



WHO COLLABORATING CENTRE
FOR INTERNATIONAL
DRUG MONITORING

Stora Torget 3
S-753 20 UPPSALA
Sweden

September 1998

ADVERSE REACTION NEWSLETTER 1998:3

**NATIONAL DRUG MONITORING CENTRES -
DRUG SAFETY ISSUES**

This newsletter contains information reported to the WHO and WHO Collaborating Centre for International Drug Monitoring; however, the

information reported does not necessarily reflect the official views, decisions or policies of the World Health Organization.

NATIONALLY CIRCULATED INFORMATION

Australia

ADRAC Bulletin, Vol 17, No 3, August 1998

Bruising and bleeding with SSRIs

SSRIs such as fluoxetine, paroxetine and sertraline have become widely used in Australia. Over the past few years their use in the treatment of depression and other disorders has increased considerably and ADRAC has been able to develop a comprehensive adverse effect profile. One effect which has emerged is bruising and bleeding, which in the majority of cases is not associated with thrombocytopenia but with platelet dysfunction.

Table 1 - Bruising and bleeding with SSRIs*

	Fluoxetine	Paroxetine	Sertraline
Total Reports	919	1036	2023
Purpura/Bruising	20	38	16
Bleeding	10	16	41
Thrombocytopenia	9	10	5
Platelet dysfunction	5	5	4

* more than one reaction may be present in a report

Purpura appears to be an important adverse effect for the SSRIs. With 38 reports submitted to ADRAC, paroxetine is one of the most commonly reported causes of purpura. Only seven of these cases occurred in the context of thrombocytopenia.

Of the 14 reports documenting platelet abnormalities, 11 occurred in association with purpura or bleeding. Five of the reports documented abnormal platelet aggregation which is consistent with the postulate that fluoxetine may diminish granular storage of serotonin in platelets, creating a haemostatic defect which disrupts the platelet aggregation process, resulting in bleeding.^{1,2,3} It has been suggested that this is probably a rare situation which only occurs in individuals with an underlying platelet disorder

or an altered platelet serotonin reuptake system.^{2,3}

References:

1. Alderman CP, Moritz CK, Ben-Tovim DI. Abnormal platelet aggregation associated with fluoxetine therapy. *Ann Pharmacother* 1992; 26: 1517-19.
2. Humphries JE, Wheby MS, Vandenberg SR. Fluoxetine and the bleeding time. *Arch Pathol Lab Med* 1990; 114: 727-8.
3. Pai VB, Kelly MW. Bruising associated with the use of fluoxetine. *Ann Pharmacother* 1996; 30: 786-8.

Drugs that make you forget

An elderly man taking allopurinol, diclofenac and gemfibrozil was prescribed simvastatin to help control his hypercholesterolaemia. After a couple of weeks he noticed a loss of memory for recent events. This problem resolved within two weeks of stopping simvastatin and recurred within a week of restarting the drug. In another report, a middle aged woman took an indomethacin capsule for back pain and developed amnesia for the 3 hour period prior to the ingestion of the capsule and for two hours afterwards. She then recalled that she had experienced a similar effect (which she did not associate with the drug at the time) two years previously after she had taken an indomethacin capsule.

Amnesia or memory impairment in association with drug therapy is a rare occurrence and of the 73,000 reports received by ADRAC over the past ten years, this adverse reaction is documented in only 219. There are some drugs such as the benzodiazepines which are established as a cause of amnesia which would not normally be the subject of a report to ADRAC because of the well-known association. Table 2 lists those drugs most commonly reported to ADRAC in association with this effect over the past 10 years. The table also lists the reports of amnesia as a percentage of the total number of reports for each drug. Since amnesia occurs in about 0.25% of the reports in the database, the reaction might be important for those drugs in which it occurs at a considerably higher percentage than 0.25%.

