *medical director*

Correspondence to:
Ms Lindquist.

BMJ 1992;305:451-2

Omeprazole is thought to act to reduce gastric acid through specific binding to the parietal cell proton pump hydrogen ion potassium ATPase. Selectivity is further strengthened by the drug's basic nature causing it to accumulate in acid spaces, where it is activated. Both cimetidine and ranitidine have been reported to cause gynaecomastia and impotence, though, unlike cimetidine, ranitidine does not bind to androgen receptors. There have been two single case reports of gynaecomastia during treatment with omeprazole.[1,2] We add further cases and also record cases of impotence related to omeprazole. All had been reported within the World Health Organisation's programme for international drug monitoring as cases, and in all cases causality seemed possible.

Case histories

The cases represent the total reported experience of these adverse drug reactions up to December 1991. There were 15 cases of impotence and 15 of gynaecomastia or breast enlargement.

Impotence—All cases of impotence were in men (mean age 52·6 years). They had been taking 20-40 mg omeprazole daily for a mean of four days (cases in which exact dates were recorded only) before onset. Other drugs were not reported in eight cases and not used in three. The treated condition was mostly reflux oesophagitis (12 cases). Full details of patients are given in the table.

Gynaecomastia or breast enlargement—Gynaecomastia occurred in 13 men (mean age of 56·8 years), and breast enlargement occurred in two women aged 41 and 77. The doses of omeprazole used were 20 mg daily in most patients, 40 mg daily in two men, 60 mg daily in one man, and either unknown or intermittent in three patients, including one woman. The mean time to onset (known in 12 cases) was 2·9 months. Most of the patients had either gastric or duodenal ulceration, only three having oesophagitis. In three cases the diagnosis was not recorded. One patient had the Zollinger-Ellison syndrome. The table gives details of the patients.

Comment

There have been two single case reports of gynaecomastia in patients taking omeprazole but none of impotence. Both reports point out that the mechanism for the gynaecomastia is not apparent from the pharmacology of the drug. The cases we report are further evidence of the adverse reaction and come from eight different countries. Furthermore, they include the hitherto unrecorded adverse effect of impotence. Confounding due to other disease or other drugs

Case descriptions of patients with impotence and gynaecomastia associated with omeprazole

Case No	Age and sex	Reaction	Report source	Onset date	Dose	Duration	Indication	Other drugs	Outcome
1	59 M	Impotence, libido decreased, gastritis	Specialist doctor	Jan 1988	20 mg Daily	Unknown	Oesophageal disease	Metoclopramide	Not recovered when reported
2	49 M	Impotence	General practitioner	Unknown	1 Dosage form daily	10 Days	Gastric ulcer	None stated	Recovered
3	44 M	Impotence (erection failure)	Hospital	Mar 1990	20 mg Daily	6 Days	Chronic oesophagitis	Sodium alginate/antacids	Recovered
4	67 M	Impotence (erection failure)	General practitioner	June 1990	20 mg Weekly	2 Days	Duodenal ulcer	None stated	Recovered
5	59 M	Impotence (erection failure), flushing	General practitioner	Feb 1990	20 mg Daily	1 Day	Oesophagitis	None stated	Unknown
6	49 M	Impotence, libido decreased	Unknown	Feb 1990	20 mg Daily	<1 Month	Peptic ulcer	None stated	Unknown
7	39 M	Impotence	Unknown	Feb 1990	40 mg Daily	<1 Month	Reflux oesophagitis	None stated	Unknown
8	57 M	Impotence	Manufacturer	Jan 1990	20 mg Daily	1 Day	Resistant oesophagitis	None stated	Recovered
9	49 M	Impotence (2nd degree erection failure)	General practitioner	May 1990	20 mg Daily	<1 Month	Reflux oesophagitis	None stated	Not recovered when reported
10	49 M	Impotence (erectile)	Unknown	Nov 1990	20 mg Daily	2 Days	Reflux oesophagitis	None stated	Unknown
11	65 M	Impotence	General practitioner	Dec 1990	20 mg Daily	5 Days	Oesophagitis	Metoclopramide, sodium alginate/antacids	50% Improvement after stopping drug
12	56 M	Impotence	General practitioner	Jan 1991	20 mg Daily	<20 Days	Oesophagitis	Lisinopril, bendrofluazide	Unknown
13	60 M	Impotence	Doctor via manufacturer	Unknown	20 mg Daily	Unknown	Severe reflux	None	Recovered
14	34 M	Impotence, libido decreased	Doctor	Feb 1990	20 mg Daily	8 Days	Barrett's oesophagitis	None	Unknown
15	53 M	Impotence	General practitioner	May 1990	20 mg Daily	1 Day	Oesophageal reflux	None	Recovered
16	38 M	Gynaecomastia, weight increase, diarrhoea	Clinical trial	Oct 1988	1 Dosage form daily	2 Months	Intractable ulcer	Cholestyramine	Not recovered when reported
17	76 M	Gynaecomastia (unilateral, tender)	Hospital	Feb 1989	20 mg Daily	7 Months	Duodenal ulcer	Digoxin, aspirin	Recovered
18	37 M	Gynaecomastia (right, tender)	Unknown	Aug 1989	40 mg Daily	1 Month	Stomach ulcer	Clofibrate, probucol, ergotamine	Not recovered when reported
19	65 M	Gynaecomastia (left, tender)	Doctor	Sept 1990	20 mg Daily	5 Months	Bleeding duodenal ulcer	Prednisone, sulphasalazine, calcium carbonate, theophylline, salbutamol, triamterene/hydrochlorothiazide	Recovered
20	75 M	Gynaecomastia	Unknown	Unknown	20 mg Daily	Unknown	Unknown	None stated	Not recovered when reported
21	68 M	Gynaecomastia	General practitioner	Jan 1989	20 mg Daily	Unknown	Gastric ulcer	None stated	Not recovered when reported
22	55 M	Gynaecomastia (left, tender)	General practitioner	Dec 1989	40 mg Daily	3 Months	Ventricular ulcer	None stated	Not recovered when reported
23	71 M	Gynaecomastia (left)	General practitioner	Jan 1990	20 mg Daily	1 Month	Ventricular ulcer	Ketoprofen	Recovered
24	44 M	Gynaecomastia (painful)	Unknown	Sept 1989	60 mg Daily	2 Months	Zollinger-Ellison syndrome	None stated	Not recovered when reported
25	74 M	Gynaecomastia (tender)	General practitioner	Nov 1989	20 mg Daily	23 Days	Oesophagitis	Cimetidine. For some years: spironolactone, salbutamol, beclomethasone, aspirin, nifedipine, isosorbide	Not recovered when reported
26	77 F	Gynaecomastia, warfarin sensitivity	Specialist doctor	Dec 1989	20 mg Daily	6 Days	Unknown	Warfarin, digoxin, amiloride/frusemide	Less noticeable Feb 5
27	41 F	Gynaecomastia	Manufacturer	April 1990	Unknown	Unknown	Unknown	None	Unknown
28	35 M	Gynaecomastia	Unknown	June 1990	20 mg Daily	1 Month	Bleeding duodenal ulcer	Ranitidine (until omeprazole was started 11 June)	Unknown
29	35 M	Gynaecomastia (left)	Unknown	July 1990	Intermittent	8 Months	Resistant gastro-oesophageal reflux	None	Resolving when reported
30	65 M	Gynaecomastia	Doctor via manufacturer	Nov 1989	Intermittent	3 Months	Oesophageal reflux	None	Not recovered when reported

*Patient had taken Tagamet (cimetidine) for some time before omeprazole; never any gynaecomastia with Tagamet.

seemed unlikely in 14 of the patients with adequate information to make a judgment.

The relation of cimetidine to gynaecomastia and impotence is explicable pharmacologically, but ranitidine has also been incriminated in a few cases. A pertinent question is therefore whether the treated disease may be implicated. Severe liver disease, in which gynaecomastia and impotence may feature, is associated with a high incidence of peptic ulceration but is unlikely to go unrecognised in so many reports. Increased prolactin concentrations occur in Wermer's syndrome (multiple endocrine neoplasia, type I) as well as peptic ulceration, but in the cases of gynaecomastia and impotence associated with omeprazole reported to date prolactin and other relevant hormone concentrations were normal. Inhibition of cytochrome *P*-450 as postulated for gynaecomastia and impotence caused by cimetidine is possible also in the case of omeprazole as it too has some properties inhibiting liver cytochrome *P*-450 enzyme.[3,4]

That seven of the patients with impotence and five of those with gynaecomastia either had recovered or were improving at the time of this report is strong evidence that omeprazole was the causative agent.

These cases occurred in several countries participating in the WHO collaborative programme, and the information was gained and assessed in different ways. Causality cannot therefore be simply determined from the information available, and our conclusion does not necessarily represent the opinion of the WHO.

We are grateful to the participating countries in the WHO programme for international drug monitoring for help in preparing this manuscript.

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(Accepted 15 May 1992)

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PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 8: S15–S25 (1999)

ORIGINAL REPORT

From Association to Alert — A Revised Approach to International Signal Analysis

MARIE LINDQUIST MSci Pharm[1]*, IVOR RALPH EDWARDS MB, FRCP (Lond), FRACP[1], ANDREW BATE BAHons (Oxon)[1], HELENA FUCIK[1], ANA MARIA NUNES MD[2] AND MALIN STÅHL M Med Sci[1]
[1]*Uppsala Monitoring Centre, Uppsala, Sweden*
[2]*Visiting Consultant, Uppsala Monitoring Centre, Uppsala, Sweden*

SUMMARY

From the inception of the WHO international drug monitoring programme, the main aim has been to detect signals of adverse reaction problems as early as possible. The Uppsala Monitoring Centre (UMC), is now in a better position to fulfil this mission. Using the latest technology, new tools have been developed which allow for rapid, robust and comprehensive data mining of the WHO database. Based on retrospective time scans made during the pilot phase the current threshold used is the 97.5% confidence level of difference from the generality of the database. To maximize the capacity for picking up signals, we intend to extend today's panel of expert consultants, as well as doing our own review. The new system includes an enhanced follow-up list of signals, a 're-signalling' procedure and a cumulative historical file of all drug–ADR associations. Already we produce some 50 signals per year, cisapride and tachycardia being an example of a controversial signal only recently accepted. With the addition of new tools for follow-up of important signals such as complex variable data mining techniques, and the combination of WHO ADR data with sales and prescription figures from the IMS, we will be able to provide more information that should benefit regulators, producers, prescribers, and most importantly, the users of medicines. Copyright © 1999 John Wiley & Sons, Ltd.

KEY WORDS — adverse drug reactions; adverse drug reaction reporting systems; signal generation; signal analysis; signal follow up; data mining; Bayesian statistics; neural network; international

INTRODUCTION

The World Health Organization (WHO) database, maintained by the Uppsala Monitoring Centre (UMC), currently contains over 1.8 million spontaneous adverse drug reaction (ADR) case reports provided by more than 50 countries around the world.[1] While many national regulatory authorities have the time and resources to assess each case report individually, this is impractical on the international level, considering that the UMC processes on average about 2000 case reports weekly. Therefore a different approach is needed which will provide information to the national centres that adds to the existing information, and aids evaluation and regulatory decision making.

The results of the UMC's investigations are communicated to regulatory authorities and pharmaceutical companies, for further investigation and action. It is the Centre's aim to serve as a clearing house for information and to be an active partner in the international pharmacovigilance field. It should be emphasized that the work done by the UMC is not intended to compete with that of national ADR centres, nor companies, but to serve as a complement.

To improve the current UMC signalling procedure, a complete revision of the existing practice was made, including the introduction of an automated system for signal detection using a Bayesian neural network methodology. The aim

* Correspondence to: M. Lindquist, Research and Development Manager, Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, Stora Torget 3, 753 20 Uppsala, Sweden. Tel:46 18 65 60 60. Telefax: 46 18 65 60 80. Email: marie.lindquist@who.pharmasoft.se

CCC 1053–8569/99/S10S15–11$17.50

Received 17 November 1998
Accepted 3 December 1998

information to promotion and development of knowledge and tools in drug safety and risk–benefit analysis. The name Uppsala Monitoring Centre (UMC) was introduced in recent years, to reflect the extended role of the Centre, and also to avoid the confusion caused by the use of various unspecific abbreviations. In the UMC's visions and goals for the future, a primary aim is still to provide an effective and efficient signalling system, with 'Never miss a signal' as a motto.

MATERIAL AND METHODS

Current procedure of signal generation

The current procedure of signal generation has been in place since the mid-eighties. Every 3 months the WHO database is screened for new drug–ADR combinations, and a variety of lists are produced as paper prints. The printouts are distributed to all National Centres participating in the Programme, and in addition, lists based on the WHO Adverse Reaction Terminology (WHO-ART) System Organ Classes (SOCs) are provided to an expert panel of reviewers. Each reviewer receives lists pertaining to a System Organ Class/group of SOCs based on the area of expertise. When the reviewers have selected associations for further assessment, UMC staff provide them with the relevant case report printouts from the database. In addition, National Centres may be contacted for original case report details. The reviewer then evaluates the case data, taking into account i.a. possible confounding, and makes other investigations, including literature searches to find out if the association is known, and if there are possible alternative explanations. Based on this assessment, the reviewer decides what associations should be signalled, and sends a summary of the findings to the UMC for publication in the 'Signal' document. This document is distributed to all National Centres, and in relevant cases to the pharmaceutical company responsible for a particular product.

Definition of 'signal' adopted by the WHO Drug Monitoring Programme: *Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.*[3]

Drawbacks of the current procedure

Sensitivity and specificity. Over the years, some drawbacks of the existing signalling system have been identified. Currently, the database screening is based purely on numbers of occurrences of drug–ADR combinations, with no background reference. A drug–ADR combination is listed in the quarterly output at two threshold levels, both with the drug recorded as suspected of having caused the reaction:

- the combination being reported at least twice, and
- when the number of reports passes five

Thus the sensitivity of the system is high, but unless an association is picked up at one of these two levels it will not be listed again in the quarterly output documents, even if there is a large influx of new reports in subsequent quarters. Many spurious associations are reported as adverse reactions, as well as case reports of ADRs that are already well known. Since there has been no automated way of separating the 'wheat from the chaff', the number of combinations needed to be considered by the review process was too high for all combinations to be assessed adequately.

Inadequate routines for follow-up. Today, the only routine follow-up mechanism is based on associations selected by the review panel. These associations are manually entered into a database where they stay for 2 years, with 6-monthly checks for changes in number of reports. A listing of the associations 'of possible interest' is sent to national centres and reviewers as part of the quarterly output. Signals that have been circulated are registered in a cumulative file, but this information is not part of the quarterly documents. There is no routine for systematic scrutiny of either of these databases, although they are consulted regularly.[4]

Assessment bias. When there is too much data to consider effectively and efficiently the likelihood of pre-judgement is increased. Thus the impact of bias based on the knowledge and interest of the assessor is magnified.

Lack of definitions of terms used. Although the definition of signal is adopted by the WHO Programme, other players — patients, doctors, regulators, pharmaceutical industry — may have different views as to what a 'signal' means.[5] The

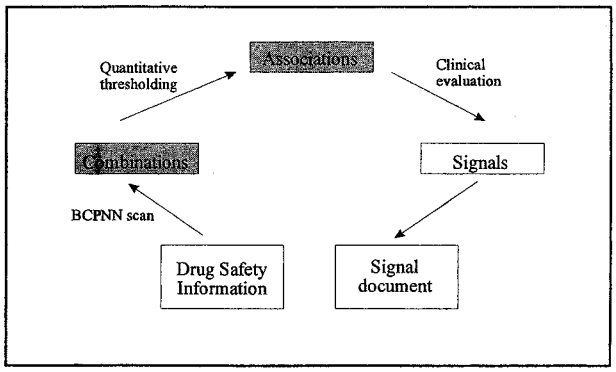

Fig. 1 — The new signalling procedure proposed by the UMC

adjustments to ensure that we provide relevant information, in formats that are useful to the recipients.

New drug safety information. The process starts when new drug safety information reaches the UMC. Normally this will be in the form of case reports received within the WHO Programme, but the intention is that other sources of drug safety information should also be considered.

Combinations. When the new data has been processed and entered into the ADR database, a BCPNN scan is run to generate statistical measurements for each drug–ADR combination. The resulting Combinations database will be made available to national centres, and to pharmaceutical companies, in the latter case including only information on the company's own patented products.

The database will be presented in a computerized form which facilitates searching and sorting of the information.

Associations. The Associations database is generated by selecting those combinations that pass a pre-set threshold. Based on the results of the test runs of the BCPNN[6] we have decided to use the threshold level for associations as that of the lower 95% confidence limit of the IC value crossing zero when a new batch of reports is added.

All associations are followed automatically for 2 years, the data being checked at 6-monthly intervals. After the final listing, an association may be reintroduced for another 2-year follow-up. The associations are also copied to a cumulative log file (history file), which will serve as a filter to exclude combinations that have in previous quarters passed the threshold level. This will prevent drug–ADR combinations with a confidence limit fluctuating around zero from being fed into the review process repetitiously.

Table 1 — Figures from a BCPNN scan of new data from the end of 1997

38800	combinations
1520	associations
536	associations on WHO-ART 'critical' terms
191	associations not in Martindale or PDR

The database will be sent to the expert review panel for evaluation, but scrutiny will also be done at the UMC. Before distributing the database, associations will be checked against standard reference sources (e.g. *Physician's Desk Reference* (PDR), Martindale), and the published literature (using e.g. Med-line and Reactions). This information is intended to facilitate the review and identify those associations that are, if not generally known, at least identified previously. Table 1 shows the result of a BCPNN scan that was made using new reports from the last quarter of 1997. Of the associations where a 'critical' term* was reported, 36% were not mentioned in the reference sources

* 'Critical' term: adverse reaction term referring to, or possibly being indicative of, serious disease states, which have been regarded as particularly important to follow-up.

