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DRUG MONITORING

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ADVERSE REACTION NEWSLETTER 1996:1

NATIONAL DRUG MONITORING CENTRES -
DRUG SAFETY ISSUES

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World Health Organization. This is an unpublished document whose circulation is restricted. Your attention is drawn to the fact that some of its contents are confidential in nature.

GENERAL INFORMATION

Spain

The Catalan Institute of Pharmacology has been nominated a WHO Collaborating Centre for Studies and Information in Pharmacoepidemiology. The new centre was inaugurated in March 1995 by Dr Antesana from WHO. The new centre includes the Pharmacology Unit of the Department of Pharmacology and Psychiatry of the free university of Vall d'Hebron, the department of Clinical Pharmacology of the university and the Catalan Institute of Pharmacology.

The Institute was representing Spain in the WHO Drug Monitoring Program from 1984 to 1992 and is presently involved in i.a postgraduate courses in pharmacoepidemiology particularly with students from Latin America.

NATIONALLY CIRCULATED INFORMATION

Canada

Canadian Adverse Reaction Newsletter, Vol 6, No 1, January 1996.

Nicotine patches and exercise

Nicotine transdermal delivery systems offer an alternative to nicotine-containing chewing gum as an aid in overcoming the smoking habit. A number of adverse reactions have been recorded and documented in the product monographs for the various nicotine patches available in Canada. Reactions associated with nicotine toxicity can occur if patients wear more than one patch at a time or continue to smoke while wearing the patch.

In three cases there has been a close time relationship which suggests an association between the use of nicotine patches and an apparent increased toxicity during exercise. As a depot of nicotine accumulates in the skin covered by the patch, increased absorption may have occurred due to increased skin temperature and increased peripheral cutaneous vasodilation and perfusion

from exercising (1).

The precise pharmacological mechanisms for the symptoms remain unsure.

(1) Barkve TF et al. Increased uptake of transdermal glyceryl trinitrate during high exercise and during high ambient temperature. *Am Heart Journal* 1986; 112: 537-41.

Terbinafine and hepatobiliary reactions

Oral antifungal therapies should generally not be used for the treatment of trivial superficial fungal infections.

Drug-induced liver disorders range from asymptomatic reversible changes in liver function tests to acute fulminant liver failure. Terbinafine hydrochloride (Lamisil®), a topical and oral antifungal agent, is no different. Since its approval for use in Canada in May 1993, the Canadian national voluntary reporting system has collected 12 cases of hepatobiliary disorders associated with the use of oral terbinafine. This case series comprises seven men and five women with an average age of 56 years (range 30 to 73). Seven of the patients experienced signs and symptoms of liver dysfunction including jaundice (7), dark urine (6), fatigue (3), nausea (3) and anorexia (2).

Confounding factors for hepatic dysfunction were present in five cases: excessive alcohol consumption, hypercholesterolemia, cholelithiasis, possible drug interactions with niacin and clarithromycin respectively.

Reports in WHO files: Liver disorders total 226 reports; Hepatic function abnormal 69, Hepatitis cholestatic 39, Jaundice 32.

See also: ADR Newsletter 1994:2, information from Belgium.

Selective serotonin reuptake inhibitors (SSRIs) and hyponatraemia

The Canadian Adverse Reaction Monitoring Program recently reviewed 12 reports of SIADH/hyponatraemia associated with fluoxetine (Prozac®), 2 with fluvoxamine (Luvox®) and 1 with paroxetine (Paxil®). Although the number of reports is small, the elderly may be at increased risk for SSRI-induced hyponatraemia as the average age of the patients involved was 75 years (range 64 to 90). In 60% of the

cases, hyponatraemia developed two weeks or less after the SSRI was initiated.

Only 20% of the reports described symptoms of hyponatraemia. These included early symptoms such as weakness, lethargy, headache and anorexia and more progressive symptoms, including confusion and convulsions. The serum sodium level was provided in 80% of the reports. The average level was 120 mmol/L and the range was 106 to 125 mmol/L (normal range 135-145 mmol/L).