Table 2 - Reports of Drug-Induced Amnesia*

Drug	Reports of Amnesia	Percentage of Total Reports for the Drug
Sertraline	19	0.9
Simvastatin	14	0.8
Paroxetine	8	0.8
Midazolam	5	2.1
Dothiepin	5	1.6
Moclobemide	5	1.0
Fluoxetine	5	0.5
Ranitidine	5	0.4

* The drug with the highest proportion of reports (7: 3.4%), dexfenfluramine, has recently been withdrawn.

Of the 219 reports of drug-induced amnesia analysed, there was a single drug suspected in the majority (84%) of the reports. Ages of the patients ranged from 5 to 98 (median: 48) years and the onset of the reaction varied from the day drug therapy was commenced to many years afterwards with most occurring during the first week of therapy. Over a quarter occurred on the day the drug was started. The reaction occurred on rechallenge in 16 of the reports and most of the patients had recovered at the time the report was submitted. A number of these cases were reminiscent of transient global amnesia suggesting that a drug cause should be considered in such instances.

Depression with isotretinoin

There has been recent publicity linking isotretinoin (Accure, Roaccutane) with depression. From 1985 to June 1998, ADRAC has received a total of 129 reports of suspected adverse reactions in association with isotretinoin. Of these, 12 have described depression. All the patients involved were young (age range: 15-40 years, median: 19 years, M:F = 9:3) and taking the drug for treatment of acne. Two reports described the re-emergence of depression and in the other 10 reports, depression was noted for the first time. Two cases were described as severe and 4 cases had psychotic features. Three patients developed suicidal thoughts and two patients attempted suicide. One of these had a fatal outcome. Of the other 11 patients, 3 had recovered after withdrawal of isotretinoin, *WHO ADR Newsletter 1998:3, page 2*

one was improving with the use of an antidepressant, and the other 7 had not recovered at the time the report was submitted

Canada

Canadian Adverse Drug Reaction Newsletter, 8, No 3, July 1998

Olanzapine: hematological reactions

Olanzapine (Zyprexa[®]) is a new antipsychotic drug indicated for the acute and maintenance treatment of schizophrenia and related psychotic disorders. It is structurally similar to clozapine, an antipsychotic drug approved for the management of treatment-resistant schizophrenia. Olanzapine has been found to improve both the positive (hallucinations, delusions, hostility) and negative (blunted affect, emotional and social withdrawal) symptoms of schizophrenia and has a lower propensity for causing extrapyramidal symptoms than does haloperidol.^{<2,3>}

With clozapine, a major limitation of its use is the high incidence of agranulocytosis. This reaction has been reported to occur in about 1% of treated patients per year and has necessitated regular blood monitoring.^{<4>} It has been postulated that a reactive metabolite is responsible for clozapine-induced agranulocytosis.^{<5>} Olanzapine received approval to be marketed in Canada in July 1996. As of April 1998 the CADRMP had received 6 reports of decreased hematological values associated with the use of olanzapine.

In the first case a 35-year-old man experienced a decreased granulocyte count with normal total white blood cell count (WBC) 1 1/2 months after starting olanzapine therapy. The physician also suspected a viral infection as a potential causative factor. Over 1 year earlier he had had a decreased WBC count during clozapine therapy. In the second case, a 75-year-old woman had a significant decrease in WBC count 3 days after starting olanzapine; the count returned to normal 1 day after olanzapine was stopped. Confounding factors in this case included the use of concomitant drugs reported to rarely cause agranulocytosis and a history of breast cancer and lymphoma. The third case involved a 46-year-old man in whom pancytopenia developed. The report indicated that the reaction was due to a medical problem of megaloblastic anemia secondary to vitamin

B₁₂ and folate deficiency and not to the olanzapine. Olanzapine therapy was restarted in this patient, with no subsequent problems. The remaining 3 cases involved men aged 34 to 66 years who had had a decreased WBC count with decreased granulocyte count (2 cases) or neutrophil count (1 case) during clozapine treatment. Although their hematological values were still low, each patient was switched to olanzapine.

In 2 cases olanzapine was started less than 1 week after stopping the clozapine. The olanzapine was stopped within 3 days because the WBC count continued to decrease. Two months later the WBC and granulocyte counts returned to normal. This recovery time contrasts with data from one study in which the mean time to recovery from clozapine-induced agranulocytosis (no exposure to olanzapine) was 3 days. No confounding medical conditions were reported in these 2 cases.