Table 4 — Signals identified from the 1997:4 BCPNN run

Finasteride — breast neoplasm malignant male	(four reports)
Rifabutin — corneal ulceration	(12 reports)
Fenfluramine — abortion	(five reports)

covigilance, vol. 22, July 1996, and in the *FDA MedWatch News*, November 1996. In September 1997, the issue was brought up as a 'current drug problem' by several countries participating in the annual meeting of national ADR centres. The stacked bars distinguish reporting countries, and as can be seen, reports keep coming in from different countries.

Signals. The signals that have been identified will be published as before in the Signal document and sent to national centres.

Table 4 shows three associations generated using the BCPNN which have undergone a first evaluation at the UMC and been circulated in the Signal document. It should be emphasized that these signals are *not* established ADRs, but 'reported information on a possible causal relationship'.

Individualized sections of the Signal document will be provided to companies on a subscription basis (only on their patented products).

To aid the expert reviewers, and also to facilitate interpretation of the information presented in the Signal document, a set of guidelines is being established.

As with the associations, all signals will be automatically reassessed on a 6-monthly basis, for 2 years, with a possibility of re-introduction for follow-up, and also copied to a history file for easy tracking.

Follow-up. With the new follow-up procedures we have introduced a mechanism by which signals can be re-evaluated following new information. This enables for example renewed consideration of associations for which there initially was not enough information to merit signalling. Signals that are later supported by new evidence can also be highlighted.

Table 5 shows how an early suspicion of cisapride causing heart rhythm disturbances, published as a signal by the UMC, was first rejected, and subsequently developed into an alert. It should be noted that alerts are normally outside the scope of the UMC, whose primary role is to identify signal and to contribute to their follow-up.

Table 5 — Cisapride–heart rhythm disorders: from association to alert

1986	Double blind study: 'cisapride produced tachycardia'
1992	WHO Signal published in *British Medical Journal*[7] Letter to *British Medical Journal*: 'no epidemiological support'[8]
1995	Case report published: 'QT prolongation and tachycardia'[9] *Lancet* publication[10] *Dear Doctor* letter in USA by manufacturer warning about heart rhythm disorders

The nature of the signal will determine what measures need to be taken in terms of follow-up. No firm guidelines have yet been agreed on when, and if, signals should be excluded from further follow-up. This applies particularly to those signals that were initially assessed as probably false, and for which no new supporting evidence has been produced.

Further signal analyses. The detection of signals is only the first part of a process, and there are several ways in which the UMC will conduct further signal analyses, to complement the work done by others, or initiated by for instance a national centre.

Apart from evaluating available case information we can use demographic and drug utilization data to add valuable information to certain drug safety issues. Such work has been carried out by combining the ADR information in the WHO database with drug sales and prescription data collected by IMS. This was done as a project, funded by the European Union (EU), in which a methodology to make use of the different data sets was developed. Results of this collaborative work have been published in the medical literature,[11–15] and a new service is being developed based on this methodology. To start with, the intention is to provide a two-level service:

- ADR data combined with sales information in terms of total number of Defined Daily Doses (DDDs) or tonnage sold; and
- ADR data combined with medical information from the IMS prescription databases.

The first level service will provide information that will help to quantify the magnitude of ADRs; the

the choice of threshold level for when a combination becomes an association is still arbitrary. This is an apparently unavoidable limitation of the methodology, which we are doing our best to minimize by testing the level so as to maximize the usefulness of the output received after this thresholding is done. The advantage of eliminating prejudgement and bias by using a quantitative selection of associations for review must be weighed against the possible disadvantages of such an approach.

Potentially important signals may never become 'associations'. For very commonly reported drugs and adverse reactions, combinations of those may never stand out as being different to the generality, even for quite big c_{xy} values. This possible weakness could be resolved by continuing to feed all drug–adverse reaction combinations into the review process once the total numbers of reports of that combination pass a certain arbitrary number (based on reports where the specific drug was reported as 'suspected'). A weekly scan picking up combinations that in the week were reported more than 20 times has been suggested.

Using the BCPNN for complex variable analyses allows us to highlight patient subgroups that may be at particularly high risk of a specific ADR, and to search for drug-related syndromes. In the routine database screening, only case reports where the drug is reported as 'suspected' of causing the adverse reaction are considered. This is to reduce the noise that would be introduced by including drugs correctly coded as concomitant medication. There may, however, be occasions where a drug has mistakenly not been suspected of causing the adverse reaction, and data mining including drugs reported as 'concomitant' could provide valuable new information. In the future, we would like to implement standard complex variable runs, but at the moment these are run on an *ad-hoc* basis only.

It must be emphasized that any result of a BCPNN run is based on the evidence available in the database, and while pointing to increased risk, this may be due to some as yet unknown factor, or merely to coincidence. Nevertheless this is valuable information that will focus continued investigation in different areas. The methodology can be used to investigate deeper into the information available about case reports. It should however be noted that a relatively large number of reports are required in complex variable analyses, since a high level of granularity reduces the number of reports in each 'cell' and therefore the results become less reliable the more detailed an analysis is made.

Further signal analysis using e.g. drug utilization data can add valuable information, and allows quantification of ADRs. This is not to be confused with incidence. Some of the inherent characteristics of spontaneous reporting systems, such as heterogeneity of data and under-reporting, merit caution when any quantitative analysis is made. Also, it is not known to what extent prescription data reflect actual consumption.

Other types of studies, e.g. nested case–control studies using clinical databases, and randomized control trials, could also be used for signal follow-up, although ethical issues need to be considered, as well as selection of endpoints for these trials.[24]

Communication of benefit and risk information

The confusion over what 'signal' means could be explained by the conflicts about who should know what, and when, from the time of the first suspicion that there may be a problem with a drug. One of the difficulties is that the drug safety information must be communicated effectively to at least four different groups: patients, health professionals, regulators and industry representatives (there are other important players, but these main groups show the challenge). These four groups have differing levels of knowledge about a particular drug and from a drug safety perspective want and indeed require different information to make decisions about a drug.[25] The challenge is to communicate effectively with each of the different groups, addressing their individual needs, but without providing information that is easily misinterpreted and thus may make the work of the other groups harder.[26] This can be difficult because a signal is just an early suspicion, and not an established drug–ADR. Degrees of suspicion are difficult to communicate and uncertainty leads to insecurities within the groups that are difficult to manage. On the other hand, waiting for certainty puts more people at risk if the suspicion is justified.

Spontaneous reporting when it is effective provides a mechanism for fast recognition of signals, however delays in reporting slow this process, and incomplete information makes causality assessment difficult. Nonetheless the early detection of signals has a clear benefit in allowing specific problems to be investigated early and therefore

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Eur J Clin Pharmacol (1998) 54: 315–321

A. Bate · M. Lindquist · I. R. Edwards · S. Olsson
R. Orre · A. Lansner · R. M. De Freitas

A Bayesian neural network method for adverse drug reaction signal generation

Received: 13 October 1997 / Accepted in revised form: 5 February 1998

Abstract *Objective*: The database of adverse drug reactions (ADRs) held by the Uppsala Monitoring Centre on behalf of the 47 countries of the World Health Organization (WHO) Collaborating Programme for International Drug Monitoring contains nearly two million reports. It is the largest database of this sort in the world, and about 35 000 new reports are added quarterly. The task of trying to find new drug–ADR signals has been carried out by an expert panel, but with such a large volume of material the task is daunting. We have developed a flexible, automated procedure to find new signals with known probability difference from the background data. *Method*: Data mining, using various computational approaches, has been applied in a variety of disciplines. A Bayesian confidence propagation neural network (BCPNN) has been developed which can manage large data sets, is robust in handling incomplete data, and may be used with complex variables. Using information theory, such a tool is ideal for finding drug–ADR combinations with other variables, which are highly associated compared to the generality of the stored data, or a section of the stored data. The method is transparent for easy checking and flexible for different kinds of search.
Results: Using the BCPNN, some time scan examples are given which show the power of the technique to find signals early (captopril–coughing) and to avoid false positives where a common drug and ADRs occur in the database (digoxin–acne; digoxin–rash). A routine application of the BCPNN to a quarterly update is also tested, showing that 1004 suspected drug–ADR combinations reached the 97.5% confidence level of difference from the generality. Of these, 307 were potentially serious ADRs, and of these 53 related to new drugs. Twelve of the latter were not recorded in the CD editions of *The physician's Desk Reference* or *Martindale's Extra Pharmacopoea* and did not appear in *Reactions Weekly online*.
Conclusion: The results indicate that the BCPNN can be used in the detection of significant signals from the data set of the WHO Programme on International Drug Monitoring. The BCPNN will be an extremely useful adjunct to the expert assessment of very large numbers of spontaneously reported ADRs.

Key words Adverse drug reactions, Database

A. Bate · M. Lindquist · I. R. Edwards (✉) · S. Olsson
The Uppsala Monitoring Centre,
WHO Collaborating Centre for International Drug Monitoring,
Stora Torget 3, S-753 20 Uppsala, Sweden
Tel.: +46-18-656060; Fax: +46-18-656080
e-mail: ralph.edwards@who.pharmasoft.se

R. Orre · A. Lansner · R. M. De Freitas
SANS, NADA, Royal Institute of Technology,
Stockholm, Sweden

Introduction

It is in the very nature of drugs that they will cause adverse reactions. However, the incidence rates of specific adverse drug reactions vary considerably from drug to drug. In the same way, certain high-risk groups of adverse drug reactions (ADRs) with specific drugs will always exist.

The World Health Organization (WHO) database is the largest international database of case reports of spontaneous reporting of suspected ADRs. This database, held by the Uppsala Monitoring Centre (UMC), now contains nearly two million reports of ADRs. One of the main responsibilities of the UMC is to produce signals, according to the accepted WHO definition: "Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information" [1]. The current procedure of signal generation is as follows: On a quarterly basis, lists of potential drug–ADR problems are generated on new reports received at the centre. A panel of experts are

then sent data on these associations, and asked to comment on them. From these comments a final list of signals is generated which is then circulated to the National Pharmacovigilance Centres as well as to the expert panel. It is then the responsibility of individual national centres to react to each signal as they see fit [2]. There are obvious limitations in the current system. Experts are only able to consider a finite amount of data in the time available and the data considered could be incorrect or more likely incomplete. Furthermore, the experts' assessments are based on judgement as well as prior knowledge, which creates a bias towards discovering signals in those drug–ADR associations that are already suspected, or have been highlighted for other reasons [3]. Many other approaches have been made to the problem of optimizing the signal generation process and have been well reviewed by Bégaud et al. [4]. It has been clear for many years that an automated signalling system would improve the current system considerably, [5] but the size of the database has made it impossible to consider all possible drug–ADR combinations in a routine, automated way. We needed a system with large computational power to consider all possible links in the database of nearly two million records, each with, currently, 49 fields. The advances in information technology, in combination with the well-established theory of Bayesian statistics, have allowed us to develop a data mining system based on a Bayesian neural network. This method helps to minimize the limitations of the current system because all drug–ADR combinations are considered in an unbiased manner. Strong associations between specific drugs and specific ADRs will be highlighted. Signals which will have been generated without either external prompting or prejudgement can then be investigated further.

Methods

The WHO database

The WHO database consists of nearly two million individual case reports of suspected ADRs for specific, but anonymous, patients. These reports are provided by doctors and other health professionals throughout the world. They contain administrative data, patient data, ADR data, medication data and other information. In total there are 49 different fields, although not all fields are filled in on each case report. For example, only approximately 10% of case reports received at the centre have the fields for onset, treatment, indication, outcome, dose, age and sex all filled in. The drug information states the drugs taken by the patient, their respective quantities and duration of use. Drugs specifically suspected of causing the reported adverse reaction are also indicated as "S" (suspected) or "I" (interacting). Concomitant medication is recorded as "O" (other).

The Bayesian Confidence Propagation Neural Network

Neural networks [6] are built from biologically inspired computing elements, neurons, which are coupled into networks. These neurons are simple, but when used in combinations, they can perform complex tasks like pattern recognition and diagnosis [7]. Each neuron receives an external input as well as several inputs from other neurons, each with an attributed weight in the network. The combination of all the inputs and their respective weights to a specific neuron, when summed together and added to a bias value, generates a single output. This output then acts as one of the inputs for the other neurons in the network.

The network we use is called a Bayesian confidence propagation neural network (BCPNN) [8]; it is a feed-forward neural network where learning and inference are done using the principles of Bayes' law. For the work presented in this paper we use it as a one-layer model [9], although it can be extended to a multilayer network[10]. Such a multilayer network will be required in further investigations of combinations of several variables in the WHO database and has already been successfully applied to areas like diagnosis [11], expert systems [12] and data analysis in paper and pulp manufacturing [13].

The main advantages with BCPNNs, as for many other neural network architectures, are that they are self-organizing and suitable for implementation on parallel computers. They also provide an efficient computational model which performs well on sequential machines. Another advantage with BCPNNs is the simple interpretation of the weights as probabilistic entities. The information stored as the weights in the BCPNN is used here for quantifying drug–ADR dependencies.

This Bayesian neural network has the computational power to consider all links and the ability to highlight potential signals. The network is transparent, in that it is easy to see what has been calculated, and robust, in that valid, relevant results can still be generated despite missing data. This is extremely advantageous as most reports in the database contain some empty fields. The results are reproducible, making validation and checking simple. The network is easy to train; it only takes one pass across the data, which makes it highly time efficient. Searches through the database are done quickly and efficiently using a sparse matrix method. This method utilizes the fact that a relatively small proportion of all possible drug–ADR combinations are actually non-zero in the database.

The Bayesian approach to signal generation

In the WHO database all adverse reactions are reported with a specific drug or set of drugs. A drug is therefore associated with, that is, occurs on the same report as, all ADRs a certain number of times between zero and C (where C is the total number of reports in the database). The number of times a specific drug–ADR combination (c_{ij}) occurs in the database is clearly dependent on the number of times the drug itself is reported throughout the database, as well as the total number of reports of that ADR. The absolute value of c_{ij} is, in itself, far from ideal in predicting the strength of association of a drug–ADR combination. We are in essence looking for values of c_{ij} which are higher than we would expect from the values of both c_i (the number of reports of a specific drug in the database) and c_j (the number of reports of a specific ADR in the database).

For any individual report in the database, there is a certain probability that a specific ADR is listed on it – the "prior probability". If that case report has a specific drug on it, the probability of the ADR now being present could be different – the "posterior probability". If the posterior probability is higher than the prior probability, then the presence of the drug on the report has enhanced the chance of the ADR being present, and the drug–ADR pair are present together in the database more often than expected.

Bayes' law states:

$$P(A/D) = \frac{P(A,D)}{P(D)}$$

This can be rewritten in the form:

$$P(A/D) = P(A)\frac{P(A,D)}{P(A)P(D)}$$

where $P(A|D)$ is posterior probability, the probability of a specific adverse reaction being present on a report given the information that a specific drug is listed on it; $P(A)$ is prior probability, the probability that a specific adverse reaction is present on a report; $P(D)$ is prior probability, the probability that a drug is present on a report; $P(A,D)$ is coincident probability, the probability that both a specific drug and an adverse reaction are present on the same report. Thus the prior probability and the posterior probability are related by a symmetrical factor $[P(A,D)/P(A)P(D)]$.

Mutual information, as defined in information theory [14], measures the amount of information we get about one variable (X) when we have information about the state of another variable (Y), that is, it measures the strength of association between two variables X and Y:

$$I(X,Y) = \sum_x \sum_y P(x,y) \log \frac{P(x,y)}{P(x)P(y)}$$

where x represents a specific state of the variable X, and y represents a specific state of the variable Y.

In information theory all measures of information are logarithmic, so that information from independent events are additive.

If we consider the variables captopril and coughing in the database, both variables are binary; both can have one of two states, either present on a report or not. There are four possible combinations of the states of the two variables, which when all are combined give the mutual information for captopril and coughing. The information component (IC) is the strength of the association between a specific state in each of two variables and is the logarithmic form of the symmetrical factor relating the prior and posterior probability stated previously:

$$\mathrm{IC} = \log_2 \frac{P(x,y)}{P(x)P(y)}$$

Thus there are four ICs which refer to the different combinations of the variables captopril and coughing.

In this paper we are only interested in the strength of the IC between specific drugs and ADRs present on the same report, not the other three possible ICs for this combination of binary variables. For the rest of this paper the IC will specifically refer to this particular combination of states of the drug and adverse reaction, which adds to the robustness and simplicity of the method since only positive reports of drug or adverse reaction need be counted (as well as the total number of reports). When the IC is positive for a drug–ADR association, this implies that the drug–ADR pair is more strongly associated than expected, compared to the c_i and c_j values and the rest of the database, the reverse applies to negative values, and IC values close to zero represent independence between the drug and ADR – that is, the prior and posterior probabilities are the same; additional information about the drug does not change the probability of the ADR being present on a specific case report. We therefore intend to search the database for positive values of IC. In the BCPNN the weight between a neuron in the adverse reaction layer and a neuron in the drug layer is equal to the IC for that specific drug–ADR combination.