Hyponatraemia has been associated with all types of antidepressants. A trend seen in the Canadian data and in literature, is that the elderly appear to be at increased risk. Thus, the possibility of hyponatraemia and SIADH should be considered if a patient, particularly an elderly one, experiences weakness, lethargy, confusion or convulsions shortly after starting SSRI therapy.

Reports in WHO files: Hyponatraemia - Fluoxetine 592, Paroxetine 222, Sertraline 103.

See also: Newsletter No 1995:1, information from New Zealand.

Canadian Adverse Drug Reaction Newsletter, Vol 6, No 2, April 1996.

Metformin - lactic acidosis

The biguanide metformin is an oral antihyperglycaemic agent used in the management of non-insulin-dependent diabetes mellitus. Phenformin, another biguanide, was withdrawn from the market in many countries because of the high risk of inducing lactic acidosis; however, metformin is associated with a very low incidence of lactic acidosis because of its different pharmacokinetic properties. For example metformin is not metabolised by the liver, therefore there are no high-risk groups demonstrating an impaired metabolism. Metformin has been available in Canada since 1972. Since marketing, the Canadian Adverse Drug Reaction Monitoring Program has received 11 reports of lactic acidosis associated with the use of metformin. The outcomes were: four people died; four recovered; two patients had not yet recovered at the time of reporting; and one recovered with residual effects. In all cases, one or more risk factors for developing lactic acidosis were present: Five cases (3 fatal), had

pre-existing renal insufficiency; in four cases, there was implicit evidence of congestive heart failure from the concomitant medications being taken (e.g. digoxin, furosemide); and in one report the patient consumed an excessive amount of alcohol while on metformin. The Canadian Adverse Drug Reaction Advisory Committee has reviewed the 11 cases of lactic acidosis and concludes that none of the cases provided evidence that metformin was definitely the cause of the acidosis, but for most patients it may have been a contributing factor.

Reports in WHO files: Lactic acidosis - Metformin 174 reactions (8.5%), Phenformin 261 reactions (31.5%)

See also: ADR Newsletter 1995:2, information from Australia.

Nefazodone: Adverse Drug Reaction Profile

Nefazodone (Serzone) is a novel antidepressant that exerts a dual effect on serotonergic neurotransmission. Postsynaptically, it acts as an antagonist at a subtype of the serotonin receptor and presynaptically it blocks serotonin uptake. Antagonism at the postsynaptic receptor may influence the side effect profile of nefazodone by neutralizing some of the more activating effects of unopposed serotonin reuptake inhibition.

In May 1994 Canada was the first country to approve and market nefazodone. As of December 1995 the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) has received 58 adverse drug reaction reports comprising 137 reactions. The patients included 47 women and 11 men with a mean age of 42 (range 16 to 76) years. Reactions associated with the central nervous system were most frequently reported (24%). However, gastrointestinal (11%), peripheral nervous system (10%) and cardiovascular (10%) reactions were relatively frequent.

The most commonly reported reactions were dizziness (12), nausea (11), paraesthesia (9), agitation (4), headache (4), hypotension (4), rash (4), vertigo (4) and vomiting (4). Most are noted in the product monograph.

Some antidepressants, including nefazodone, inhibit the cytochrome P450IIIA4 isozyme; thus there is the potential for drug interactions. In 15 of the 58 reports,

patients were also taking a benzodiazepine. As described in the product monograph, the plasma concentrations of some benzodiazepines (triazolam, alprazolam) increased when co-administered with nefazodone; thus avoidance or adjustment of the dosage of the benzodiazepine may be required. Potential interactions between nefazodone and other drugs metabolized by this isozyme (e.g., cyclosporin, midazolam, nifedipine, quinidine, lidocaine and erythromycin) should also be considered.

Nefazodone is a new drug with limited post-approval experience. Therefore, the CADRMP would greatly appreciate the reporting of all clinically important adverse reactions in order that the ADR profile of nefazodone may be further defined.

Reports in WHO-file: Nefazodone - reports from United Kingdom and USA; Dizziness 120, Headache 105, Paraesthesia 59, Nausea 85, Agitation 28, Confusion 88, Somnolence 53, Vision abnormal 45.

Reference: Sussman N. The potential benefits of serotonin receptor-specific agents. J Clin Psychiatry 1994; 55[2,suppl]: 45-51.

