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Uppsala

REPORTS

For everyone concerned with the issues of pharmacovigilance and toxicovigilance



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Greetings from *Uppsala*

A Message from Ralph Edwards, Director

The Uppsala Monitoring Centre

We were delighted with the warm and positive response to the first edition of Uppsala Reports. Please do keep your reactions and contributions coming in!

With this edition you'll find a simple form on which you are warmly invited to record your opinion - or to send us news and views for possible inclusion in the next edition.

Do fax or mail or e-mail a few words to us.



One of our concerns is that health professionals still rely heavily on publications with only lists of adverse reactions. We believe that the communication of risk (and benefit) information should be developed much more imaginatively.

This concern underlies the joint workshop described below, which we hope will contribute to pushing this issue forward in research and practice.

With our Annual International meeting coming up in Lisbon, Portugal, just a few weeks away, we're looking forward to renewing old friendships - and making new ones - and addressing the many important issues in drug safety which have emerged since Bangkok 1995. From all member countries we hope to have some representation - even if it is only a written communication of your interests and preoccupations. But we look forward to seeing many of you in person!

I and the team here wish you all the very best - and hope, as always, that you'll contact us if we can be of any service to you.

Ralph Edwards.

この度は、ウプサラ報告第2編纂をご購読頂き有難うございます。私どもは、当書が皆様のお役にたつ事を心より願い、また今後の編纂の為、ご意見・ご感想をお寄せ頂けたら幸いです。私どもウプサラのチーム一同、今後とも皆様のますますのご繁栄をお祈り申し上げます。

New *Publication*

Directory of National Pharmacovigilance Centres

Within the next few months we will be publishing a directory of 45 national pharmacovigilance centres from all over the world participating in the WHO programme. Each centre is described in detail in a "country profile" providing facts about sources of information, methods of case follow-up, recording, assessment, decision making, contact names and communications details.

In part II of the directory there is an international overview of procedures used at National Centres, which demonstrates how widely approaches to pharmacovigilance differ. An appendix displays the various data elements requested in national ADR reporting forms.

The information is based on responses to a comprehensive questionnaire sent out by us. Data was verified by national centre staff during 1995.

It will be in a loose-leaf format, so it can be quickly updated. We shall need lots of help from our friends around the world to ensure that the information is as contemporary as possible.

If you are interested in this publication and wish to receive an offer at the time of its release, please let us know. For national pharmacovigilance centres the publication will be free of charge.

歡迎閱讀亞普薩拉第二版。希望您會喜歡，請告訴我們您的意見，或為下版投稿。亞普薩拉全體員工祝您萬事如意。

COMMUNICATIONS IN PHARMACOVIGILANCE

Verona Study Group

The University of Verona, The Uppsala Monitoring Centre and CIOMS are sponsoring an exploratory study group to look at all aspects of communications in pharmacovigilance this autumn.

The group will bring together clinicians, pharmacists, regulators, lawyers, journalists, consumer interests and industry to examine current problems, dilemmas and opportunities for improved understanding and practice.

It is intended that the proceedings of the meeting should be published and that they should pave the way for a major international symposium next year.

The Uppsala Team in *San Diego*

Presenting our latest work

The annual meeting of the Drug Information Association (DIA) was held in San Diego, California, USA, 9-13 June, 1996. At the meeting the Centre was given the opportunity to present many of our current development activities:

1

A new data model for storage of ADR case information based on the proposal of the CIOMS IA working group

2

A new data model of the extended WHO Drug Dictionary including the proposals of the CEN working group for identification of pharmaceutical products (see back page)

3

A data model intended to collect detailed pathophysiological and clinical data from cases with severe ADRs or intoxication (TOXICASE) has been developed under the auspices of IPCS (International Program on Chemical Safety).

4

Recording of adverse reaction diagnoses with the aid of a controlled vocabulary approach as

an alternative to hierarchical terminologies. This topic was presented by Dr Harley Quilliam from University of Guildford, UK.

5

The use of artificial neural networks in the analysis of large adverse reaction databases for the identification of new adverse reaction signals. Mr Roland Orre from the Royal Institute of Technology, Stockholm, made the presentation.

6

The ADR Signal Analysis Project, ASAP, combining adverse reaction reporting data from the WHO database with drug utilization statistics from IMS and official demographical statistics. Dr Norman Taylor of IMS contributed in the presentation of this issue.