There is a "finite" probability of any drug being reported with, that is, suspected of being associated with, any ADR. This probability may be extremely small, so it may never have occurred, much less been reported. The pharmacovigilant community, by various efforts to increase awareness and reporting rates, is trying to obtain as accurate an estimate of this probability as possible. The IC that we calculate is a measure of the strength of association of a drug–ADR combination – as the IC is only calculated on a finite number of reports it is merely an estimate of the real 'IC'; the more reports we have, the more accurate this estimate becomes. In our database the numbers of reports of individual drugs, ADRs, and drug–ADR combinations vary enormously. However, the higher the values of c_i, c_j and c_{ij}, the more accurate an estimate of the IC we have. Thus for every drug–ADR combination, we determine an interval estimate of the IC as a measure of certainty of the value of the IC. The combination of the absolute value of the IC and its interval estimate gives us an estimate of the probability of a specific association between a drug and an ADR based on the spontaneous drug reports in our database. Having highlighted the association, it can then be investigated further using the current signalling procedure in place at the Uppsala Monitoring Centre.

The Bayesian approach is based on the following: an estimation of a prior probability is made. This estimate is then improved when some new information is received by calculating a posterior probability based on both the prior probability estimate and the new information. This process is then repeated and the estimate will be constantly improved as more information is obtained.

As we do not know the "real" probability of $p(A)$, $p(D)$ or $p(A,D)$, we assert a beta distribution [15] for each probability. From these distributions we calculate the "expectation values" and variances of the beta distribution of each variable. The expectation value of each beta distribution is the estimate of the probability. As the counters c_i, c_j, c_{ij} and C increase we calculate new beta distributions for $p(A)$, $p(D)$ and $p(A,D)$, based on the prior distributions and these new counters, and therefore new expectation values and variances for each of the three. These distributions become narrower as we obtain more information (i.e. the variance always decreases). As the counters increase in value, the previous posterior distributions become the new prior distributions, and a new set of posterior distributions can be calculated.

This Bayesian approach allows us to estimate the probabilities, and hence the IC, even for low counter values. The calculation of the variance for $p(A)$, $p(D)$ and $p(A,D)$ as well as the IC provides an indication of the certainty of these probability estimates.

The Gaussian approximation to calculating the variance of a function of many variables allows us to calculate the variance of the information component $[V(\mathrm{IC})]$ from the variances of $p(A)$, $p(D)$ and $p(A,D)$.

Using this method, $V(\mathrm{IC})$ is calculated by:

$$V(\mathrm{IC}) \approx \left(\frac{1}{\log 2}\right)^2 \left[\frac{C - c_{ij} + \gamma - \gamma_{11}}{(c_{ij} + \gamma_{11})(1 + C + \gamma)} + \frac{C - c_i + \alpha - \alpha_1}{(c_i + \alpha_1)(1 + C + \alpha)} + \frac{C - c_j + \alpha - \alpha_1}{(c_j + \alpha_1)(1 + C + \alpha)}\right]$$

where α_1 and α_0 are factors in the beta distribution of $p(A)$ and $p(D)$ and γ_{11} and γ are the corresponding factors for the joint probability $p(A,D)$ [15]. Both pairs of factors reflect our beliefs in the probabilities given by the prior beta distributions. An a priori assumption is made of equal probability distribution for $p(A)$ and $p(D)$, as any probability is as likely as any other without further information; in a beta distribution this corresponds to the constants α_1 and α_0 (where $\alpha = \alpha_1 + \alpha_0$) being defined as: $\alpha_1 = \alpha_0 = 1$. γ_{11} and γ define the joint beta distribution $p(A,D)$. We set $\gamma_{11} = 1$ and define γ (Orre and Lansner, personal communication) by:

$$\gamma = \frac{\gamma_{11}}{p(A)p(D)}$$

such that the IC tends to zero as c_{ij} and C tend to zero, because we assume an independent relationship between a drug and an ADR when we have no reports of the drug or the ADR.

Implementation of BCPNN on the WHO database

All experiments done using the BCPNN followed the same procedure: To calculate the ICs between all drugs and all adverse reactions in the database we needed to calculate c_i, c_j and c_{ij} for all possible combinations. Thus we specified that we wanted to associate all drugs recorded as "suspected" or "interacting" with all adverse reactions, by giving a layer specification to the ANN software, such that one layer contained neurons representing drugs in the database and another layer contained neurons representing adverse reactions. The relevant adverse reactions and drugs were then specified and a counter generated for each. The network was trained by reading from the database and updating these statistical counters. Training and learning in the network occurred during the same run over the whole database and a matrix was generated containing the c_i, c_j and c_{ij} values for the specified drug–ADR

combinations, which could then be further analysed. This matrix was limited in size by the use of the sparse matrix method, which creates the statistical counters as they are required, hence only non-zero counters occur in the database and run times are shortened considerably. Having generated the counters, the ICs and their corresponding 95% confidence limits are then calculated.

In order to generate signals on the basis of ICs and their associated interval estimates, it was important to demonstrate that the ICs increased in value over time for a signal as the data on the particular association increased. Several time scan experiments were done by specifying a particular drug–ADR combination and calculating the ICs and confidence limits at quarterly time intervals. The results were graphed.

From these time scans three examples were chosen to illustrate:

- When a signal of high probability would have been generated on current information compared with the world literature reports cited in MEDLINE (captopril and coughing).
- The behaviour of false-positive signals over time for both a drug–ADR association that has a low c_{ij} value (digoxin and acne) and a drug–ADR association that has a high c_{ij} value (digoxin and rash). Digoxin is one of the most commonly reported drugs in the database. However, digoxin is reported exceptionally rarely with the common adverse reaction "acne", whereas digoxin and the commonly reported ADR "rash" are frequently reported together.

In a routine operation for finding signals, we intend to do quarterly updates. All ADRs and drugs that occur in the latest quarterly production will be selected, and the effect of these newly received case reports on drug–ADR associations throughout the database will be examined. To test this, we selected a test set of case reports, approximately 36 000 from the end part of 1995, to represent a new quarter of reports received at the centre (all later reports were excluded completely from this test), and selected all drugs and ADRs that occurred in this list by doing the search on the whole database, up to but excluding this "test" quarter; we then repeated the scan having added the "new" data set. The ICs and their associated 95% confidence limits were then compared before and after the new information was added. The criterion for a signal was drug–ADR combinations where the lower 95% confidence limit of the IC changed from a negative to a positive value on addition of the test quarter. That is, all drug–ADR combinations where the probability of a relationship between the drug and the ADR based on the spontaneous reports in the database changed from below 0.975 to above, on addition of the test quarter.

Results

Example of early signal detection

Figure 1 shows the time scan obtained when a run was done of captopril (reported as "suspected" or "interacting" drug) and coughing from the first quarter of 1979 to the first quarter of 1996. The IC increases considerably in value over time, as the number of reports of the drug–ADR (c_{ij}) association increases, and as the total numbers of reports of the drug (c_i) and the ADR (c_j) increase, so the interval estimate of the IC decreases, that is, our estimate of the "real" IC becomes more precise. The combination of these two effects is that the lower 95% confidence limit increases in value markedly towards and above zero. As can be seen in Fig. 1, the lower 95% confidence limit crosses above zero at time 81/3, that is, once the reports from the third quarter of 1981 have been added. At this time there were three reports of this association in the database. When this lower 95% confidence limit is equal to zero, this is a very strong statistical association which demands to be investigated pharmacologically, clinically and epidemiologically. An isolated report of this now well-known signal was published in Dutch in July 1983 [16], but the signal was not widely reported in the literature until 1986. It should be noted that the confidence interval estimate of an IC estimate becomes smaller as we base the estimate on more samples and as the IC value stabilizes. A decrease in the confidence interval of ICs as time passes is a property of all drug–ADR time scans. Thus a stabilized positive value IC for a drug–ADR association will imply an ever-increasing likelihood of a real signal as further reports are added to the database.

Examples of false-positive signal avoidance

1. The time scan of digoxin (suspected or interacting) against acne from the first quarter of 1967 to the start of 1996 is shown in Fig. 2. The IC decreases throughout the time scan, because no reports are received of this association – apart from a slight increase after quarter 1988/4 when the combination was reported once. As the associated 95% confidence interval diminishes with the numbers of reports of drug and ADR increase, this makes our IC estimate better and demonstrates the diminishing possibility of a causal relationship between digoxin and acne.
2. When a time scan of digoxin and rash is observed (Fig. 3) the IC increases initially (1968), indicating a trend to a possible association (but with a large 95% confidence interval), but then decreases markedly towards a distinct negative value. The 95% confidence interval also decreases rapidly because of the rate of increase in the number of reports of digoxin, rash and digoxin-rash association. This definite negative IC represents a situation where, although digoxin and rash are

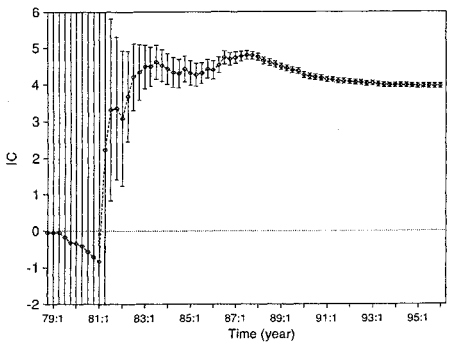

Fig. 1 The change in IC between 1979 to 1996 for the association captopril–coughing. The IC is plotted at quarterly intervals with 95% confidence limits shown

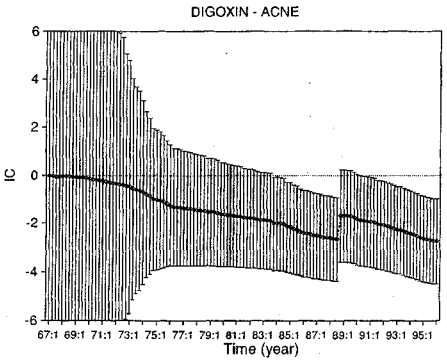

Fig. 2 The change in IC between 1967 to 1996 for the association digoxin–acne. The IC is plotted at quarterly intervals with 95% confidence limits shown

reported together often (high c_{ij}), relative to the values of c_i and c_j joint reporting is not frequent. Thus this association does not stand out in our database as being more common than the generality. The probability of rash being reported on a specific case report with an unidentified drug is not increased if the drug is digoxin. This means that in our database there is no unexpectedly strong association between digoxin and rash. Therefore, this would not be signalled on our criteria.

Quarterly update test

In order to simulate a regular quarterly screening of the database, an examination of the signalling criteria was done using historic data from a 3-month batch of 36 000 reports from the start of 1996, using the procedure described above. In this way a list was generated containing 1004 different drug–ADR associations where the lower 95% confidence limit of the IC estimate crossed above zero as a consequence of the addition of the "test" quarter. This list contained 307 associations of ADR terms in the WHO "Critical Terms List". "Critical" terms are defined as referring to, or possibly being indicative of, serious disease states, and have been regarded as particularly important to follow up. A serious disease is one that may be fatal, life-threatening, causing or prolonging inpatient hospitalization, or resulting in persistent or significant disability or incapacity. Of these 307 associations, 53 concerned "new" drugs, that is, drugs first reported since the start of 1990. These 53 associations were compared with entries for the relevant drugs in the latest editions of *Martindale's Extra Pharmacopeia* (Micromedex healthcare series, volume 93), the *Physician's Desk Reference: Drug Interactions, Side Effects, Indications, Contraindications System TM, May 1997* (*PDR*), and *Reactions Weekly online* (ADIS Press). Of these 53 associations, 12 were not recorded in *Martindale*, *PDR*, or *Reactions* at the time of writing (Table 1).

Whilst the procedure is close to the routine previously used to find important signals, no clinical assessment has been made to exclude confounding drugs or disease (which may account for the relationship between fluvastatin and myocardial infarction, for example). On the other hand, some judgement has been made over the selection of the final 12 associations on the basis that the reported term in the database was notably different from any described in the literature sources used. It is noteworthy that, whilst the association of alendronic acid and oesophagitis was well referenced, the more serious ulceration was a topic of concern and debate at the last annual meeting of the national centres participating in the WHO Programme for International Drug Monitoring, October 1997, Geneva.

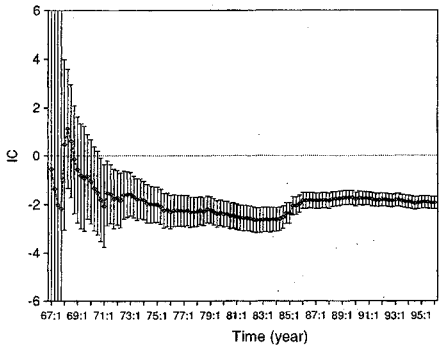

Fig. 3 The change in IC between 1967 to 1996 for the association digoxin–rash. The IC is plotted at quarterly intervals with 95% confidence limits shown

Discussion

Since the instigation of the WHO drug monitoring programme, the potential benefits and need for an automatic signalling system were envisaged [5]. The BCPNN, based on Bayesian statistics and neural network architecture and methods, allows us to find and quantify relationships between two or more data fields, such as a drug and ADR, that differ significantly from the background of inter-relationships in the database. We are thus able to highlight potential signals by the behaviour of a selected IC over time, and have demonstrated that it will be possible to find such relationships at earlier stages in the drug's life than at present. As such it is a suitable tool for the signalling of ADRs.

The limitations of spontaneous reporting of ADRs, from varying degrees of under-reporting, to delays in reporting, to misreporting, to incomplete information,

Table 1 Signals on new drugs (recorded in the WHO database after 1990) and WHO "Critical Terms" identified in test run on data from the end of 1995

Drug	Adverse reaction	Comments[a]
Clarithromycin	Laryngismus	–
	Renal failure acute	–
Losartan	Cardiac failure	–
	Pulmonary oedema	–
	Peripheral ischaemia	–
Alfuzosin	Coma	–
	Angina pectoris	*Martindale* refers to prazosin for adverse effects; chest pain mentioned for prazosin
Sertraline	Arrhythmia	–
Fluvastatin	Myocardial infarction	–
Venlafaxine	Delirium	*Reactions* mentions hypomania in August 1997
Measles, mumps and rubella vaccine	Paralysis	–
Alendronic acid	Oesophageal ulceration	Oesophagitis listed in *Martindale*; one case of oesophageal ulcer reported in *Reactions* in May 1997

[a] In the absence of comments, there has been no mention of the listed reactions in the reference sources

are well understood [17]. Despite the limitations, spontaneous reporting has established itself as an effective tool in drug monitoring, once these limitations are appreciated [18]. The intention behind a signal is to bring a particular drug–ADR combination to the attention of the pharmacovigilance community as quickly as possible on the basis of spontaneous ADR data, so that it can be investigated in more detail to maximize drug safety. A signal is not "right" or "wrong". It is merely a suggestion of a possible problem, aimed at highlighting potential drug problems not discovered in clinical trials. On the basis of our proposed signalling production criteria, we would have produced a signal relating captopril with coughing with considerable confidence on the strength of the reported relationship before the third quarter of 1981. That would have been 2 years in advance of its first mention in the literature. We have also shown that false-positive signals can be avoided.

The quarterly update demonstrated the BCPNN system's ability to highlight potential signals from a large amount of data and verified that computationally we are able to search for IC values through the whole database. This new system is to be used in conjunction with the current signalling process. All drug–ADR pairs will be considered in the quarterly updates. The quantitative certainty of substantial difference from the background of reports in the database attributed to some drug–ADR association will highlight them for the benefit of clinical reviewers. This will emphasize the need for further work on the reported signal. However, a high IC, like strong statistical correlation, does not imply that there is a direct causal relationship between, say, drug and a reaction, it merely suggests the possibility of one.

The environment of our database is dynamic. Many factors may influence the database: new drugs are frequently added to it, new countries start reporting, drug uses and advertising approaches will change. Thus there is a shifting background of associations, which means that ICs and their distributions will change over time as the database gradually evolves, irrespective of additional data affecting any two fields. The problem of getting early *and useful* ADR signals from two million case records is like finding the proverbial "needle in a haystack". Data mining is like a magnet in providing a powerful tool for finding signals. Then the whole database becomes the control, so that any new association highlighted can be contrasted, with a determined level of significance, against the background of all reported information. In this case the "haystack" size becomes an advantage in providing a stable norm for adverse drug report experience.

This BCPNN methodology will continue to be developed. Further investigation of drug–ADR associations will be possible by examining the behaviour of the combined IC of more than two fields, such as ADR, drug and other reported fields like age, gender and drug indication, to arbitrary complexity. Also, other categories of "*C*" than the total database could be used, such as all reports on antibiotics, or all reports on females.

All searches of the database so far have been for drug–ADR associations where the drug has been reported as being "suspected"; reports where the drug has been recorded as concomitant medication have been excluded. In future work investigation will be made on the impact of the drug causality on the possibility of a signal, since clinical/pharmacological preconceptions in drug causality should be avoided in determining new signals, because they reflect biased assessment of the drug–ADR association. There may be drugs which are not known to cause an adverse reaction, and are inappropriately encoded as "other" drugs. However, a large number of false signals would occur, including many for those drugs used frequently in combination with drugs known to cause specific ADRs.

As described above, the test quarterly update was thresholded using a positive value of the lower 95% confidence limit of the IC as the criterion for a reasonably certain signal. Further investigation will be carried out to verify or improve this thresholding level. Although the existing BCPNN is robust in situations where there is missing data, some improvements can be made by inference calculations for the incomplete fields. This could improve the sensitivity of the system. This new methodology is intended to enhance, not replace, the systems that are currently used to detect signals. The value of experts in the field cannot be overestimated, as the qualitative risk-benefit assessment of potential signals is an essential step in the process of their detection and evaluation.