ADR reporting 1995

Close to 5,000 Canadian spontaneous case reports were submitted to the CADRMP in 1995. Most reports were received from manufacturers, hospitals, Regional Centres and community pharmacists. Compared with previous years, the proportion of reports submitted by physicians and hospitals has decreased. This may be because these reports are included in those cases submitted by the Regional Centres.

Denmark

Ugeskr Læger 158/6, 5 February 1996.

Tamoxifen information about risk of endometrial cancer

In December 1994 the Danish Sundhedsstyrelsen received information from Germany about the risk of genotoxicity and increased risk of endometrial cancer in women treated with tamoxifen. The following has been introduced in the product information in Germany:

- Studies, both in vivo and in vitro, have shown that tamoxifen has a genotoxic potential after hepatic activation
- Clinical reports suggest that tamoxifen treatment increases the risk of endometrial cancer.

Following this information Sundhedsstyrelsen has in cooperation with involved companies decided to introduce the following warning in the product information for tamoxifen in Denmark:

"An increased number of endometrial changes have been reported, including hyperplasia, polyps and cancer in connection with tamoxifen treatment. The number and the pattern of this increase suggest that the mechanism behind this is related to the oestrogen properties of tamoxifen. All patients who experience abnormal bleeding during tamoxifen treatment should immediately be examined".

The approved indication for tamoxifen in Denmark is "palliative treatment of cancer mammae", but in the USA and many EU countries it has been tried as a prophylactic treatment in women with a special risk of developing breast cancer.

Sundhedsstyrelsen had, up to 2 October 1995, received one report of endometrial cancer with a possible relationship to tamoxifen treatment. In this particular case, however, it is more likely that the neoplasm was present when treatment was started. The risk of developing endometrial cancer was in a Swedish study (covering 2,729 breast cancer patients) found to be six times higher in women who had been treated with tamoxifen. The cumulative frequency after nine years was 16.8/1,000 as compared with 2.4/1,000 in non-treated women.

Reports in WHO files: Various types of uterine and endometrial neoplasms from 11 countries - 228 reactions. Breast fibroadenosis 4 from USA, breast neoplasm malignant UK1, USA 1.

Reference: Rutqvist LE, Johansson H, Signomklao T et al. Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. J Natl Cancer Inst 1995; 87: 645-51.

See also: ADR Newsletter 1994:4, information from New Zealand and ADR Newsletter 1995:1, information from USA.

Finland

Tabu, Vol 4, No 2, 1996.

Reporting of ADRs in 1995

For 30 years ADRs have been collected by the National Board of Health in Finland. This register now includes over 12,000 cases of suspected ADRs. A total of 626 new cases were reported last year by physicians or dentists. Less than 10 % of the cases were reported to the National Agency for Medicines by marketing authorization holders; the requirement that they report ADRs was promulgated as recently as last October, hence changes attributable to it are not yet visible.

Although the annual ADR reports concern some 200 medical substances, about 30% of the reports are concentrated on the 10 medicines giving rise to most of the ADR reports. This list of the most frequently reported substances is by no means a list of the 'most harmful' medicines, but it is a good indicator of what was considered the most problematic adverse effects of drug therapy. Table 1 shows a list of the 10 most frequently reported medicines in 1994 and 1995.

Table 1.

1994		1995	
clozapine	28	cefaclor	28
amoxicillin	22	clozapine	25
cefaclor	21	amoxicillin	21
terbinafine	20	sulpha-trimethoprim	19
nitrofurantoin	18	terbinafine	18
sulpha-trimethoprim	18	enalapril	14
cefuroxime	15	cefuroxime	13
enalapril	14	nitrofurantoin	12
itraconazole	14	fluoxetine	11
carbamazepine	14	azithromycin	9