In the third case the patient was switched to olanzapine within 3 weeks after receiving clozapine; he died after 2 weeks of olanzapine therapy. His WBC and neutrophil counts had increased after switching to the olanzapine. Three days before death the olanzapine dosage had been increased to 20 mg, and the day before death fever developed. Concomitant medications included methotrimeprazine (300 mg/d), and the addition of lithium (600 mg/d), lorazepam (2 mg/d) and chloral hydrate (2 g/d) the day before he died. The cause of death was reported as unknown.

References

1. Budavari S, editor. *The Merck index*. 12th ed. Whitehouse Station (NJ): Merck Research Laboratories; 1996. p. 411, 1170.
2. Beasley CM Jr, Tollefson GD, Tran PV. Efficacy of olanzapine: an overview of pivotal clinical trials. *J Clin Psychiatry* 1997;58(Suppl 10):7-12.
3. Beasley CM Jr, Tollefson GD, Tran PV. Safety of olanzapine. *J Clin Psychiatry* 1997;58(Suppl 10):13-7.
4. Fulton B, Goa KL. Olanzapine – a review of its pharmacological properties and therapeutic efficacy in the management of schizophrenia and related psychoses. *Drugs* 1997;53:281-98.
5. Uetrecht J, Zahid N, Tehim A, Fu JM, Rakhit S. Structural features associated with reactive metabolite formation in clozapine analogues. *Chem Biol*

Interact 1997;104:117-29.

6. Flynn SW, Altman S, MacEwan GW. Prolongation of clozapine-induced granulocytopenia associated with olanzapine. *J Clin Psychopharmacol* 1997;17:494-5.

Valproic acid (Depakene®) - pancreatitis

Three cases of pancreatitis occurring with the administration of valproic acid for the treatment of seizures were recently reported to the CADRMP. They involved 2 children (3-year-old boy and 14-year-old girl) and 1 patient of unknown age and sex. The adverse event was diagnosed 18 months after starting therapy in 1 patient and 9 months after in another patient, who was also taking sucralfate, cisapride, omeprazole and chloral hydrate. All 3 patients were admitted to hospital. At the time of reporting, 1 patient had not yet recovered; the outcomes of the other 2 were not provided.

Cefaclor (Ceclor®) - hypersensitivity myocarditis

Noteworthy is the reported and published case of a 12-year-old girl in whom hypersensitivity myocarditis developed due to an allergic reaction to cefaclor given to treat otitis media (*J Pediatr* 1998;132:172-3). The patient was admitted to hospital with acute renal failure and a rash compatible with erythema multiforme 1 week after starting the antimicrobial therapy. Subsequently, she showed signs of low cardiac output. The report states that the patient had clinical and histologic features of hypersensitivity myocarditis. The child's condition dramatically improved within 48 hours after stopping the drug and starting corticosteroids and immunoglobulins.

Latanoprost (Xalatan™)

Latanoprost, a new prostaglandin, is indicated for the reduction of intraocular pressure in the treatment of glaucoma. Two reports of serious suspected cardiovascular reactions were received in 1997. One case involved a woman who experienced a racing heart and palpitations. She was not taking any concomitant drugs and had no history of drug allergy. The second involved a 71-year-old man with a history of myocardial infarction and of "much greater than normal drug sensitivity."

Within 20 minutes after instilling 1 drop of latanoprost diluted with distilled water to one-fifth its strength, he experienced headache and, 12 hours later, chest pain and bronchial constriction lasting for 10 hours. Mild chest discomfort then occurred for 24 hours. After the symptoms subsided latanoprost was resumed at one-twenty-fifth its strength, with no side effects.