Acknowledgements The authors are indebted to the national centres mentioned in this study, who contributed data. The opinions and conclusions, however, are not necessarily those of the various centres nor of the WHO

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VII

ORIGINAL RESEARCH ARTICLE

Drug Safety 2000 Dec; 23 (6): 533-542
0114-5916/00/0012-0533/$20.00/0

A Retrospective Evaluation of a Data Mining Approach to Aid Finding New Adverse Drug Reaction Signals in the WHO International Database

Marie Lindquist, Malin Ståhl, Andrew Bate, I. Ralph Edwards and *Ronald H.B. Meyboom*

The Uppsala Monitoring Centre, Uppsala, Sweden

Abstract

Background: The detection of new drug safety signals is of growing importance with ever more new drugs becoming available and exposure to medicines increasing. The task of evaluating information relating to safety lies with national agencies and, for international data, with the World Health Organization Programme for International Drug Monitoring.

Rationale: An established approach for identifying new drug safety signals from the international database of more than 2 million case reports depends upon clinical experts from around the world. With a very large amount of information to evaluate, such an approach is open to human error. To aid the clinical review, we have developed a new signalling process using Bayesian logic, applied to data mining, within a confidence propagation neural network (Bayesian Confidence Propagation Neural Network; BCPNN). Ultimately, this will also allow the evaluation of complex variables.

Methods: The first part of this study tested the predictive value of the BCPNN in new signal detection as compared with reference literature sources (Martindale's Extra Pharmacopoeia in 1993 and July 2000, and the Physicians Desk Reference in July 2000). In the second part of the study, results with the BCPNN method were compared with those of the former signalling procedure.

Results: In the study period (the first quarter of 1993) 107 drug–adverse reaction combinations were highlighted as new positive associations by the BCPNN, and referred to new drugs. 15 drug–adverse reaction combinations on new drugs became negative BCPNN associations in the study period. The BCPNN method detected signals with a positive predictive value of 44% and the negative predictive value was 85%. 17 as yet unconfirmed positive associations could not be dismissed with certainty as false positive signals.

Of the 10 drug–adverse reaction signals produced by the former signal detection system from data sent out for review during the study period, 6 were also identified by the BCPNN. These 6 associations have all had a more than 10-fold increase of reports and 4 of them have been included in the reference sources. The remaining 4 signals that were not identified by the BCPNN had a small, or no, increase in the number of reports, and are not listed in the reference sources.

ready in the database. The higher the value of the IC, the more the combination stands out from the background.

From the distribution of the IC, expectation and variance values are calculated using Bayesian statistics. The standard deviation for each IC provides a measure of the robustness of the value. The higher the C_x, C_y and C_{xy} levels are, the narrower the confidence interval becomes. If a positive IC value increases over time and the confidence interval narrows, this shows a likelihood of a positive quantitative association between the studied variables.

In this study we used drug as variable 'x' and adverse reaction as variable 'y'. The term 'association' denotes a drug-adverse reaction combination where the lower 95% confidence limit of the IC value is above 0.

Test of BCPNN Predictive Value in Signal Detection

A retrospective standard quarterly BCPNN database screening was made for the first quarter of 1993. We selected for analysis drug–adverse reaction combinations which in this quarter became positive 'associations' (the lower 95% confidence limit of the IC value changed from a negative to a positive value), and which included new drugs (first reported to the WHO database in 1990 or later). We also selected combinations referring to new drugs, for which the upper 95% confidence limit of the IC changed from a positive to a negative value in the study period. In this paper these are referred to as negative associations.

We then analysed if these positive and negative associations were widely known at the time. This was done by checking if they were listed in the 30th edition of Martindale[5] published in 1993. Martindale was chosen as it is a standard compendium of drug information, available worldwide and containing monographs based on published information.

We subsequently analysed if the selected associations had been strengthened or confirmed over the 7 year period from 1993 to 2000. The associations were therefore checked against Martindale, the July 2000 online edition,[6] and also against the July 2000 online version of the US Physicians' Desk Reference.[6] The latter reference source contains labelling information approved by the US Food and Drug Administration (FDA) and was used as a second reference, because of its comprehensive listing of ADRs, recognised as well as suspected.

All reports in the WHO database are coded using the WHO Adverse Reaction Terminology. This is a hierarchical classification, with the following levels:

- system organ class: a group of adverse reaction terms pertaining to the same body organ system
- high level term: a grouping term for qualitatively similar preferred terms
- preferred term: main terms for coding of adverse reactions
- included term: lower level terms, e.g. synonyms with, or more specific terms than, the preferred terms.

In the analysis we used the WHO preferred terms of the selected associations and compared those against the listed terms or descriptions used in Martindale and the Physicians' Desk Reference.

The following codes were used:

- N = the drug was found in the source but no matching ADR or corresponding high level terms were described for the drug or for the drug group;
- NA = not applicable, i.e. the drug was not found in the source, or was noted as being withdrawn from the market
- Y+ = a high level term pertaining to the 'preferred term' of the ADR, but not the specific ADR, was described for the drug; or, the same ADR, or a high level term, was listed for the group to which the drug was referred to but not listed for the drug itself
- Y = the drug was found and the same ADR, or a synonym, was listed for the drug.

Comparison of New BCPNN Approach to Previous Signalling Procedure

We made retrospective BCPNN scans to identify if, and when, drug–adverse reaction safety signals circulated to national pharmacovigilance centres fulfilled the association threshold criteria.

Table II. Result of an analysis of the July 2000 online versions of Martindale and Physicians Desk Reference[6] for positive and negative associations selected from a BCPNN retrospective screening of drug-ADR combinations entered into the WHO database first quarter 1993

Type of association	Number of associations
Positive	
Associations not listed in Martindale or PDR (N or NA)	29
Associations listed in Martindale or PDR (Y or Y+)	78
Total	**107**
Negative	
Associations not listed in Martindale or PDR (N or NA)	5
Associations listed in Martindale or PDR (Y or Y+)	10
Total	**15**

ADR = adverse drug reaction; **BCPNN** = Bayesian Confidence Propagation Neural Network; **N** = the drug was found in the source but no matching ADR or corresponding high level terms were described for the drug or for the drug group; **NA** = not applicable (the drug was not found in the source, or was noted as being withdrawn from the market); **Y** = the drug was found and the same ADR, or a synonym, was listed for the drug; **Y+** = high level term pertaining to the 'preferred term' of the ADR, but not the specific ADR, was described for the drug; or, the same ADR, or a high level term, was listed for the group to which the drug was referred to but not listed for the drug itself.

Table IV lists as yet unconfirmed positive associations, excluding the 12 on withdrawn drugs. For each there is a short commentary based on a preliminary analysis.

Comparison of New BCPNN Approach to Previous Signalling Procedure

There were a total of 10 drug–adverse reaction combinations from the first quarter of 1993 'level 2' listing which were subsequently signalled in the previous procedure. The result of a BCPNN scan of these, and checks against the June 1999 online version of Martindale[7] and the June 1999 online version of Physicians' Desk Reference[7] are shown in table V. The increase in the number of reports from the first quarter of 1993, to the first quarter of 1999, is also shown in table V. On analysis, 6 of the 10 signals have fulfilled the BCPNN association criteria. The remaining 4 drug–adverse reaction combinations still had no more than 4 case reports for each at the end of the first quarter of 1999. On the other hand, the 6 signals that were BCPNN associations have all had more than a 10-fold increase in number of reports to date.

Four of the 6 signals that passed the associations threshold did so before being circulated within the WHO Programme. Two did not, and, although sumatriptan and confusion became an association in the fourth quarter of 1993, the quantitative strength of the relationship has since decreased.

Discussion

At the start of the WHO International Drug Monitoring Programme in the late 1960s quantitative and statistical methods were proposed for adverse reaction signalling purposes.[8] Because of constraints in computational power these were not realised at the time. Lately, however, there has been a renewed interest in statistical methods applied to signal generation in pharmacovigilance. We are aware of work being done in several countries based on proportional reporting ratios and odds ratios, and, in the US, a Bayesian data mining tool for signal generation has been developed for the FDA.[9]

The assessment of an ADR signalling system is difficult because there is no 'gold standard' for comparison. Also there are different definitions of the

Table III. Predictive value of the Bayesian Confidence Propagation Neural Network in new signal detection[a]

Associations	Signals[b]	Nonsignals[c]	Total
Positive	42	53	95
Negative	2	11	13

a Associations referring to withdrawn drugs are excluded.

b Listed (Y/Y+) in the July 2000 online versions of Martindale and the Physicians' Desk Reference[6] and not listed (N) in the 30th edition of Martindale.[5]

c Not listed (N) in the July 2000 online versions of Martindale or the Physicians' Desk Reference;[6] or listed (Y/Y+) in the 30th edition of Martindale.[5]

N = the drug was found in the source but no matching ADR or corresponding high level terms were described for the drug or for the drug group; **Y** = the drug was found and the same ADR, or a synonym, was listed for the drug; **Y+** = high level term pertaining to the 'preferred term' of the ADR, but not the specific ADR, was described for the drug; or, the same ADR, or a high level term, was listed for the group to which the drug was referred to but not listed for the drug itself.

Table IV. Positive associations identified by the Bayesian Confidence Propagation Neural Network from the first quarter of 1993 which are not listed in the July 2000 online versions of Martindale (MD) or the Physicians' Desk Reference (PDR)[6][a]

Drug name	WHO-ART term	MD 2000	PDR 2000	Ratio of reports (Q1 1999/Q1 1993)	Comments
Insulin ('Humulin')	Therapeutic response decreased	N	N	1.3	These reports suggest that occasionally the therapeutic effect may decrease after some time of use. A minority of reports refers to suspected interactions with other drugs
Ketorolac	Cholelithiasis	N	N	1.0	Only 3 patients, who all simultaneously had several other serious suspected adverse reactions, e.g. pancreatitis, duodenal ulcer, GI haemorrhage, ileus
Ketorolac	Hiccup	N	N	1.3	Hiccup occurred in association with, and probably secondary to, other suspected adverse reactions (e.g. vomiting, ulcer and haematemesis, abdominal pain): probably nonspecific stimulation of the phrenic nerve and not a pharmacological effect
Ketorolac	Peritonitis	N	N	2.5	In all but 1 report peritonitis occurred in patients with intestinal perforation, i.e. as a complication of another suspected adverse reaction, GI ulcer
Ketorolac	Renal tubular disorder	N	N	1.0	Concern over the high incidence of adverse reactions, including acute renal failure, has led to regulatory actions and, in some countries, withdrawal[b]
Ketorolac	Renal tubular necrosis	N	N	9.3	Concern over the high incidence of adverse reactions, including acute renal failure, has led to regulatory actions and, in some countries, withdrawal[b]
Lomefloxacin	Drug level increased	N	N	2.3	These reports refer to signs of – mainly cardiac or nervous system – toxicity. All patients simultaneously used theophylline and the term suggests that during use of lomefloxacin increased blood concentrations of theophylline were found, i.e. a suspected interaction. According to the July 2000 online version of Martindale,[6] lomefloxacin is considered not to interact significantly with theophylline or caffeine
Lomefloxacin	Tolerance increased	N	N	1.3	In these 4 reports no other drugs were recorded, and no other explanation was given
Moxonidine	Angina pectoris	N	NA	3.3	Age and concomitant illness in hypertension patients are associated with a high risk of atherosclerosis and angina pectoris. Several other groups of antihypertensive drugs are known occasionally to cause (increased) angina pectoris. These 22 reports suggest that moxonidine occasionally precipitates or aggravated angina pectoris, that the effect promptly disappears after stopping and that it may also fade when the drug is continued
Nafarelin	Lacrimation abnormal	N	N	1.0	Lacrimation disturbance and xerophthalmia have also been reported to the WHO database with the related drugs buserelin, goserelin, leuprorelin and octreotide
Nafarelin	Taste perversion	N	N	1.4	Disturbances of taste and smell have also been reported to the WHO database with the related drugs buserelin, goserelin, leurporelin and octreotide
Nicotine	Breast enlargement	N	N	2.5	Breast enlargement is reported in 11 pre- or postmenopausal women in 4 countries; 5 patients simultaneously used hormone preparations. In addition, there are 2 reports of men with gynaecomastia during the use of nicotine patches. Perhaps this is a secondary effect to decreased enzyme induction after stopping heavy smoking

Continued next page

Table IV. Contd.

Drug name	WHO-ART term	MD 2000	PDR 2000	Ratio of reports (Q1 1999/Q1 1993)	Comments
Nicotine	Hypercholesterolaemia	N	N	1.3	Reports in 2 countries. A follow up may be interesting
Nicotine	Libido increased	N	N	1.3	Small number of poorly documented cases from a single country
Nicotine	Penis disorder	N	N	1.0	Small number of poorly documented cases from a single country
Nicotine	Sudden death	N	N	1.8	Cause of death not specified. It is known, however, that nicotine may cause serious cardiac arrhythmia. One probable duplicate report
Technetium^{99m} sestamibi	Nausea	N	NA	4.0	Nausea usually occurred as part of a more general reaction after intravenous injection, together with urticaria, myalgia, agitation, headache

a In the study, Martindale and Physicians' Desk Reference were the standards, but for all unconfirmed associations a comprehensive literature search would be indicated.

b July 2000 online version of Martindale.[9]

GI = gastrointestinal; **N** = the drug was found in the source but no matching ADR or corresponding high level terms were described for the drug or for the drug group; **NA** = not applicable (the drug was not found in the source, or was noted as being withdrawn from the market); **WHO-ART** = World Health Organization Adverse Reaction Terminology.

term 'signal'. According to the definition used in the WHO Programme a signal is essentially a hypothesis together with data and arguments, and it is not only uncertain but also preliminary in nature: the situation may change substantially over time.[4,10]

For the purpose of the paper we felt we would achieve a reasonable estimate of the predictive power of the BCPNN tool by checking historical associations identified by the BCPNN against standard reference sources. Martindale has worldwide coverage, recognition and wide availability and was used as a standard for well known, recognised ADRs. The Physicians' Desk Reference, though not international, gives very recent information on drugs. It has a comprehensive ADR listing, generally more inclusive than that of Martindale. However, the Physicians' Desk Reference also includes suspected adverse reactions, whether substantiated or not. We considered an ADR listed in the Physicians' Desk Reference an indication of a possible drug–adverse reaction relationship. Table IV lists the positive associations still not mentioned in the reference sources. These cannot simply be dismissed as 'false positives', since at least some of them may be true signals of ADRs that are not yet established. The reader can draw some conclusions about them in addition to the comments in the table. Several of the associations in table IV raise the point that there may well be alternative explanations, relating, for example, to the way in which the drug is used, or confounding underlying disease. However, the reviewer should not dismiss the drug as causal too readily. Similarly also 'true negatives' might be as yet unrecognised signals.

The length of time chosen for the retrospective check against the literature was not arbitrary, but based on the assumption that 7 years would be sufficient for ADRs to be included in the reference sources, allowing for the maximum reporting for new drugs to have taken place (the Weber effect). We know however that 1 new association appeared in Martindale between 1999 and 2000, and 7 years still may not be long enough. Publishing delay must be considered in the use of these reference sources, but

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work has been done on any of the medical terminologies in use or proposed to determine their relative value in searching for new drug signals.[11]

We found that 44% of the BCPNN signals are strengthened or confirmed in the current reference sources while not mentioned at all in the 30th edition of Martindale (1993).[5] The 84% negative predictive value indicates that combinations not highlighted for review, if not already known, are unlikely to become signals. This indicates that the BCPNN is a valuable tool in the filtering of combinations for clinical review, and that it has the ability to find early signals. The normal methods for assessing the power of a method are difficult to apply to the BCPNN, because of the reasons above.

The BCPNN associations, which are not yet reported in the current literature, are included in table IV. If these associations were to emerge in the literature in the coming years, it would increase the positive predictive value of the BCPNN.

The BCPNN has the power to analyse signals further.[3] We are developing its use for looking at complex variables to see whether parameters such as gender, age, and other drug use increase the strength of association, and whether 'syndromes' of reported terms are present. However, as with any subdivision of data, a very large amount is necessary initially, to attain statistical significance in subsets. This is a major advantage of using the large pooled WHO database, and we are trying to maximise this potential.

The BCPNN is not a panacea for drug safety monitoring. The drug–ADR combinations which reach statistical significance, do so only in comparison with the background experience of 2 million case reports. This is particularly important for commonly reported ADRs, which, however serious, would not reach significance until the quantitative experience for a drug and such an ADR is excessive. Sumatriptan and confusion is an example of this issue, passing the BCPNN association threshold after being circulated as a signal.

We have stressed[1] that although the BCPNN approach has its limitations and is not a substitute for expert review, it does have a place particularly where large volumes of data are involved. It is reassuring, however, that all signals identified in the previous system that went on to become frequently reported in the WHO database were also identified in the retrospective BCPNN analysis.

Conclusions

This retrospective evaluation of the new statistical signalling tool used at the Uppsala Monitoring Centre has shown that the BCPNN has a high predictive value, and that it can identify early signals of adverse drug reactions. It has further strengthened our view that the BCPNN will provide a useful tool in international pharmacovigilance.

To our knowledge, this is the first time an ADR-signalling method has been subjected to a rigorous performance analysis. The lack of a 'gold standard'. and the dynamic nature of signal finding with time make conventional validation methods difficult to apply.

Acknowledgements

The authors are indebted to national centres contributing data to the WHO International Drug Monitoring Programme. The opinions and conclusions, however, are not necessarily those of the various centres nor of the WHO.

Disclaimer

The WHO database contains summary reports of individual suspected adverse reactions to medicines, received from national centres in countries participating in the WHO International Drug Monitoring Programme. No causality assessment is made at the Uppsala Monitoring Centre, but if such an assessment has been made by the national centre submitting the report, this is stored in the database. Since these reports constitute suspicions of adverse drug reactions, further investigation and research is needed for a full interpretation of the data.