7

The development of a classification system for herbal remedies compatible with the ATC-system. The project is designed in collaboration with the Royal Botanic Gardens in Kew, (UK), Exeter University, (UK), and the Royal Dutch Association for the Advancement of Pharmacy, (The Netherlands). Obviously input from experts from all parts of the world, representing different therapeutic traditions, will be indispensable in carrying out this project.

In addition to presenting the above projects the Centre had all its current products and services on display in the exhibition area of the DIA conference. We have also reached an agreement with DIA that our home-page on the Internet will have a link from theirs.

نرحب بكم في الطبعة الثانية من تقارير
"أبسالة" التي نأمل أن تتمتعوا بها. كما نرجو
أن تفيدونا بأرائكم حولها أو أن ترسلوا إلينا
مساهماتكم لنشرها في المطبوعات القادمة.
مع أطيب تمنيات فريق العمل في "أبسالة".

NEWS FROM WHO COLLABORATING CENTRES

Norway

The WHO Collaborating Centre for Drug Statistics Methodology in Oslo, responsible for management of the ATC-system for classification of pharmaceuticals and for establishment of DDDs (Defined Daily Doses) recently came under the aegis of Division of Drug Management and Policy at WHO headquarters, Geneva, through an agreement between WHO and Norway. Previously the Oslo centre was connected to the WHO Regional Office for Europe.

South Africa

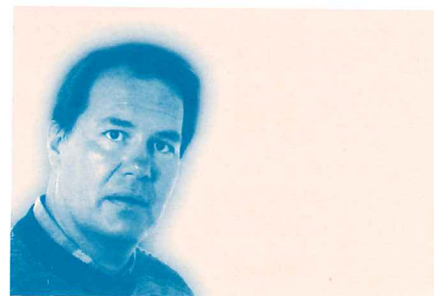
The Department of Clinical Pharmacology of the University of Cape Town Medical School was recently designated a WHO Collaborating Centre for Drug Policy and Safety Monitoring. Director of the Centre is Professor Peter Folb. The address is: Observatory 7925, South Africa, fax: + 27-21-4486181

Spain

Last year the Catalan Institute of Pharmacology at the Autonomous University of Barcelona was designated a WHO Collaborating Centre for Research and Education in pharmacoepidemiology. Professor Joan-Ramon Laporte of the Centre may be contacted at the following address: Ciutat Sanitaria Vall d'Hebron, 08035 Barcelona; fax: +34-3-4285112

Sweden

A WHO Collaborating Centre for Drug Utilization Studies has been established at the Department of Clinical Pharmacology, Karolinska Institute, Huddinge Hospital, 14186 Huddinge, Sweden. Director of the Centre is Professor Folke Sjöqvist. Fax number is +46-8-7468821.



New Face in Uppsala

Mats Persson joined the staff of the Uppsala Monitoring Centre in July. He has a degree in Business Management and Marketing and has long experience in working with different sales and marketing activities for the Swedish pharmaceutical industry. At the Centre he will be in charge of sales and promotion of WHO dictionaries and other publications to users in commercial companies.

Bem vindo à segunda edição dos relatórios Uppsala. Esperamos de que goste e que nos dê a conhecer a sua opinião ou contribuições para futuras publicações. Os melhores cumprimentos da equipa na Uppsala!

What happens to SIGNALS issued by *the Centre?*

The Centre here uses a panel of experts to assist us in assessing early indications from the database of new drug-reaction associations, not previously described or insufficiently documented. Short summaries prepared by the experts are compiled in a document with a bright yellow cover called SIGNAL, which is made available to National Centres at regular intervals, normally six to eight times a year.

As this scheme has been in operation since 1990 we decided to contact the member countries of the WHO Drug Monitoring Program to find out if the information in the SIGNAL document has had any impact in the various countries and to get their thoughts and opinions about the material.

New Alerts

Another question closely related to this matter was if the produced signals are genuine new alerts, later substantiated by other findings. To investigate this we made a thorough literature search comparing the signals found over the past five years with the medical world literature. This research resulted in a paper presented at the DIA Annual Meeting in Florida last June. It was also recently published in the Drug Information Journal (H.Fucik., I.R. Edwards; Impact and Credibility of the WHO Adverse Reaction Signals 1996;30:461-464).

A questionnaire was sent to National Centres in member countries and associate member countries, - a total of 60 centres. The response rate was 60%. Of those who responded 11% thought the SIGNAL material was always useful and 50% found it often useful.