Finland

Tabu, Vol 6, No 4, 1998

Fluoroquinolones and their adverse effects on the central nervous system

Fluoroquinolones differ from other antimicrobials, not only structurally, but also by their mechanism of action and quite unique profile of adverse drug reactions. The adverse reactions include the more unusual characteristic of tendinitis. Other characteristics, almost as rare, are the adverse drug reactions on the central nervous system, attributable to all drugs in this group. Adverse drug reactions related to the central nervous system are observed in ½ - 2% of patients treated with fluoroquinolones, depending on the substance and the dosage. Fluoroquinolones can cause convulsions in susceptible patients especially when taken with anti-inflammatory analgesics. The increased tendency to convulsions due to interaction is reason enough to avoid the consumption of fluoroquinolones with anti-inflammatory analgesics, also bearing in mind the patient's potential consumption of OTC analgesics. Furthermore, the interaction of fluoroquinolones with malaria drugs, especially mefloquine, is worth remembering when looking for causes for sudden unusual psychiatric symptoms.

Sweden

Information from the Medical Products Agency, Vol 9, No 3 June 1998

Sulfasalazine, mesalazine and retrosternal pain

A 34-year-old woman diagnosed with Mb Chron was treated with rectal steroids and mesalazine. After a month the patient experienced retrosternal pain. Mesalazine was changed to sulfasalazine and the pain disappeared, but

returned when the dose was increased. The medication was terminated and the pain disappeared.

Alendronate - risk of oesophageal stricture

Fosamax (alendronate) was registered in Sweden in 1995 for the treatment of postmenopausal osteoporosis. After receiving reports of oesophagitis and oesophageal ulceration, the MPA accentuated the recommendation on how to take the medication. The MPA has sixteen cases of oesophagitis, seven cases of stricture and six cases of ulceration. Some of the patients had more than one diagnosis. The symptoms started between four days and one and a half year after they began treatment with Fosamax. After X-ray or endoscopy to establish injury of the oesophagus, withdrawal of Fosamax took up to six months. This shows a lack of attention from the doctors. In the twelve cases of injury without stricture, there was no delay between onset of symptoms and withdrawal of Fosamax, except from one patient with a delay of six weeks. This indicates that continued treatment after onset of symptoms is an important risk factor for the development of oesophageal stricture. The MPA makes the conclusion that patients and doctors need more information on this matter.

Isotretinoin and psychiatric disorders

Since the introduction of Roaccutane (isotretinoin), several cases of depression have been reported throughout the world. The MPA has received twelve cases of psychiatric adverse reactions in connection with Roaccutane. No deaths have been reported. The MPA is planning a study to follow-up 5800 patients treated with the drug.

See also Nationally Circulated Information from Australia above.

Calcium antagonists - depression and suicide

There are reports describing depression/suicide in connection with calcium antagonists. The MPA makes the conclusion that there is a need for further information to establish a possible relationship between depression/suicide and calcium antagonist. Among patients with heart disease there are many factors that may increase the risk of depression. There are reports of

depression/suicide in connection with calcium antagonists as well as with beta blocking agents and ACE-inhibitors.

Reported ADR's in 1997 after vaccination

An essential part of all reported ADR's concerns different types of vaccines. The most common ADR is injection site reaction. Comparing the great use of vaccines there are relatively few ADR reports. This probably reflects a considerable underreporting. It could also reflect that the used vaccines are safe. Since vaccines generally are used in healthy, often very young people, it is essential that vaccines are safe.

Psychiatric disorders after inhalation of corticosteroids

During the 90's, the use of corticosteroids for inhalation for treatment of asthma has increased in Sweden. Aggressive behaviour, depression, hallucination and neurosis have been reported. A majority of the cases concerns children less than sixteen years of age. After stopping the medication or decreasing the dose, these symptoms subsided and vanished. Physicians should be aware of the risk of developing psychiatric disorders, especially among children.

Toradol (ketorolac) - acute renal failure

The MPA has received six case reports of decreased renal function in connection with Toradol. Five patients were between seventeen and twenty-three years of age and were undergoing minor surgery. They all developed acute non-oliguria renal failure after 1-2 days of treatment with ketorolac. None of these patients had any known riskfactor for developing renal failure after treatment with NSAID's. The sixth patient was older (60 years), underwent a greater surgery and was treated with cephalosporins. This patient developed acute oliguria renal failure. It is well known that NSAID's may cause renal failure when perfusion of the kidneys is decreased. When ketorolac is used for treatment of postoperative pain, it is important to make sure the patient is well hydrated.