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VIII

Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: data mining study

David M Coulter, Andrew Bate, Ronald H B Meyboom, Marie Lindquist, I Ralph Edwards

Abstract

Objectives To examine the relation between antipsychotic drugs and myocarditis and cardiomyopathy.
Design Data mining using bayesian statistics implemented in a neural network architecture.
Setting International database on adverse drug reactions run by the World Health Organization programme for international drug monitoring.
Main outcome measures Reports mentioning antipsychotic drugs, cardiomyopathy, or myocarditis.
Results A strong signal existed for an association between clozapine and cardiomyopathy and myocarditis. An association was also seen with other antipsychotics as a group. The association was based on sufficient cases with adequate documentation and apparent lack of confounding to constitute a signal. Associations between myocarditis or cardiomyopathy and lithium, chlorpromazine, fluphenazine, haloperidol, and risperidone need further investigation.
Conclusions Some antipsychotic drugs seem to be linked to cardiomyopathy and myocarditis. The study shows the potential of bayesian neural networks in analysing data on drug safety.

Introduction

The antipsychotic drug clozapine has been reported to cause myocarditis or cardiomyopathy.[1,2] other drugs in the same therapeutic class may share similar toxicity. Data mining of a large database of suspected adverse reactions can find such new signals. As part of the World Health Organization's programme for international drug monitoring, national pharmacovigilance centres in 60 countries report adverse reactions to a central database maintained by the Uppsala Monitoring Centre in Sweden.[3]

To analyse this large database an approach using bayesian statistics implemented in a neural network architecture has been developed. The approach is able to look for new adverse reactions from combinations of drugs and also to identify previously unknown patterns, such as risk factors for adverse events with specific drugs—for example, patient age, underlying diseases, and drug interactions. We used the bayesian approach to look for cardiac effects related to antipsychotic drugs in the WHO database of adverse reactions.

Methods

We used the bayesian confidence propagation network, which implements bayesian statistics in a neural network architecture, in the WHO database. The network was used to test reports of clozapine and all other antipsychotic drugs suspected of causing myocarditis or cardiomyopathy against a background of all reports in the database. We calculated the strength of dependency between a drug (or drug group) and adverse reaction using a logarithmic measure of disproportionality called the information component.[4] An association between the drug and the reaction was considered significant if the information component minus 2 standard deviations was positive. The value of the information compo-

Centre for Adverse Reactions Monitoring and Intensive Medicines Monitoring Programme, Department of Preventive and Social Medicine, University of Otago, Dunedin, New Zealand
David M Coulter *head*

continued over

BMJ 2001;322:1207–9

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Details of the methods are available on the BMJ's website

Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, S-75320 Uppsala, Sweden
Andrew Bate *programme leader, signal research methodology*
Ronald H B Meyboom *medical adviser*
Marie Lindquist *head of research and development*
I Ralph Edwards *director*
Correspondence to: I R Edwards ralph.edwards@who-umc.org

nent is based on the number of case reports for drug(s) "x" (Cx); the number of case reports of adverse reaction(s) "y" (Cy); the number of reports of the specific combination (Cxy); and the total number of reports (C). Further details of the methods are available on the *BMJ*'s website.

Results

Myocarditis and cardiomyopathy were reported rarely as suspected adverse drug reactions, accounting for less than 0.1% (2121) of almost 2.5 million reports. The table shows the antipsychotic drugs reported to have caused either myocarditis or cardiomyopathy on two or more occasions. Clozapine has a much higher information component than other antipsychotics together and than the general background database. Most reports predated recent publicity about clozapine. The statistical associations of clozapine with myocarditis and cardiomyopathy individually were also significant. The group of other antipsychotics drugs was significantly associated with myocarditis and cardiomyopathy together (table) and individually compared with the general database, although these associations were much weaker than for clozapine.

Chlorpromazine, lithium, and fluphenazine were significantly associated with myocarditis and cardiomyopathy. The 16 cases with risperidone were not more than expected given the high overall reporting of the drug in the database. Chlorpromazine was also significantly associated with myocarditis and cardiomyopathy separately. Lithium, fluphenazine, and risperidone were significantly associated with cardiomyopathy but not myocarditis. In contrast, haloperidol was associated with myocarditis but not cardiomyopathy.

Discussion

Our analysis suggests that antipsychotic drugs other than clozapine may be associated with myocarditis and cardiomyopathy. The findings may have three explanations. The conditions for which antipsychotics are used could be risk factors for myocarditis and cardiomyopathy; the antipsychotic drug could be an innocent bystander; or there may be a causal association. Despite patients taking clozapine being intensively monitored for agranulocytosis, the former two are unlikely explanations for the strong relation between clozapine and myocarditis and cardiomyopathy.[5] The association with clozapine cannot be explained by coprescribed drugs. In some of the cases in the other antipsychotics group the patient was also taking clozapine or non-antipsychotic drugs known to cause myocarditis or cardiomyopathy. However, standardised clinical evaluation[6] shows that there were sufficient cases with adequate documentation and apparent lack of confounding to constitute a signal for cardiomyopathy or myocarditis in the other antipsychotics identified above.

Antipsychotic drugs (anatomical, therapeutic, chemical drug classification N05A) for which two or more reports of cardiomyopathy or myocarditis have been registered in WHO database

Drug	No of case reports	Total No of reports for drug	Information component	Information component −2SD
Clozapine	231	24 730	3.34	3.14
Other antipsychotics*	89	60 775	0.71	0.40
Lithium	17	6 315	1.45	0.76
Risperidone	16	10 746	0.69	−0.01
Chlorpromazine	14	5 386	1.38	0.63
Haloperidol	11	8 257	0.53	−0.31
Fluphenazine	8	2 242	1.59	0.62
Olanzapine	8	6 135	0.48	−0.48
Thioridazine	5	3 973	0.41	−0.77
Pericyazine	2	317	1.23	−0.45
Pimozide	2	536	1.02	−0.65
Quetiapine	2	709	0.88	−0.79
Trifluoperazine	2	1 703	0.26	−1.41
Zuclopenthixol	2	623	0.95	−0.72

*All antipsychotic drugs other than clozapine.
In this table a single case report is counted for more than one drug adverse reaction combination if there are two or more suspected antipsychotic drugs in that case report.

What is known on this topic

Clozapine has been reported to be associated with myocarditis and cardiomyopathy

What this study adds

The WHO database shows that clozapine is significantly more frequently reported in relation to cardiomyopathy and myocarditis than other drugs

Myocarditis and cardiomyopathy were also particularly associated with chlorpromazine, lithium, fluphenazine, risperidone, and haloperidol

These associations need to be investigated further to establish whether they are causal

Data mining is a useful tool in pharmacovigilance

Choice of methods

Our results were obtained by a data mining approach. A concern had been raised about myocarditis with clozapine. We then examined the association between the group of antipsychotics with myocarditis or cardiomyopathy. Having discovered a quantitative association between the antipsychotics group and cardiomyopathy and myocarditis, we investigated individual antipsychotic drugs and then performed a case by case analysis. Our study shows that data mining can be used successfully to detect signals of adverse reactions in the WHO database.

Our results could have been shown using a simpler method. However, the simpler methods rely on someone deciding to look for an association.[7] A data mining approach that routinely looks for associations between all possible combinations of drugs and adverse reactions is computer intensive (hence the use of a neural network). However, it increases the objectivity of signal detection by introducing an effective quantitative filtering step before clinical analysis.[8] We believe that this is enormously beneficial.

Implications

The summaries of case histories in the database do not allow us to draw definite conclusions about the likelihood of the possible causes of the associations we observed between antipsychotic drugs and myocarditis and cardiomyopathy. Adverse drug reactions are

greatly underreported worldwide. Further study is needed to determine if antipsychotics other than clozapine cause myocarditis or cardiomyopathy, particularly lithium, chlorpromazine, fluphenazine, haloperidol, and risperidone, and to consider the comparative risks and effectiveness of antipsychotics. This is especially important given the recent finding that older and newer drugs have similar efficacy.[9] Antipsychotic drugs should also be considered in unexplained sudden deaths in psychotic patients.

We thank the national centres that contribute data to the WHO international drug monitoring programme. The opinions and conclusions, however, are not necessarily those of the various national centres or of the WHO. Roland Orre was central in developing the bayesian confidence propagation neural network as a routine tool for signal detection in the WHO database of drug adverse reactions.

Contributors: DMC suggested the study and made a provisional investigation of the data, AB and IRE planned and designed the study; AB carried out the study; and IRE, AB, and ML evaluated the results. RHBM drafted the first report of the study, AB and IRE wrote the paper, and all authors contributed to modifying the manuscript and the final editing of the paper. IRE is the guarantor.

Funding: None.

Competing interests: None declared.

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(Accepted 20 February 2001)

IX

ORIGINAL RESEARCH ARTICLE

Drug Invest. 8 (2): 73-80, 1994
0114-2402/94/0002-0073/$04.00/0

New Pharmacovigilance Information on an Old Drug

An International Study of Spontaneous Reports on Digoxin

M. Lindquist,[1] *J. Sanderson*,[2] *C. Claesson*,[3] *J.-L. Imbs*,[4] *A. Rohan*[5] and *I.R. Edwards*[1]

1 WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden
2 IMS International, London, England
3 National Corporation of Swedish Pharmacies, Stockholm, Sweden
4 CHRU Hôpital Civil, Strasbourg, France
5 Adverse Drug Reactions Advisory Committee, Department of Community Services and Health, Canberra, Australia

Summary

Suspected adverse drug reactions for digoxin from Australia, France, Germany, Sweden, the UK and the US, which were reported to the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring since 1968, were examined for qualitative and quantitative differences between countries. Intercontinental Medical Statistics (IMS) data on drug utilisation and demographic information were used to explain a much higher reporting of suspected reactions from Australia and a later peak of occurrence with age in France. Australia has a greater number of elderly patient visits to doctors resulting in a prescription, but it is unclear whether this is due to a greater number of patients taking digoxin or to more frequent prescriptions. In France, doctors used higher doses of digoxin in the over 80 years age group than in other countries, which may account for more dose-related effects.

The primary aim of the World Health Organization (WHO) International Drug Monitoring Programme, established 25 years ago, is to generate the earliest possible signals of new drug adverse reactions. Retrospective studies have shown that indications of new suspected adverse drug reactions (ADRs) were often reported to the WHO database before being published in the medical literature. In some instances there were well documented case reports of possible ADR associations in the database that had not been published.[1,2]

Although the spectrum of adverse reactions to many drugs in use is well established, it is clear that there are differences in reporting patterns in different countries.[3] This study analyses spontaneous ADR reports by combining the information available in the WHO database with relevant drug utilisation and demographic data.

By looking at the total information available for

digoxin, which is a drug registered worldwide and which has been used for a long time, an evaluation can be made regarding the influence of different parameters on reporting, over time and in several countries.

Materials and Methods

Using a common recording format, spontaneously reported cases of suspected adverse reactions from the current 38 member countries of the WHO Collaborative Programme for International Drug Monitoring are stored in a database maintained by the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden.

The data forwarded to the centre is heterogeneous with respect to a variety of factors, such as causality assessments performed, which may lead to the exclusion of some reports being forwarded and variation in the drugs regarded as suspect; some countries only forward drug/ADR associations sent to them directly, excluding those submitted via the pharmaceutical industry.

The database at present contains well over a million individual case records, thus providing a valuable source of ADR information.

The WHO Database

The information transferred in a WHO case report consists of *administrative data* [reporting country, national identity (ID) number, source of report, type of report], *patient data* (age, gender, outcome of reaction), *ADR data* (description of reaction, date of onset), *medication data* [drug(s), dosage regimen, route of administration, treatment dates, indication for drug use], and *additional information* (dechallenge, rechallenge, predisposing/contributing factors, and causality assessment made by the national reporting centre). The minimum information required for acceptance of a report is reporting country and ID, a reaction and a drug.

Drugs can be listed as suspected of having caused the reaction, as interacting, or as 'other' (concomitant medication). The reactions are recorded according to the WHO Adverse Reaction Terminology, which was developed at the start of the international drug monitoring programme.

Information regarding suspected adverse reaction reports for all brands of digoxin from a total of 2832 patients (in Germany a single brand name included acetyldigoxin in one of its formulations) was taken from the WHO database. These were all reports concerning suspected digoxin adverse reactions received from 1968 up to June 1992 from Australia, Germany, Sweden, the UK and the US. Data from France were available from 1983, but excluded reports to the national centre through the pharmaceutical industry. The 6 countries were selected to represent different, well established national reporting systems that had submitted a large number of digoxin reports.

Drug Utilisation Data

Drug utilisation data was obtained from Intercontinental Medical Statistics (IMS) International and the National Corporation of Pharmacies in Sweden for the years 1986 to 1992.

IMS have been collecting data on drug use for many years in the major markets of the world, and their database contains the only internationally comparable data relevant to the problem of providing a valid denominator, with the exception of ex-manufacturer sales.

The data collected by IMS are of two types: (a) census audits of drug sales, and (b) continuing studies of disease and therapy. In these latter studies, selected panels of doctors [general practitioners (GPs) in this study] record all data on prescriptions (including patient data, diagnoses and prescribed products) for a specified period (usually 5 to 7 days). Each doctor records data no more frequently than 4 times per year. The data are then analysed and statistically projected using methods agreed by the International Pharmaceutical Research Group and European Pharmaceutical Research Association (for details see Wetherell and Sanderson[4]) to reflect the total relevant doctor and patient populations at the lowest level of stratification possible.

Table I. Digoxin average daily dose by age group in Australia, France, Sweden and the UK

Age (y)	Average daily dose (mg)			
	Australia	France	Sweden	UK
40-49	0.25	0.24	0.24	0.22
50-59	0.26	0.25	0.23	0.19
60-69	0.21	0.25	0.21	0.17
70-79	0.19	0.25	0.18	0.15
80-89	0.15	0.24	0.16	0.14
90-99	0.15	0.24	0.14	0.10

Such data were used for the estimation of average daily doses of digoxin in Australia, France, and the UK (table I). This information was not available from Germany and the US. The samples, while not truly random, are thought to be representative of average general medical practice.

For Sweden, the analogous information was obtained from the National Corporation of Pharmacies Diagnosis and Therapy Survey. These data are taken from the prescriptions written by a continuously rotating sample of practising physicians in Sweden. Each year 2000 out of 18 000 eligible doctors participate in the study for 1 week.

Population Figures

The population figures were taken from the 1988 version of PC Globe, a publicly available computer software program providing international demographic data, including population statistics by age and gender.

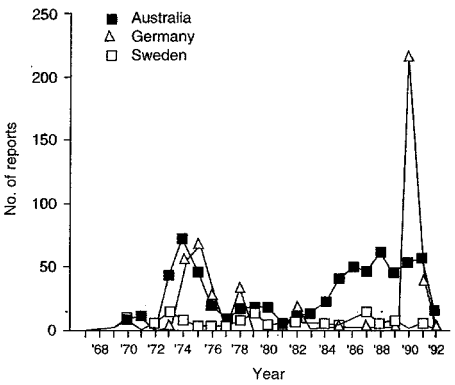

Fig. 1. Number of digoxin reports by year.

The digoxin ADR reports from the 6 countries were analysed for the following parameters: secular trend (numbers of reports/year [fig. 1]), concomitantly reported drugs as stated on each report, type of reaction and outcome (table II), source of report, and digoxin dose (in mg/day).

The total reports for each country were allocated to decade age bands (fig. 2); thereafter the absolute numbers were corrected for population size, divided into the same age bands for each country (fig. 3). These figures were then compared with the reporting rates for all drugs in the 6 countries (fig. 4).

Drug utilisation data were analysed for number of visits to GPs and doses used, within the same age groups as used for the ADR data.

A ratio of the chances of a person being over 70 years of age, being on digoxin and visiting a doctor compared with the populations in the different countries aged over 70, is given in table III.

Results

Australia had the second highest total number of digoxin ADR reports after the US (total number of digoxin reports – Australia: 665; France: 181; Germany: 497; Sweden: 137; UK: 142; US: 1210). In all countries there was an increase in the reporting of digoxin ADRs with age, reaching a peak in all countries except France in the 70- to 79-year-old age group. In France, this peak occurred between 80 and 89 years (fig. 2).

Table II. Outcome distribution (%) of digoxin ADR reports in Australia, France, Germany, Sweden, the UK and the US

Outcome	Australia	France	Germany	Sweden	UK	US
Recovered	46.4	69.0	30.6	36.5	40.8	32.0
Recovered with sequelae	1.1		0.4	0.7		5.0
Not yet recovered	26.2	11.6	1.8		12.0	8.1
Died – due to ADR	5.5	1.7	1.6	11.0	19.7	12.9
Died – drug may be contributory	3.0	5.0	0.2			1.5
Died – unrelated to drug	0.5	4.4		3.7	1.4	0.5
Unknown	17.3	8.3	65.4	48.1	26.1	40.0

Abbreviation: ADR = adverse drug reaction.

Digoxin ADR Reports in the Elderly

The number of Australian digoxin ADR reports in the elderly, expressed as numbers of reports per million inhabitants in the different decade age groups, was greatly in excess of the other countries, and was consistent over time (fig. 3).

The corresponding rates for all ADR reports from the 6 countries are shown in figure 4. Whilst Australia had the highest reporting rate in the elderly, this was by no means as marked as that observed for digoxin. From these data, therefore, 2 pharmacovigilance phenomena were considered further: (a) the apparent excess of Australian digoxin reports in the elderly, and (b) the older age peak of digoxin reporting in France.