Action

When asked about what actions had been taken in response to the 44 signals sent out from the WHO Centre in 1994, 24 National Centres stated that associations were recorded for follow-up at a national level, 8 centres initiated a total of 38 further investigations (from 1 to

15 per centre) and considered 10 associations as being supported. Nine National Centres stated that they distribute the information to people concerned within their country. If those stating that they publish the signals in their National Drug Bulletin are included (19 centres) this figure is considerably higher. Labelling changes were reported by 9 centres in up to 5 cases per centre. Approaching manufacturers was mentioned by 8 centres to have occurred in 10 cases.

Impact

As shown above the impact of SIGNAL varies considerably across member countries - from little or none, suggested by the remark that 'the information in SIGNAL is too tentative to take action upon' - through to substantial, for example, in taking specific regulatory action such as labelling changes. The tentative nature of an early signal should not normally lead to decisive regulatory action, but neither should it lead to no activity at all! It seems that more discussion on how to use a signal is warranted and we welcome your thoughts and suggestions.

A Five - year Perspective

To compare the signals from the past five years with the world literature we used Reactions Weekly (by Adis press), Medline and our own literature reference follow-up. The 248 signals compared were serious (based on the WHO Critical Terms List) or of interest to an expert clinical panel. We found that 30 of the signals have been

reported in articles in internationally acknowledged journals. Many of them were picked up as new signals through the WHO database 2-3 years before they were found in other literature.

Industry

A final issue was that few authorities approached pharmaceutical manufacturers with the material from SIGNAL. This must relate, at least in part, to a view about the tentative nature of the signals. It does however appear that many drug safety professionals working in industry would like to have access to the material in SIGNAL to compare with their own information and ensure that they can fulfil their own responsibilities optimally. The Uppsala Centre has a prime responsibility to provide information for member states; it is each of those regulatory agencies which becomes the distribution focus for SIGNAL and other WHO information. This is a second area where discussion may be needed.

Conclusion

Our conclusion is that the WHO Programme for International Drug Monitoring is successful in its mission in finding new drug-ADR associations at an early stage and in providing useful information to National Centres. It needs to be emphasized that the purpose is to increase the safety of drug products by keeping an open dialogue with all parties involved. The ultimate concern is to optimise drug use and drug safety worldwide.

Nous avons le plaisir de vous présenter la seconde édition des rapports d'Uppsala. Nous espérons qu'elle suscitera votre intérêt et nous vous serions reconnaissants de nous faire parvenir vos commentaires et vos contributions aux prochaines éditions. L'équipe d'Uppsala vous présente ses meilleures salutations !

Product *News*

- The computerized versions of the WHO Drug Dictionary and the WHO Adverse Reaction Terminology presently provided to customers contain information up to and including the second quarter of 1996. A supplement to the paper print version of the WHO Drug Dictionary 1995, covering amendments made Jan/June 1996, will be ready in September.
- A new manual for on-line users of the WHO adverse reaction database has been developed. The new manual has been sent to all present on-line users. Another manual describing the customised services offered by our Centre has also been produced. Both manuals may be obtained by anyone interested by contacting us here in Uppsala.



- We are in the midst of a major product sales and awareness campaign in Canada and Japan where we are hoping to extend the use and influence of the Drug Dictionary, WHO-ART and DD Access considerably.

Participant's *perspective*

Ambrose O. Isah, Nigeria

The annual Training Course was held from the 20th-31st May, 1996. There were twenty-five participants with varied backgrounds and experience in pharmacovigilance from twenty-two countries round the world.

A Warm Welcome

The course began with a very warm informal welcome ceremony and this set up a cordial atmosphere which was maintained throughout the course.

There were three blocks - (i) Clinical manifestations and mechanisms of adverse drug reactions, (ii) Spontaneous adverse reaction reporting, (iii) Pharmacoepidemiology.

Lecture after lecture, the erudite facilitators presented their high quality materials in a masterly fashion. The learning process was further enhanced by the participatory and interactive nature of many of the sessions.

Spontaneous Reporting

The five-day block allotted to the spontaneous reaction reporting was very interesting. The sessions unravelled the operations of the Uppsala Monitoring Centre and its network. It revealed the vastness of available information as well as the actual and potential uses of a well-coordinated international reporting scheme.

In the session on country experiences and plans, contributions from the varied backgrounds of the participants were a great asset. A number of developing countries had no monitoring schemes while others had schemes at various levels of development and sophistication.