Cefaclor was top of the list in 1995 and this refers to 20 cases of urticaria-arthritis reactions similar to serum sickness, 7 cases of similar type and one case of *Cl. difficile* diarrhoea. There were 20 cases of neutropenia and agranulocytosis among the clozapine reports. Among the sulpha-trimethoprim reports there were two cases of erythema multiforme, two of leucopenia and one of aplastic anaemia. Terbinafine has continuously featured in the reports, mainly due to skin reactions, among

them one case of erythema multiforme. Loss of taste has also been observed. Nitrofurantoin was reported with pulmonary reactions (9) and hepatitis (2). The publicity around fluoxetine may have stimulated reporting for this drug, the 11 reports include tremor, priapism and loss of libido. Fluoxetine has also been associated with potentiated effects of atenolol and felodipine. The reports of azithromycin, a new substance rapidly growing in use, mostly concerned cases of rash. However, the yet unpublished study of adverse reactions to antimicrobials, conducted by the National Agency for Medicines last year, does not support the idea that azithromycin would cause more skin reactions than other macrolides.

The number of reports received directly from physicians increased towards the end of 1995, and this elevated activity has continued during the first two months of 1996. If this new level of activity persists, Finland will soon reach a reporting frequency comparable with the other Scandinavian countries.

Melatonin

There is no scientific evidence of many of the alleged magical effects of melatonin, such as delayed ageing and life-prolonging properties. The secretion of melatonin by pineal gland is controlled by ambient light. The secretion is at maximum in the dark at night.

A few studies have been conducted where effects on circadian sleep-wake rhythm, its immuno-modulatory effects and other potential effects, for instance on the human reproductive mechanisms, have been noted. These suggest that melatonin meets the criteria of a prescription drug. The observations referred to are based on a limited number of studies, and in only a few studies has the patient material been sufficient for the results to be reliable. Most studies failed to use the necessary control substance.

See also: Information from Germany below.

France

Minutes from the French Pharmacovigilance Commission meeting, 11 January 1996.

Desernil-Sandoz (methysergide) and fibrosis

In spite of one month's interruption in the use of methysergide every six months, patients are not guaranteed to avoid developing retro-peritoneal or pulmonary fibrosis. With this therapeutic scheme the risk is strongly decreased, but not completely eliminated.

The frequency of reported cases of fibrosis in patients using this scheme is low (1 case in 40,000 months of treatment).

Reports in WHO file: Pulmonary fibrosis 24 reports, retroperitoneal fibrosis 77 reports (treatment scheme unknown).

Quinolones of the first generation - anaphylactoid reactions

Anaphylactoid reactions like shock, urticaria and Quincke's oedema that generally appear within two hours after taking the first tablet, have been associated with Negram® (nalidixic acid), Pipraf® (pipemidic acid), Apurone® (flumequine) and Eracine® (rosoxacin) for some of their galenic forms but the frequency of these effects is low. Such reactions to Urotrate® (oxolinic acid) have not been reported. Noted risk factors are particularly atopy or medical allergy. Because of the risk of cross allergy between quinolones and chemically related substances, caution is needed when prescribing quinolones.

Reports in WHO file: Nalidixic acid 72 cases, pipemidic acid 9 reports, flumequine 18 reports, rosoxacin 0 reports, oxolinic acid 1 report.

Spasfon® (phloroglucinol)

The low number of ADRs collected confirms the low toxicity of the widely used phloroglucinol. However, after receiving a third report of allergic reaction the National Commission considered it necessary to add the term hypersensitivity to the product information. The risk of developing atropine-like effects from the use of phloroglucinol has been discussed because of some reactions of anticholinergic manifestations.

Reports in WHO files: No relevant reports found.

Dicynone® (etamsylate) - fever

The answers to a questionnaire about pharmacovigilance have confirmed the hypothesis of

etamsylate causing fever. Positive rechallenge was noted in more than half of the cases, dechallenge was always positive and other drugs taken were almost always less suspected.

Reports in WHO file: Fever 7 reports.

Germany

Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin (BgVV), Pressedienst, 30 October 1995.

Melatonin

BgVV in Berlin informs that manufacturers of the 'miracle drug' melatonin, want to sell it as a food supplement. This substance is, however, due to its pharmacological effects, not a food supplement. Any usage of melatonin without a doctor's prescription is at one's own risk.

All food supplements are under the food legislation. Therefore, they do not need to be registered in Germany, but the manufacturer is responsible for selling a healthy and hygienic product.

Reports in WHO files: Breast enlargement 1, Hypotrichosis 1, Dreaming abnormal 1. All reports from USA.