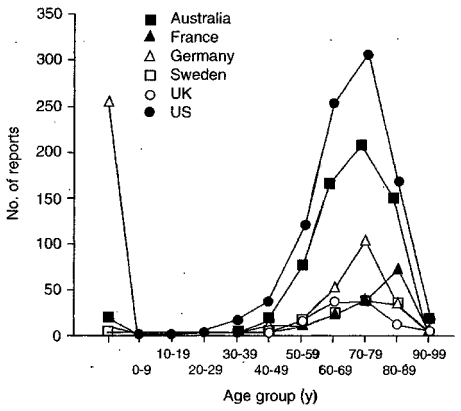

Fig. 2. Number of digoxin reports by age group.

In Australia, the average doses taken by elderly patients with suspected ADRs were: 0.24mg (70 to 79 years), 0.22mg (80 to 89 years) and 0.15mg (90 to 99 years). However, in a quarter to one-half of the patients in these age groups, the doses were either not reported or were uninterpretable.

A review by the French national centre of 26 patients, 90 years of age and over, who had adverse events plausibly related to digoxin, showed that they were prescribed a mean dose of 0.19 mg/day (personal communication).

Secular Trend Analysis

The secular trend analysis of the digoxin reports showed that in Australia and Germany there was an increased reporting frequency during the period 1973 to 1974 (fig. 1). Interestingly, the peaks of reports in Australia and Germany were of apparently less severe reactions.

In Australia, following a decline in the late 1970s, the reporting frequencies again increased starting in the mid-1980s. Over the years, digoxin reports constituted on average 1.2% of all Australian reports (with a maximum of 4.6% in 1974 and between 1 and 1.3% during 1986-1991), whereas in the other countries, the average percentage ranged from 0.1% (UK) to 0.64% (Germany). The increase in reporting in Australia in the 1980s coincided with an increase in the number of outcomes described as 'not yet recovered' at the time of reporting.

Suspected Concomitant Medication

From 1983 onwards, the number of drugs per report that were suspected of causing the adverse reaction (digoxin plus any concomitant medication also reported as suspect) increased in Australia to reach an average of 4.5 drugs in 1990, compared with the averages in previous years, which ranged from 1 to 2.7 suspect drugs per report.

Drugs also commonly listed as suspected were: furosemide (notified in 154 out of the total of 665 reports), followed by potassium (97 of 665), captopril (51 of 665), quinidine (40 of 665), and enalapril (35 of 665). No similar increase in the number of suspect drugs was seen in the other countries.

Organ System and Patient Outcome Analysis

In the total of 665 Australian patient reports, 1398 reactions were mentioned. Grouped by Organ System Class, the most frequently reported reactions were gastrointestinal (356), dermatological (176), general (152), and heart rate and rhythm disorders (130). In Australia, the gastrointestinal/heart ratio was 2.7, whereas in the other countries this ratio ranged between 0.5 (Sweden) and 1.5 (Germany). These differences in suspected ADR report types were persistent over time.

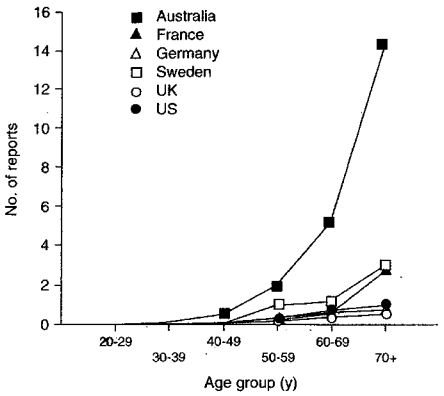

Fig. 3. Number of digoxin reports per million inhabitants by age group.

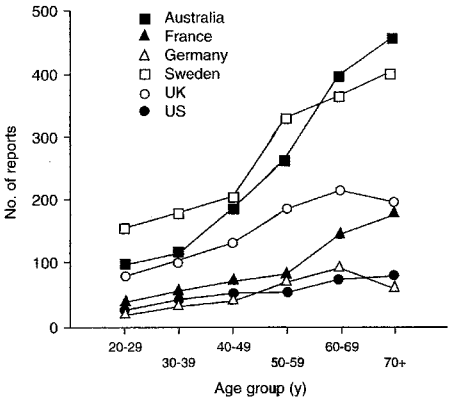

Fig. 4. Number of adverse drug reaction reports per million inhabitants by age group.

The digoxin ADR reports were analysed for patient outcomes (table II). Apart from those mentioned above, there were similar differences in outcome reported over the years.

Reporting Source Analysis

In Australia, France, Germany and Sweden, hospitals were recorded as the main reporting source (Australia 65%, France 89%, Germany 36%, and Sweden 71%). Only in the UK were GPs the most frequent reporters (twice as many reports as hospital reports), whereas in Australia GPs accounted for only 15% of the reports (one-quarter of the number of hospital reports). A similar ratio applied to Sweden, and in France and Germany the hospital reports far outweighed the GP reports.

The average daily doses recorded in the samples taken from IMS and the National Corporation of Pharmacies statistics (table I) showed that the doses used in the 40- to 49-year-old age group ranged from 0.22 to 0.25mg. In all countries (except France, where the dose was 0.24mg even in the very elderly), the average daily dose was reduced with age to between 0.1 and 0.15mg.

Table III. Doctor visits in connection with digoxin use in the elderly in Australia, France, Germany and the UK

	Australia	France	Germany	UK
Population >70 years (%)	9.5	13.9	14.8	14.5
No. in sample of digoxin users >70 years (%)	70.4	73.3	68.9	71.4
RR of being on digoxin and visiting a GP in >70-year age group	7.4	5.3	4.7	4.9

Abbreviations: GP = general practitioner; RR = relative risk.

Combining the population statistics and the IMS drug utilisation figures provided a 'relative risk' of being on digoxin and visiting a GP in the 70 years and over age group (table III).

Discussion

The ADR data viewed against demographic data brought out differences between the countries. The main findings were a consistently higher reporting rate of digoxin ADRs in the elderly in Australia, and the reporting peak occurring in the 80- to 89-year-old age group in France, in contrast to the other countries.

The use of population data as a denominator clearly provides a different picture than actual drug use in different age groups. However, this latter parameter was only available from samples of prescribers, and it was deemed inappropriate to project from such samples to overall sales figures per country.

Drug Utilisation Data

Drug utilisation data, for a contemporaneous time period to the ADR reports, showed that France was the only country where the average daily dose of digoxin did not reduce with age. This provides a plausible explanation for the higher ADR reporting frequency in the very elderly. This is supported by the somewhat lower but still high mean dose in the 90-year-old and over patients in France suspected of digoxin-related ADRs.

In Australia too, there were higher mean dose levels reported in patients with ADRs between 70 to 89 years.

The pharmacokinetic changes, known to occur in the elderly, imply the need for dose reduction in order to avoid dose-dependent adverse reactions.[5] The most frequently reported digoxin reactions in France were heart rate and rhythm disorders and gastrointestinal disturbances, which are often dose-related.[5] It is possible that an historical view of the data from other countries may have revealed other relationships between drug use and suspected ADRs, but this was not investigated in the present study.

Drug utilisation data indicated that there were more GP visits resulting in a prescription in the over 70-year-old age group in Australia than in other countries. However, it is not clear whether this means that there were more patients on digoxin or that those receiving the drug visited the doctor more frequently.

Changes in Reporting over Time

A review of the changes in reporting with time showed few changes apart from a reporting peak during the period 1973 to 1975 for Australia and Germany, which is possibly explained by a general concern at that time over the risk of ADRs with digoxin in connection with the reformulation of an old product into one that was not bioequivalent.[6,7]

From the mid-1980s the number of reports again increased in Australia. This may be explained by an emphasis on the sensitivity of signal generation in the Australian report evaluation, whereby all drugs with a reasonable time relationship to the reaction were recorded as 'suspected'. From 1968 onwards, Australia had considered the highest number of drugs as suspect per report, together with France (both about 2.5 on average). Furthermore, the number of suspected drugs increased in Australia from 2.7 in 1983 to 4.5 in 1990. The reporting of multiple drugs in this way increases the

sensitivity of spontaneous reporting as a signalling system, but decreases specificity. Possible drug interactions are also more likely to be recognised; consideration of all drugs mentioned in a report is essential if potential interactions are not to be missed.

Further investigations of drugs included in the digoxin reports might therefore yield additional information regarding interactions.

Serious Adverse Reactions and Outcome

The high ratio of gastrointestinal to heart rate and rhythm reactions in Australia, in addition to a higher proportion of skin reactions than in any of the other countries, suggests that less serious and well known digoxin reactions were also reported.

In many countries, doctors are encouraged to report only new and/or serious adverse reactions to old drugs, while in other countries, health professionals are left to report anything they feel may be relevant. This difference in philosophy could be the reason for some of the differences in the reaction patterns observed between the countries.

The seriousness of the reported reactions as indicated by outcome remained consistent quantitatively over the years and showed that there was a lower proportion of reported deaths in Australia than in the UK, but higher than in France and Germany. This again may be due to differences in reporting practices. Australia had the highest proportion of cases recorded as 'not yet recovered' at the time of the report. Some of these could result in death, but the frequency of the use of 'not yet recovered' as an outcome code may reflect very prompt reporting of adverse reactions, whether they were serious or not.

Another factor which may reflect on both outcome and seriousness is the origin of the report. The UK and the US were the only countries in which hospital reports were not the major source. In the US, the reporting of digoxin followed the general pattern in that country of a majority of reports being submitted by drug manufacturers. In the UK, hospital reports accounted for only 9.2% of the reports compared with 21.8% for GPs. The figures for the UK are, however, uncertain, since more than 60% of the reports did not give a source, although a high proportion of the deaths (28%) were reported from hospitals, as might be expected.

The relatively high proportion of deaths reported in the UK (19.7%) may be related to that country's policy of encouraging reporting of only the more serious ADRs to well established drugs.[8]

Digoxin Dose and ADR Reports

The dose of digoxin given on the ADR reports would have provided important information. Unfortunately, this information was commonly given as number of dosage forms/time, in countries where more than one dosage form was available. In other instances, the dose was clearly inaccurate (for example 125mg daily). Thus, complete analysis has been impossible.

One important conclusion derived from this study is that all details of the patient – the drugs used, the suspected adverse reaction, and the clinical state of the patient - including the indications for the drugs used, should always be reported. Renal function and the extent of the use of digoxin plasma concentrations to monitor the reported patients are unknown, and may influence some of the differences seen.

The data presented indicate that France has an above average frequency of ADRs in the very elderly, which may be related to a failure to reduce digoxin dose in those patients. Since these reports contain a relatively high number of patients with arrhythmias, this may be an important pharmacovigilance signal.

The Australian situation is less clear. A generally high level of reporting (even higher with digoxin), and the inclusion of a greater proportion of gastrointestinal reactions suggests a greater awareness by professionals in Australia, which might increase reporting rates compared with those of other countries. It is also clear that the inclusion of more suspected drugs from the mid-1980s to increase signalling sensitivity might lead to a greater and

possibly even excessive inculpation of digoxin. On the other hand, the possibility that more elderly patients could have been prescribed digoxin than in the other countries merits further consideration. In Australia, higher doses seem to be related to ADRs occurring in the elderly but, generally, lower doses were prescribed in keeping with the other countries.

Conclusions

We have demonstrated that differences between countries can be examined using international ADR information, drug utilisation data and demographic statistics. New pharmacovigilance information has been produced, and it seems likely that at least one important drug safety issue has been raised relating to dosage of digoxin in elderly patients in France.

The WHO database contains very heterogeneous data, both in relation to the original report and to national analysis. We are also very much aware of the deficiencies of routine spontaneously reported ADR data, and drug use data based on a small selected cohort of prescribers. This paper has indicated just some of the ways in which these factors may affect conclusions drawn from a superficial analysis of the data.

The views expressed in this paper are the authors' own and do not necessarily reflect those of the WHO, IMS International or any of the other sources of data.

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Correspondence and reprints: Prof. *Ralph Edwards*, WHO Collaborating Centre for International Drug Monitoring, S-751 03 Uppsala, Sweden.

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Pharmacology & Toxicology
ISSN 0901-9928

How Does Cystitis Affect a Comparative Risk Profile of Tiaprofenic Acid with Other Non-Steroidal Antiinflammatory Drugs? An International Study Based on Spontaneous Reports and Drug Usage Data

The ADR Signals Analysis Project (ASAP) Team: Marie Lindquist[1], Monica Pettersson[1], Ivor Ralph Edwards[1], Joel H. Sanderson[2], Norman F. A. Taylor[2], A. Peter Fletcher[2] and Jens S. Schou[3]; and Ruth Savage[1]

[1]The WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden, [2]IMS International, London, UK and [3]Department of Pharmacology, University of Copenhagen, Denmark

(Received October 28, 1996; Accepted December 11, 1996)

Abstract: Series of well-documented case reports strongly suggest a causal association between tiaprofenic acid and a form of aseptic cystitis, which can cause serious and long-term morbidity if the drug is not withdrawn promptly. These findings are supported in the Australian and UK spontaneous reporting data-bases. Using sales data as the denominator, a comparison of NSAIDs in the WHO drug monitoring data-base indicates that the reaction is specific to tiaprofenic acid and cannot be accounted for by changes in reporting patterns in certain countries or years. Delayed recognition is an important feature of this reaction and possible reasons for this are discussed. Comparison of the risk profiles of seven NSAIDs indicated that tiaprofenic acid had the poorest risk profile, compared with NSAIDs of similar efficacy, when cystitis reports were included. The results suggest that combining spontaneous reports, classified according to severity, with sales data may enhance the ability of drug monitoring data-bases to contribute to risk benefit appraisals.

Tiaprofenic acid is a non-steroidal propionic acid derivative (NSAID). It is indicated for the treatment of various arthropathies, other musculoskeletal disorders and post-operative and post traumatic pain. It was first released in the northern hemisphere in 1982, and until 1991, when it was first marketed in Australia, its adverse effect profile was thought to be similar to NSAIDs in general. Series of case reports and spontaneous reports over the last four years have now strongly suggested an association between tiaprofenic acid and chronic aseptic cystitis.

The first report of an association between tiaprofenic acid and cystitis appeared as a case series in the British Medical Journal in 1991 (Ahmed & Davison 1991). A Medline search in November 1995 revealed four further case series, all published in 1994, from the United Kingdom (Mayall *et al.* 1994; Harrison *et al.* 1994), Australia (O'Neill 1994) and Canada (Greene *et al.* 1994). The total number of patients in all the case series was 32, comprising 27 females and five males with an age range of 47 to 83 years. Only three patients were less than 60 years old.

All patients experienced distressing symptoms of cystitis, over prolonged periods, which did not respond to conventional treatments. Symptoms included frequency, dysuria, nocturia and suprapubic pain. Investigations revealed sterile pyuria, proteinuria and microhaematuria and, unless there was ureteric involvement, a normal upper urinary tract after intravenous urography, but often a small irregular bladder. Cystoscopic examination revealed severe generalised mucosal inflammation. O'Neill (1994) described the typical histopathological features of the bladder biopsies in his series as acute on chronic inflammation with mucosal erosion, submucosal oedema and congestion with a dense mononuclear inflammatory cell infiltrate, and lymphoid follicles in some cases extending into the muscle layer. Mayall *et al.* (1994) also noted the presence of eosinophils, supporting the diagnosis of drug-related inflammation. In three patients (Mayall *et al.* 1994; Harrison *et al.* 1994) the inflammatory process had extended into the ureters. Fibrosis of the bladder and ureters leading to obstruction also occurred.

Because of a lack of awareness of the association with tiaprofenic acid, most patients experienced significant morbidity. Four patients underwent cystectomy. One patient developed hydronephrosis and renal impairment due to obstruction.

In the five case series referred to above, patients for whom the dose was recorded were taking 600 mg daily, except for one, who was taking 300 mg. The time from starting the drug to start of symptoms varied from 12 to 54 months, and resolution after withdrawal usually occurred within a few days to eight weeks. Resolution was confirmed by cystoscopy in several patients. A total of 24 patients fully

Author for correspondence: Marie Lindquist, WHO Collaborating Centre for International Drug Monitoring, Box 26, S-751 03 Uppsala, Sweden (fax +46 18 507840).

recovered after drug withdrawal and two experienced a rapid recurrence of symptoms on rechallenge. Of the remaining patients, four had had surgery and four had partially recovered.

O'Neill (1994) also cited two other case reports published in Australia in 1993 (Stenning *et al.* 1992) and, in 1989, an internal report from the Pharmacovigilance Department of Roussel-Uclaf of 13 patients with urinary disorders, six of whom were symptomatic only. The others had some positive investigations for cystitis and one progressed to a vesicovaginal fistula.

In 1993 and 1994 reports concerning tiaprofenic acid and cystitis also came from national centres collecting spontaneous adverse reaction reports. Early in 1993, two years after its introduction to the Australian market, the Australian Adverse Reaction Advisory Committee (ADRAC) had received 11 reports of urinary symptoms in patients taking tiaprofenic acid, and a diagnosis of cystitis was made in four cases by cystoscopy and histopathology (ADRAC 1993). One patient took multiple NSAIDs and developed renal failure. Withdrawal of the drug was recommended if any urinary symptoms developed. It was also noted that there had previously been reports of dysuria with another NSAID, diflunisal.