Hands on Sessions

The practical sessions on the computerised dictionaries/classification systems and terminologies for ADRs and those on casualty assessment were exciting and intellectually stimulating as they provided a simulated "hands on" experience for us. There were sessions on drug-abuse related adverse drug reactions as well as on the newly developed scheme for traditional herbal remedies undergoing a process of harmonisation of the classification systems.

The two-day pharmacoepidemiology block highlighted the relevance of this area to pharmacovigilance. The importance and approach to population based studies were put in proper perspective.

The informal sessions with the amiable and dedicated staff of the Centre with Ralph Edwards and Sten Olsson were most useful in providing a model for the development of national collaborating centres.

Time Off

Sandwiched between the very busy sessions was a most educational tour round the City of Uppsala, as well as to the City Hall and Old City of Stockholm. No doubt the pleasant memories of Swedish hospitality from the Centre's staff and those of the Medical Products Agency (headed by Prof. B.E. Wiholm) will linger in the minds of participants for a long time.

As the course came to a close, the participants showed much enthusiasm and determination to participate effectively in pharmacovigilance activities, pledging to strengthen in their own ways the WHO database through effective reporting.

The course created a starting-point for the formation of a network which will further promote the concept of safety in drug use worldwide.

Dr. Isah is senior Lecturer at the University of Benin, Nigeria, and a Consultant Physician and Clinical Pharmacologist.

Bienvenidos a la segunda edición de los informes Uppsala. Esperamos que lo hayan disfrutado. Envíenos sus opiniones al respecto, así como sus aportaciones para publicaciones futuras. ¡Los mejores deseos del equipo en Uppsala!

News from *Around the World*

Japan

In June 1996 a decision was taken by the Japanese parliament which will mean that the present system of specially designated drug monitoring hospitals and pharmacies which submit case reports on suspected ADRs to the Ministry of Health and Welfare will be abandoned. All physicians will now be asked to take part in the drug monitoring activity.

Republic of Korea

Dr Byung-Woo Moon is now in charge of activities at the Centre.

Norway

Ms Ingebjorg Buajordet, who has been heading the Norwegian national centre for many years, has taken 3 year research leave. During this period she will be engaged in the study of ADRs in children and drug

related deaths in a hospital setting. She is still employed part-time at the national centre but her position as head of the centre is now taken by Ms Krystyna Hviding.

Sweden

At a ceremony in London on 4 July, 1996, Dr Bengt-Erik Wiholm, head of the Swedish pharmacovigilance centre, was accepted as a fellow of the Royal College of Physicians of London (FRCP). The citation for Dr Wiholm read, "Dr Wiholm is one of the foremost pharmacoepidemiologists in the world. He is both a specialist physician in general medicine and a clinical pharmacologist. Dr Wiholm was one of the founder members of the European Union Pharmacovigilance Research Group. He has been an active member of the WHO Collaborating Programme on International Drug

Monitoring for many years, and his expertise is frequently sought in countries as far flung as the United States, Hungary and China. His international status has already been recognised by his Presidency, some three years ago, of the International Society for Pharmacoepidemiology. As in clinical medicine, wisdom is an important commodity in overall drug risk-benefit evaluation, and it is fitting that the College should acknowledge a colleague whose wise council enhances therapeutic safety worldwide."

Tanzania

Ms Rose Shija, head of TADATIS, the Tanzania Drug and Toxicology Information Services, is on study leave for one year. She is spending that year in Germany studying Public Health. During her absence Mr Henry Irunde is acting head of TADATIS.

THE WHO INTERNATIONAL DRUG SAFETY PROGRAMME

Annual Meeting

Lisbon 15-17 September 1996.

Papers relating to the meeting have been circulated to all National Centres. If yours have gone astray or you need more copies, please contact us. Please do let us have your thoughts and suggestions about the agenda and the format of the meeting - we are keen to make sure your wishes and needs are met.

Contact Sten Olsson at the centre here with any problems or queries.

European Medicinal Product Identification Standard

In 1994 the European Committee for Standardisation (CEN) set up a working group with the intention of establishing a European Standard for identification of pharmaceutical products. Marie Lindquist, our research and development manager here in Uppsala, was elected a member of the core team of this working group.

In January 1996 the proposal of the working group was accepted as a pre-standard which means that it will be circulated for review among CEN member countries. After a review period of around two years the pre-standard might eventually, after due consideration of comments, be converted into a standard. Copies of the CEN pre-standard on medicinal product identification are available from us here in Uppsala.

The Uppsala Team

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Science and Quality Assurance Manager: Cecilia Biriell

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