Bundesinstitut für Arzneimittel und Medizinprodukte, No 1/96.

Iotrolan and iodixanol associated with hypersensitivity

Non-ionised low osmolar monomer X-ray contrast media, iotrolan and iodixanol, were in a literature article in 1993 (1) considered to induce less adverse reactions than the traditionally used X-ray contrast media.

However, since then reactions of redness of skin, itching, face oedema and urticaria have been reported. Only a few cases described respiratory oedema, hypotension and allergic shock. These hypersensitive reactions were not of the immediate type, but occurred later as a delayed type hypersensitivity when the patient might already have left the doctor.

Reports in WHO files: Iotrolan - allergic reaction DEN1, GFR 1.

Reference: (1) Waller PC, Wood SM. *Pharmaceutical Medicine* 1993; 7: 47-55.

Japan

Information on Adverse Reactions to Drugs, No 133, September 1995.

Todralazine hydrochloride and fulminant hepatitis

Todralazine hydrochloride is an antihypertensive drug of the hydralazine class approved in Japan in 1971. Serious hepatic damage such as fulminant hepatitis has been reported in eight cases when using this drug.

In cases reported, patients were receiving other medications as well, some of which are known to be a potential risk of liver damage.

Reports in WHO files: Hepatitis 1 from JPN, Hepatic necrosis 1 from JPN

Interferon-alfa and interferon-beta in association with diabetes mellitus

Serious aggravation, or development of diabetes mellitus following treatment with interferon (IFN) has been documented in 61 cases; aggravation, including blood glucose elevation in 36 cases, and development in 25 cases.

The cases in which diabetes mellitus developed were generally as follows: The patients, 15 men and 10 women, ranged in age from 28 to 68 years with a primary disease of chronic active hepatitis C in 24 cases and renal cancer in one case. The diagnosis of diabetes mellitus was made between 15 days and 10 months after the start of IFN therapy. Eight patients had a diabetic diathesis such as a positive test for urinary glucose or impaired glucose tolerance before the start of IFN medication. This would indicate that appropriate pre-treatment clinic questioning and examinations may permit early detection of the development of the adverse condition. Of the 25 cases reported, no particular treatment was required after attaining a satisfactory control of blood glucose in 10 cases, while the other 15 cases required continued control of blood glucose with insulin or hypoglycaemic agents. There were three patients whose disease progressed into diabetic coma.

Reports in WHO files: Diabetes mellitus 13 reactions from 7 countries, Diabetes mellitus aggravated 5.

Unoprostone isopropyl and corneal disorder

Unoprostone isopropyl is a prostaglandin metabolic for the treatment of glaucoma and ocular hypertension, approved in Japan as of July 1994. Corneal disorders associated with the administration of unoprostone isopropyl have been reported in five cases. Most patients in the cases reported were elderly and the adverse reactions usually occurred with multiple eyedrop medication.

Reports in WHO files: Corneal ulceration 1, Keratitis 3 all from JPN.

Information on Adverse Reaction to Drugs in Japan No 134, 1995.

Domperidone and anaphylactic shock

The Japanese authorities have previously informed about the risk of anaphylactic shock with intravenous injection or the use of domperidone as suppositories. Four cases of anaphylactic shock have now been reported also with oral administration. In all cases the patients were females between 19 and 70 years of age. Since symptoms in all cases appeared immediately following oral medication with domperidone, relationship with the drug cannot be ruled out. One of the patients was concomitantly treated with pranoprofen (a NSAID).

Reports in WHO files: Anaphylactoid reaction 7 after oral administration

Malaysia

Berita Ubat-Ubat, Vol 9, No 4, 1995.

Flucloxacillin - liver toxicity

The Drug Control Authority (DCA) has decided that a warning statement be included with flucloxacillin product information:

"Flucloxacillin can cause severe hepatitis and cholestatic jaundice, which may be protracted. This reaction is more frequent in elderly patients and in those who take the drug for prolonged periods." Hepatic reactions to flucloxacillin is, however, relatively uncommon. Adverse reactions to flucloxacillin may be unrecognised because of its delayed onset (6 weeks) after drug administration. There are 10 preparations of flucloxacillin registered in Malaysia.