Whether cystitis is a peculiar adverse effect to tiaprofenic acid was also considered in New Zealand (Ghose 1993) where three reports of haemorrhagic cystitis in patients taking tiaprofenic acid had been received in 1990 and 1991. Two reports of haemorrhagic cystitis and one of haematuria had been received for indomethacin from 1965. Unlike the indomethacin cases, in which the relationship between the medicine and the adverse event was assessed as "possible" or "unclear", two of the patients exposed to tiaprofenic acid were thought to have had a "probable reaction" and one of them had a positive rechallenge. However, there were also 11 reports of haematuria with other NSAIDs.

In 1994, following O'Neill's case series in the Medical Journal of Australia, an ADRAC report (ADRAC 1994) stated that 79 reports of urinary tract disorders associated with tiaprofenic acid had been received, including 53 cases of cystitis. The number of cystitis reports was greater than for all other NSAIDs combined over their marketing periods. Subsequently, a report from the UK Committee on Safety of Medicines (CSM 1994) revealed a similar pattern of reporting, with 69 reports of tiaprofenic acid-associated cystitis over the 12-year period since marketing.

Materials and Methods

A project is currently underway to explore, using Intercontinental Medical Statistics (IMS) drug usage data as a denominator, the possibility of refining the information that can be obtained from the World Health Organisation (WHO) spontaneous reporting data-base maintained by the WHO Collaborating Centre for International Drug Monitoring. Within the WHO programme a common adverse reaction terminology is used. Some of the terms are denoted as "critical", defined as referring to or possibly being indicative of a serious disease state. A serious disease is one that may be fatal, life-threatening, causing or prolonging inpatient hospitalisation, or resulting in persistent or significant disability or incapacity.

One aspect of this work is to use sales data and critical terms to compare risk profiles of medicines in the same therapeutic class, in order to facilitate risk benefit analyses.

The present study is a review of the literature and spontaneous reporting data relating to tiaprofenic acid and cystitis. As the reports came from a small number of countries, the data-base was inspected for any evidence of reporting bias. The risk profiles of tiaprofenic acid and six NSAIDs with similar efficacy were compared.

The WHO data-base was searched for countries from which there were reports of adverse reactions to tiaprofenic acid. There were 24 such countries, and 15 had forwarded reports relating to the urinary tract. As computerised sales data were available from the IMS from 1984 onwards, the period chosen for study was 1984 to 1994 inclusive. The countries with the highest sales of tiaprofenic acid, from which there also were the most reports in the WHO data-base were Australia, the German Federal Republic (GFR), France and the United Kingdom (UK). For the study period, sales data expressed as kilograms sold, were obtained from IMS, and adverse reaction case data were retrieved from the WHO data-base for the same countries.

There were 123 reports of urinary tract disorders with tiaprofenic acid from Australia, 19 from France, 3 from the GFR and 178 from the UK.

The number of reports of urinary disorders associated with tiaprofenic acid received from the listed countries was documented on an annual basis from the years 1984 to 1994. The reporting rate was then calculated as reports per million defined daily doses (DDDs) and chronological and geographical comparisons were made. This process was repeated, including only the adverse event terms cystitis and haemorrhagic cystitis. Six other NSAIDs (diclofenac, ibuprofen, indomethacin, ketoprofen, naproxen and piroxicam) for which there was a large number of adverse reaction reports were chosen for comparison. The reporting rates for urinary disorders and cystitis were calculated for these drugs. For the purposes of this study, NSAIDs were considered to have similar efficacy.

As disorders of the skin and gastrointestinal system are the adverse events most commonly attributed to NSAIDs, a comparison was made of the reporting rate ratios for the integumentary, gastrointestinal and urinary systems for each NSAID to ascertain if they had similar ratios, and if there were reporting trends with time and country.

The DDDs for the NSAIDs studied were diclofenac 100 mg, ibuprofen 1200 mg, indomethacin 100 mg, ketoprofen 150 mg, naproxen 500 mg, piroxicam 20 mg and tiaprofenic acid 600 mg.

After separating the reported adverse reaction terms into three categories, the comparative toxicity of the NSAIDs was studied. The categories used were "cystitis" (cystitis and cystitis haemorrhagic), "critical terms" (defined above), and "non-critical terms" (all other terms, excluding cystitis/cystitis haemorrhagic). As the published case series indicated a potential for serious morbidity, the effect of adding cystitis to the critical terms list was also investigated.

Doses taken by patients recorded in the WHO adverse reaction reports were compared on the basis of whether the report contained "cystitis", a "critical term" or a "non-critical term". If reports contained more than one type of term, they were recorded in the precedence cystitis>critical>non-critical.

Results

Table 1 shows the number of urinary reactions attributed to tiaprofenic acid, reported by country. Fifty-four percent of urinary reports were of cystitis or haemorrhagic cystitis and there were additional reports of symptoms that are associated with cystitis, i.e. dysuria, haematuria, micturition

Table 1.

Urinary disorders reported to tiaprofenic acid in WHO database 1984–1994.

Adverse reaction/symptom	AUS	FRA	GFR	UK	Total
Anuria				2	2
Cystitis	65			93	158
Cystitis haemorrhagic	7		1	8	16
Dysuria	39	1		19	59
Face oedema	7	11		20	38
Haematuria	27	1		23	51
Hydronephrosis	1				1
Micturition disorder	17			2	19
Micturition frequency	50		2	18	70
Micturition urgency				1	1
Nephritis interstitial	1			3	4
Nephrosis				1	1
Nocturia	14		2	5	21
Oliguria	1	2	1	1	5
Pyuria	2			2	4
Renal failure acute	2	4	1	1	8
Renal function abnormal				9	9
Renal function abn. glomer.				1	1
Renal pain		1		1	2
Strangury	3		1		4
Urethral disorder				1	1
Urinary incontinence	13			6	19
Urinary retention	1	1		2	4
Urine abnormal				1	1
Total number of reactions	250	21	8	220	499
Total number of reports*	123	19	3	178	323

* One case report may list up to six different reactions/symptoms.

disorder, micturition frequency, nocturia, pyuria and strangury.

Fig. 1 shows the number of reports of urinary disorders associated with tiaprofenic acid for each country studied by year, and indicates an increase in the number of reports from the UK from 1989, and Australia from 1992, which was also reflected in the reporting rate shown. This pattern of reporting is of interest as tiaprofenic acid had been used in the UK since 1982, but not until 1991 in Australia. No increase in reporting rate was seen for the other countries studied, or for the six other NSAIDs.

Fig. 2 shows the reporting rate and number of reports of cystitis and haemorrhagic cystitis associated with tiaprofenic acid for the countries studied from which there were such reports. The reporting trend closely follows that for urinary disorders (fig. 1).

Only 13 reports of cystitis were received for the six NSAIDs studied compared with 174 for tiaprofenic acid between 1984 and 1994 (table 2). In the UK, even though the reporting rate was low between 1984 and 1989, there were 21 reports of cystitis associated with tiaprofenic acid compared with two for the other NSAIDs.

Fig. 3 shows the reporting rate profiles for gastrointestinal, skin and urinary disorders in the UK for tiaprofenic acid, diclofenac, ibuprofen and naproxen. Tiaprofenic acid was the only NSAID for which urinary disorders were reported more often than those affecting the gastrointestinal tract or skin. Examination of the reporting profiles for all NSAIDs by country (data not shown) revealed that the excess of urinary disorder reports in the UK and Australia was specific for tiaprofenic acid, and that it was not due to reporting patterns peculiar to these two countries.

The reporting rates for critical terms, non-critical terms and cystitis for tiaprofenic acid by country shown in fig. 4 demonstrates a higher reporting rate for all terms for tiaprofenic acid from the United Kingdom and Australia compared with the other countries. However, there were also higher reporting rates for critical and non-critical terms from these two countries for the other six NSAIDs, without a comparable increase in cystitis reports (table 3 shows reporting rates by country for critical terms.)

The reporting rates of critical and non-critical terms were compared for the NSAIDs studied in fig. 5. Tiaprofenic acid together with indomethacin, piroxicam and ketoprofen showed above average (0.95/million DDDs) reporting rates for critical terms compared to ibuprofen, diclofenac and naproxen. The figure also demonstrates that if cystitis were added to the list of critical terms, tiaprofenic acid would have had the poorest risk profile.

The mean daily dose recorded for patients in the WHO case reports was, for cystitis, 543 mg (median 600 mg). For critical term reports, the corresponding figures were 539 (600), and for all remaining reports they were 547 (600). It

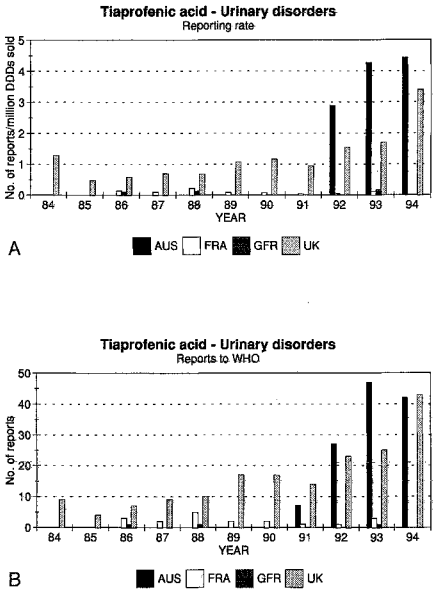


Fig. 1. Reporting rats/number of reports of urinary disorders associated with tiaprofenic acid for each country studied by year, for the years 1984–1994.

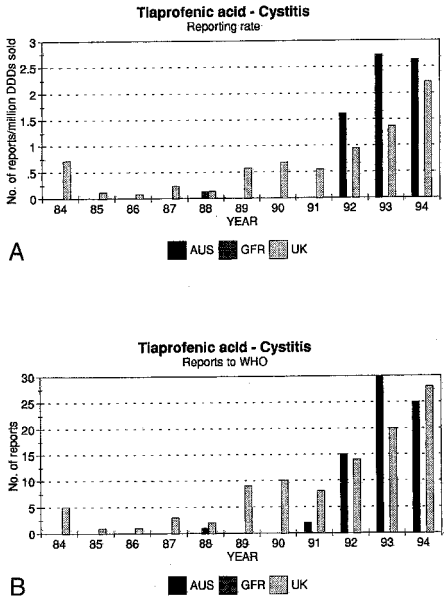


Fig. 2. Reporting rates/number of reports of cystitis and haemorrhagic cystitis associated with tiaprofenic acid for the countries studies, from which there were such reports, for the years 1984–1994.

should be noted that a daily dose was only reported in 79/174 cases of cystitis/cystitis haemorrhagic, in 96/563 reports containing critical terms, and in 210/827 of the reports containing neither term category.

Discussion

The results confirm the reported association between tiaprofenic acid and cystitis. The highest reporting rate was from Australia and was 2.72/million DDDs in 1993 which would equate to 1 in 12,255 monthly prescriptions. The actual incidence is likely to be higher.

Although the number of reports of cystitis with other NSAIDs increased after 1990, they were very infrequent. Comparison with other NSAIDs confirmed that the increased reporting rate for cystitis with tiaprofenic acid could not be attributed to a change in overall reporting frequency for urinary disorders associated with NSAIDs, or to higher reporting rates for all NSAIDs from some countries, or in certain years.

It is a matter of concern that there was a delay of eight or nine years from the release of tiaprofenic acid in the northern hemisphere to the recognition of its association with a serious form of aseptic cystitis. Some delay is to be expected as the disorder seems to be associated with long-term use.

Table 2.

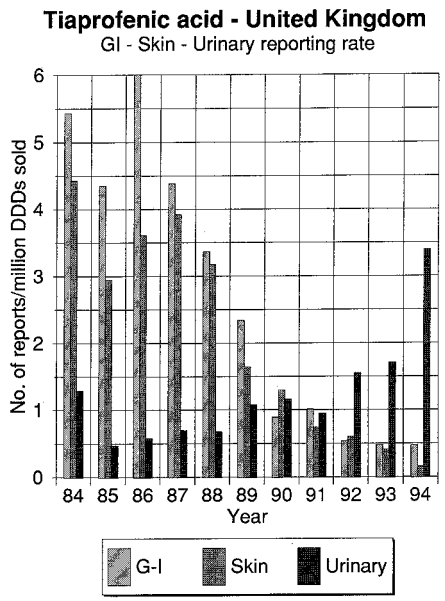
Cystitis reporting rate by country and year for 7 NSAIDs.

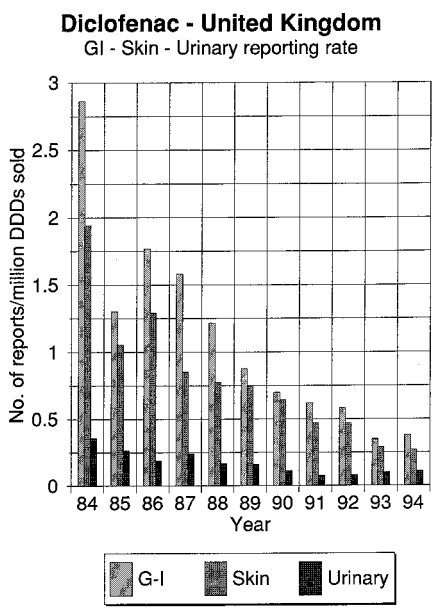
Drug name	Country	Year	No. of reports to WHO	Sales (mill. DDD)	Reporting rate (#reports/ sales)
Diclofenac	UK	94	1	197.00	0.01
Ibuprofen	GFR	88	1	25.17	0.04
	UK	91	1	133.00	0.01
		93	1	163.92	0.01
		94	1	171.08	0.01
Indomethacin	AUS	90	1	9.66	0.10
	UK	87	1	57.00	0.02
Ketoprofen	AUS	90	1	42.00	0.02
	UK	89	1	46.00	0.02
Naproxen	AUS	92	1	53.80	0.02
		94	1	58.00	0.02
	UK	94	1	120.60	0.01
Piroxicam	GFR	92	1	50.78	0.02
Tiaprofenic acid	AUS	91	2	0.00	
		92	15	9.33	1.61
		93	30	11.00	2.73
		94	22	9.50	2.32
		94	3	9.50	0.32
	GFR	88	1	7.67	0.13
	UK	84	5	7.00	0.71
		85	1	8.50	0.12
		86	1	12.17	0.08
		87	3	13.00	0.23
		88	2	14.83	0.13
		89	9	15.83	0.57
		90	10	14.67	0.68
		91	8	14.83	0.54
		92	14	14.83	0.94
		93	20	14.67	1.36
		94	28	12.67	2.21

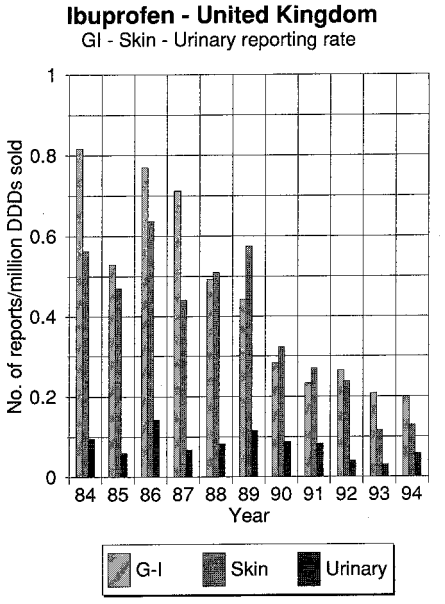
Cystitis is a common condition, but it is unusual for it to be an adverse drug reaction; except with some cytotoxic medicines. Because it is often not initially thought to be a serious condition, there may also be a delay in referral to specialists, who, in this case, will be more likely to recognise the association.

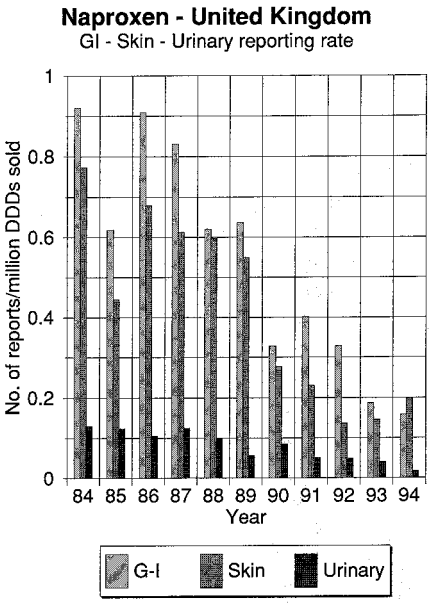
There are several possible reasons for the earlier recognition of cystitis after the introduction of tiaprofenic acid into Australia. First, it was introduced in the same year as the first case series report (Ahmed & Davison 1991). Second, in the Australian case report evaluation an emphasis is put on the sensitivity of signal generation, in that all drugs with a reasonable time relationship to the reaction are recorded as "suspected". Third, tiaprofenic acid has, since it was marketed, been listed by ADRAC as a "drug of special interest" indicating that prescribers are asked to report all

Fig. 3. Reporting rate profiles for gastrointestinal, skin and urinary disorders in the UK for tiaprofenic acid (A), diclofenac (B), ibuprofen (C) and naproxen (D), 1984–1994.


Tiaprofenic acid - United Kingdom
GI - Skin - Urinary reporting rate
No. of reports/million DDDs sold
0
1
2
3
4
5
6
84 85 86 87 88 89 90 91 92 93 94
Year
G-I
Skin
Urinary


Diclofenac - United Kingdom
GI - Skin - Urinary reporting rate
No. of reports/million DDDs sold
0
0.5
1
1.5
2
2.5
3
84 85 86 87 88 89 90 91 92 93 94
Year
G-I
Skin
Urinary


Ibuprofen - United Kingdom
GI - Skin - Urinary reporting rate
No. of reports/million DDDs sold
0
0.2
0.4
0.6
0.8
1
84 85 86 87 88 89 90 91 92 93 94
Year
G-I
Skin
Urinary


Naproxen - United Kingdom
GI - Skin - Urinary reporting rate
No. of reports/million DDDs sold
0
0.2
0.4
0.6
0.8
1
84 85 86 87 88 89 90 91 92 93 94
Year
G-I
Skin
Urinary

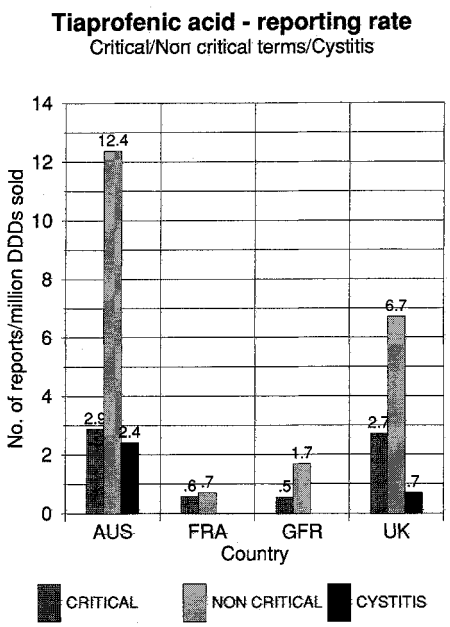


Fig. 4. Reporting rates for critical terms, non-critical terms and cystitis by country.

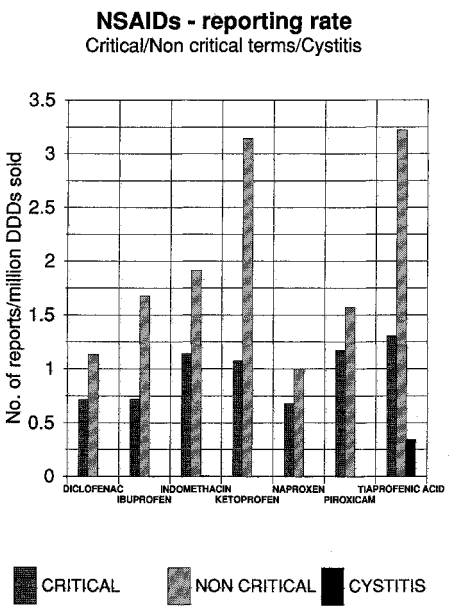


Fig. 5. Reporting rates for critical terms, non-critical terms and cystitis by NSAID.

adverse events in patients taking this medicine. In the UK it would also, in common with all new medicines, have been intensively monitored, but only for the first two years after its introduction. Considering that the sales of tiaprofenic acid on a population basis were much greater for Australia in the initial years after marketing (565,000 DDDs/million people in 1992) as compared with 125,000 DDDs/million people in the UK in 1984), two years might not have been long enough for the recognition of this particular reaction in the UK.

The lack of recognition of the problem of cystitis in those countries where tiaprofenic acid was available, and by the WHO International Drug Monitoring Centre prior to 1991, is largely due to the small number of reports, although it might have been recognised if cystitis had been a critical term or the more serious fibrotic condition had been reported differently.

The mechanism by which tiaprofenic acid may cause cystitis has not been elucidated. Its structure contains a thienyl ring, which is not present in the other propionic acid derived NSAIDs. It is not possible to ascertain if there is a dose-duration relationship for cystitis as almost all patients in the published series had taken 600 mg daily, usually in two divided doses. There does not appear to have been any change in the recommended daily dose between 1984 and 1994.

In the WHO case reports, there was no apparent difference in the median and average doses of tiaprofenic acid in cases of cystitis compared to case reports containing a critical term, or those containing neither cystitis nor a critical term.

Long term use of tiaprofenic acid is most likely to cause cystitis, so accumulation of the parent drug or its metabolites with a direct toxic effect may be responsible. However, the presence of eosinophils in the inflammatory lesions and the very rapid return of symptoms on rechallenge suggest the possibility of an immunologic phenomenon.

In terms of benefit/risk appraisal, a review of comparative studies (Plosker & Wagstaff 1995) has indicated that tiaprofenic acid at 600 mg daily has similar efficacy to diclofenac, ibuprofen, indomethacin, naproxen and piroxicam in the treatment of rheumatoid arthritis and osteoarthritis in

Table 3.

Reporting rate of critical terms (#reports/million DDD sold).

Drug	AUS	FRA	GFR	UK
Diclofenac	0.95	0.42	0.42	1.38
Ibuprofen	0.64	1.98	0.46	0.75
Indomethacin	2.53	0.90	0.41	1.39
Ketoprofen	1.39	0.70	0.77	1.42
Naproxen	0.68	0.25	0.47	0.89
Piroxicam	1.62	0.49	0.63	2.40
Tiaprofenic acid	2.88	0.57	0.54	2.72

doses similar to or higher than the DDDs used in this study. A recent study suggests that tiaprofenic acid has an advantage over indomethacin in terms of cartilage degradation (Huskisson *et al.* 1995).

Differences between NSAIDs in the risk of gastrointestinal toxicity reported in a recent meta-analysis of pharmacoepidemiologic studies (Henry *et al.* 1996) were partly reflected in the reporting rates of critical terms shown in fig. 5. When only gastrointestinal critical terms were included there was a close correlation. Tiaprofenic acid has not been ranked for gastrointestinal toxicity in pharmacoepidemiological studies because of its low market share in the study localities. Tiaprofenic acid and diclofenac were shown to be less gastrotoxic than indomethacin in animal studies, which was correlated with the extent to which these agents reduced mucosal PGI_2 levels (Plosker & Wagstaff 1995).

The advantage of the present study was that the whole risk profile could be studied rather than particular disorders common to the whole therapeutic group. Sources of reporting bias could also be examined. One disadvantage was that in the 11 year period studied the NSAIDs had been available for different time periods, and in some countries it had been introduced before 1984. This may have disadvantaged more recently introduced agents in comparing risk profiles. There was a particularly high reporting rate for gastrointestinal reactions to ketoprofen in Australia as its market share increased. Since computerised IMS data are available from 1984, in future studies comparisons at equivalent times since introduction should be possible for more recently marketed drugs.

In the 1994 "Side Effects of Drugs Annual" (Del Favero 1994) it was concluded that the benefit/risk ratio of tiaprofenic acid need reassessment. The present study showed that tiaprofenic acid had among the highest reporting rates of serious reactions, compared with other commonly used NSAIDs of similar efficacy, and additional risk of cystitis. These findings suggest that the benefit/risk profile of tiaprofenic acid is low, lending support to a further conclusion that, on current evidence, the indications for use of tiaprofenic acid should be considered very carefully.

Acknowledgements

The authors are indebted to the national centres mentioned in the study who contributed data. The opinions and conclusions, however, are not necessarily those of the various centres nor of the WHO or IMS International.

The ASAP team was aided by a grant from the European Commission under its BIOMED I concertation procedure.

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XI

CORRESPONDENCE

Risks of non-sedating antihistamines

SIR—France has recently discontinued terfenadine, and a proposal has been made to take it off the market in the USA. Since the safety of at least one other of this piperidine class of drugs—astemizole—can be questioned on a similar basis to terfenadine it seems prudent to examine the risk profiles of some of the common non sedating antihistamine drugs together.

The spontaneous adverse drug reaction (ADR) report profiles of five widely used non-sedating antihistamines, with apparently similar efficacy and the largest sales internationally, were examined with the use of data from the WHO ADR database, and sales data, expressed as kilograms sold, from IMS International. A methodology for combining this type of data was elaborated during a 2-year pilot project funded under a European Community Biomed grant, which has been described previously.[1,2]

17 countries, for which sales data were available, contributed 9976 ADR reports (99% of the total for these drugs). Reporting rates were then calculated as reports per million defined daily doses (DDDs) sold. The DDDs were: acrivastine 24 mg, astemizole 10 mg, cetirizine 10 mg, loratadine 10 mg, and terfenadine 120 mg. The study periods chosen were 1986–91 and 1992–96. These periods correspond with those before and after, respectively, the first published concerns about cardiac rhythm disorders were related to terfenadine. Reporting rate profiles by body system organ class were calculated, and for a subset of cardiac rate and rhythm disorders: arrhythmia, ventricular arrhythmia, cardiac arrest, ventricular fibrillation, QT prolonged, supraventricular tachycardia, ventricular tachycardia, torsade de pointes, and cardiac fibrillation. Rates for fatal outcomes were also determined.

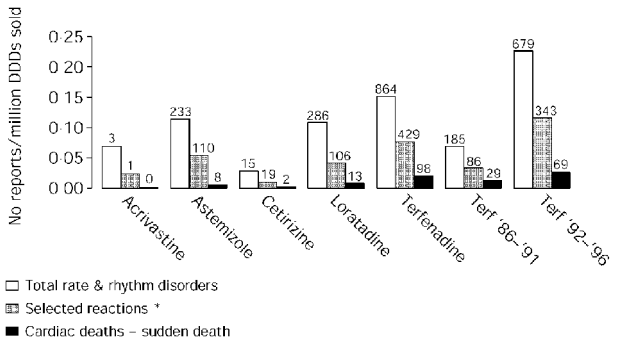
The overall reporting rate profiles for the five non-sedating antihistamines had many similarities. The rates per body system organ class were low (all less than 0·25 reports per million DDDs sold). Central nervous system, psychiatric, special sensory and general reactions accounted for most of the reports over 0·1/million DDDs sold. Deaths were reported mainly under the heading of "general" and "cardiac rate and rhythm disorders". The figure shows the reporting rates of cardiac rate and rhythm disorders, for the selected subset, and for deaths, including reports of sudden death.

Terfenadine and astemizole both have a propensity to block cardiac muscle potassium channels, which has been linked with QT prolongation and cardiac arrhythmia. By contrast, loratadine has been shown not to block potassium channels.[3] A further analysis was made of 57 reports in the WHO database only concerning ventricular arrhythmias associated with loratadine. Of those, 27 reports had no mention of confounding/interacting drugs: there were five deaths in these patients. Individual case reports should be analysed carefully at source for causality and confounding.

On the basis of existing data from the WHO and IMS databases, we were able to provide rapidly a measure of the international spontaneous report levels, allowing comparison between drugs. These crude rates reflect doctors' concerns with these products, but do not provide a definitive answer. Nevertheless, the data indicate that some of the alternatives to terfenadine may have similar problems, suggesting that thorough consideration of the comparative benefit risk profile of all non-sedating antihistamines is wise.

Marie Lindquist, I Ralph Edwards
Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, Box 26, S-751 03 Uppsala, Sweden

1 ADR Signals Analysis Project (ASAP) Team. Omeprazole and visual disorders: seeing alternatives. *Pharmacoepidemiol Drug Safety* 1996; **5**: 27–32.
2 ADR Signals Analysis Project (ASAP) Team. How does cystitis affect a comparative risk profile of tiaprofenic acid with other non-steroidal antiinflammatory drugs? An international study based on spontaneous reports and drug usage data. *Pharmacol Toxicol* 1997; **80**: 211–17.
3 Ducic I, Ko CM, Shuba Y, Morad M. Comparative effects of loratadine and terfenadine on cardiac K channels. *J Cardiovasc Pharmacol* (in press).



Antihistamines reporting rates 1986–96 for cardiac rate and rhythm disorders, subset of these disorders, and death as a result of a cardiac rate/rhythm reaction or reported as sudden death

*Arrhythmia, ventricular arrhythmia, cardiac arrest, ventricular fibrillation, QT prolongation, supraventricular tachycardia, ventricular tachycardia, torsade de pointes. Numbers on bars are actual numbers of ADR reports. Terf=terfenadine.

APPENDIX II. Acronyms

ADR	Adverse Drug Reaction
AERS	Adverse Event Reporting System (FDA)
ATC	Anatomical Therapeutic Chemical (WHO)
CIOMS	Council for International Organizations of Medical Sciences (WHO)
CNS	Central Nervous System
DDD	Defined Daily Doses
DIA	Drug Information Association
EFTA	European Free Trade Association
EMEA	European Agency for the Evaluation of Medicinal Products
EC	European Commission
EU	European Union
FDA	Food and Drug Administration (USA)
DSRU	Drug Safety Research Unit (UK)
GPRD	General Practice Research Database
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IMMP	Intensive Medicines Monitoring Programme (New Zealand)
ISOP	International Society of Pharmacovigilance
ISPE	International Society of Pharmacoepidemiology
Lareb	Netherlands Pharmacovigilance Foundation (Landelijke Registratie en Evaluatie van Bijwerkingen, Netherlands)
MA holder	Marketing Authorisation holder
MCA	Medicines Control Agency (UK)
MEMO	Tayside Medicines Monitoring Unit
NSAID	Nonsteroidal Anti-inflammatory Drug
PEM	Prescription Event Monitoring System
SPC	Summary of Product Characteristics (EMEA)
SRS	Spontaneous Reporting Systems
UMC	Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization

APPENDIX III. Definitions

For the purpose of this thesis the following definitions apply:

Note! When a defined term is referred to in the text below , it is written in *italics.*
'Includes' does not imply an exhaustive listing.
'Synonym' means that the term given as a synonym can be used interchangeably with the defined term.

Adverse event
: any untoward medical occurrence that may present during treatment with a *medicinal product* but which does not necessarily have a causal relationship with this treatment
Synonym: Adverse experience

Adverse reaction
: response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function
Synonyms: Adverse drug reaction (ADR); Suspected adverse (drug) reaction.
Note. An adverse reaction, contrary to an *adverse event*, is characterised by the suspicion of a causal relationship between the drug and the occurrence, i.e. judged possible by the reporting or a reviewing *health professional.*

Consumer
: person taking a *medicinal product*
Note. A person may or may not be an actual consumer of *health care* or medicines at a given time, but all members of the general public are potential consumers.
For the latter group the term *general public* is used instead of consumer.
The term *patient* is used when referring to actual consumers of medical or *health care.*

Continuing education
: enhancement or expansion of an individual's knowledge or skills by further schooling, usually after formal education has ended

Developing country
: in the process of moving towards the economic and social model of the longer established industrialised countries
Note. The term developing country represents a concept that does not

lend itself to a precise definition. The use of developing country often reflects a value judgement, and the term refers to a large number of countries which are not homogenous. In some situations it might be useful as a grouping term, although, when possible, more specific descriptors should be used. For *pharmacovigilance* communication, the following characteristics are important:
i) insufficient funds for public health
ii) insufficient access to medical care
iii) insufficient control of quality and distribution of medicines
iv) illiteracy or language problems in relation to medical and *health care* communication.

Drug (see *Medicinal product*)

Effectiveness
ability to achieve the desired effect as shown in normal clinical use

Efficacy
ability to produce a desired effect under optimal circumstances

General public
people collectively as members of the community
Synonym: The public

Harm
damage qualified by measures of frequency of occurrence, severity or duration
(cpr. *risk*).

Health care
maintaining, restoration or improvement of health by *health professionals*

Health care professional (see *Health professional*)

Health professional
person who is trained and licensed to provide *health care* to humans
Synonym: Health care professional
Includes: doctor, nurse, dentist, pharmacist, midwife
Excludes: veterinarian

Media
means of communication
Note. This term includes any means of communication, and may also refer to those engaged in them

Medicinal product

product intended to be administered to humans for treating or preventing disease, with the view to making a medical diagnosis or to restore, correct or modify physiological functions
Synonym: Medicine
Note. For the purpose of this thesis, the term 'drug' should be interpreted as equivalent to the concept medicinal product

Medicine (see *Medicinal product*)

Patient

person awaiting or under medical care or treatment by a *health professional*
Note 1. This definition is wider than most standard definitions of patient in that it includes people who are not ill or injured, e.g. individuals who are prescribed *medicinal products*, the indications for which are not a disease or prevention of a disease (e.g. oral contraceptives). However, in relation to *pharmacovigilance* communication issues it is useful to have one term that covers all individuals who are in contact with *health professionals*.
Note 2. It has been argued that the linguistic connotation of patient is a passive sufferer and that the word therefore should not be used. On the other hand, it can be argued that modern usage of the word has expanded its meaning to cover active individuals who can and will act as equal partners, and that, in the absence of another generally accepted term that covers the concept described above, patient is the preferred term to use.

Pharmacovigilance

the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible problems related to *medicinal products*

Player

individual, or group of individuals, with a legitimate interest and responsibility in a human endeavour, e.g. *pharmacovigilance*
Synonym: Stakeholder

Postgraduate

course of study carried on after graduation, especially after taking a first degree

Prescribe

to indicate a *medicinal product* to be administered, usually done by writing a *prescription*

Prescriber

health professional licensed by law to *prescribe*
Note. A prescriber may have a limited licence, for instance allowing *prescription* of certain categories of *medicinal products*, e.g. in some countries midwives are licensed to *prescribe* only oral contraceptives.

Prescription

direction or order for dispensing and administering *medicinal products*, issued by a *prescriber*

Prevalence

number of existing cases of an outcome in a defined population at a given point in time

Regulation

laws, rules and guidance governing pharmacovigilance
Synonym: Regulatory requirements

Regulatory authority

an agency charged with the responsibility for *regulation* in a territory
Synonyms: Regulatory agency; Regulatory body; Regulator
Note. The jurisdiction of a regulatory authority is normally within one country. An exception is the European Union, where countries are subject both to national and pan-European regulation.

Relative risk

ratio of the *risk* in an exposed population (absolute risk) and the risk in an unexposed population (reference risk)

Risk

probability of developing an outcome
Note. Contrary to *harm*, the concept of risk does not involve severity of an outcome.

The public (see *General public*)