Omeprazole - warfarin interaction

A 43-year-old woman with a history of rheumatic fever and valvular disorder since childhood. She had had several operations since 1972 and she had taken warfarin since the 70's. In 1997 she was prescribed omeprazole for dyspepsia, and amoxicillin and metronidazole during one week for infection with *Helicobacter pylori*. The PK-value decreased from 15-19% to 8%, which is below normal value, when treatment with omeprazole started. When treatment was ended, the PK-value was normalized. The dyspepsia still remained and omeprazole was once more used with the result that the PK-value decreased and the dose of warfarin had to be decreased. Since the PK-value decreased when the patient was taking omeprazole, it could be suspected that omeprazole or one of its metabolites inhibit the metabolism of warfarin. It is therefore important to check the PK-value when treatment with omeprazole is started.

Cardiomyopathy and tricyclic anti-depressants

A 55-year-old man, alcoholic, with diabetes type II and hypertonia, seeks medical advise due to shortness of breath and deteriorated general condition. He used clomipramine since many years for neckpain. Investigation showed cardiomyopathy, and treatment with ACE-inhibitors and diuretics began. The patient was also switched to insulin-therapy. One year later his diabetes had improved but the cardiomyopathy hadn't changed. The myopathy was suspected to be caused by clomipramine. After lowering the dose of clomipramine, the patient's condition improved and diuretics were no longer needed. Two years later, his heart function was normalized.

United kingdom

Current Problems in Pharmacovigilance, Vol 24, May 1998

The safety of inhaled and nasal corticosteroids

Following a review of the available evidence, the committee on safety and MCA have concluded that clinically important systemic adverse effects can occur at licensed doses of these products. The risks of these effects occurring are increased following prolonged, high dose

therapy, although susceptibility to these effects varies between individuals. The risks with intranasal corticosteroids are generally lower than with inhaled steroids as the doses used in clinical practice are lower. Five main areas of concern were identified: adrenal suppression, osteoporosis or changes in bone mineral density, growth retardation in children, cataracts and glaucoma. Following our assessment of these areas, the following conclusions have been reached:

1. The dose should be titrated to the lowest dose at which effective control of asthma or rhinitis is maintained.
2. The potency of corticosteroids varies between individual drug substances. Greater potency does not, however, necessarily equate with greater efficacy. All inhaled corticosteroids have the potential to cause systemic side-effects, the frequency and severity of which will be dependent upon the dose and duration of treatment.
3. Systemic effects of inhaled and nasal corticosteroids may occur, particularly at high doses prescribed for prolonged periods. Possible systemic effects with inhaled corticosteroids include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. In children receiving nasal corticosteroids at licensed doses, growth retardation has been reported.
4. It is recommended that the height of children receiving prolonged treatment with inhaled or nasal corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled or nasal corticosteroid, if possible, to the lowest dose at which effective control of asthma or rhinitis is maintained. In addition, consideration should also be given to referring the patient to a paediatric specialist.
5. Prolonged treatment with high doses of inhaled corticosteroids, or higher than recommended, doses of nasal corticosteroids may result in clinically significant adrenal suppression. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

Systemic corticosteroids in pregnancy and lactation

No evidence of an increase in congenital malformations in man

The following conclusions have been reached and are being added to product information:

1. The ability of corticosteroids to cross the placenta varies between individual drugs. For example, betamethasone and dexamethasone readily cross the placenta while 88% of prednisolone is inactivated as it crosses the placenta.
2. Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate/lip and effects on brain growth and development. However, in humans, there is no convincing evidence that systemic corticosteroids cause an increased incidence of congenital abnormalities, such as cleft palate or lip.
3. When administered for *prolonged* periods or *repeatedly* during pregnancy, systemic corticosteroids significantly increase the risk of intra-uterine growth retardation (IUGR). There is no evidence for an increased incidence of IUGR following short-term treatment, such as prophylactic treatment for neonatal respiratory distress syndrome.
4. There is a theoretical risk of adrenal suppression in the neonate following prenatal corticosteroid exposure. However, this usually resolves spontaneously after birth and is rarely clinically important.
5. Prednisolone is excreted in small amounts into breast milk. However, doses of up to 40 mg of prednisolone daily or equivalent are unlikely to cause systemic effects in the infant. Infants of mothers taking higher doses than this should be monitored for signs of adrenal suppression. No data are available on the transfer of other systemic corticosteroids into breast milk.

Calcort (deflazacort): advertising has been withdrawn

Promotional claims of improved safety relative to prednisolone withdrawn

Recent promotion of Calcort (deflazacort) claimed that it has a lower incidence of steroid induced side effects compared to prednisolone. A recent review of the data cited in support of claims relating to the relative safety of Calcort (deflazacort) has resulted in the revision of these claims at the request of the MCA. All current advertising and promotional material making relative safety claims has been withdrawn for the present time.

All systemic corticosteroids may produce clinically significant adverse reactions which are primarily dependent on dose and duration of use. These adverse reactions are included in product information. The British National Formulary gives doses of different systemic corticosteroids equivalent to 5 mg of prednisolone. Six mg of deflazacort is of approximately equal potency to 5 mg of prednisolone.

Advice about adverse drug reaction reporting

New medicines

1. Report ALL suspected reactions, that is, any adverse or unexpected effect, however minor, which could conceivably be attributed to the medicine.
2. Please report even if the reaction is well recognised or if you are unsure of the causal relationship.
3. New medicines have an inverted black triangle in the British National Formulary, MIMS and the Compendium of Data Sheets and Summary of Product Characteristics.

USA

FDA Medical Bulletin, Vol28, No 1, SUMMER 1998

Standardized grass pollen extract

Standardized grass pollen extracts are now available for use in diagnosing and treating grass-allergic patients. These products have a more accurate potency determination, greater lot to lot consistency, and better

defined stability than was available previously. They will benefit patients by reducing dose variability, permitting a more consistent response to immunotherapy, while decreasing the risk of adverse reactions due to incorrect dosing. They must be used with great care in treating highly sensitive grass-allergic patients.

The eight standardized grass pollen extracts include:

COMMON NAME	BOTANICAL NAME
1. Kentucky (June) Bluegrass	Poa pratensis
2. Meadow Fescue	Festuca elatior
3. Orchard	Dactylis glomerata
4. Perennial Rye	Lolium perenne
5. Redtop	Agrostis alba
6. Sweet Vernal	Anthoxanthum odoratum
7. Timothy	Phleum pratense
8. Bermuda grass	Cynodon dactylon

DRUG WITHDRAWALS

Australia

ADRAC Bulletin, Vol 1, No 3, August 1998

Worldwide withdrawal of mibefradil

Mibefradil (Posicor) is the first of a new class of calcium antagonists which blocks both T and L type channels. In Australia it had been approved for treatment of hypertension and/or chronic stable angina pectoris. Early in June the drug's sponsor announced a worldwide withdrawal of the drug because of its interactions with many other drugs.

Up until this time, ADRAC had received 55 reports of suspected adverse reactions associated with mibefradil. Bradycardia was the single most common reaction and accounted for almost half the reports. Three other reports

documented interactions of mibefradil with other drugs. Two reports described rhabdomyolysis with gross elevation of creatine kinase after mibefradil was added to long term simvastatin therapy and the other report of a suspected interaction involved a 36 year old man whose cyclosporin level became elevated after mibefradil was added to his other therapy.

At the time of the withdrawal, more than 25 drugs were suspected of interacting with mibefradil. It was considered by the sponsor that this number and diversity of drugs could not be practically addressed by standard warning labels. Included in the potentially interacting drugs are amiodarone, astemizole, cisapride, cyclosporin, erythromycin, quinidine, simvastatin and terfenadine.

Reports in WHO file: Bradycardia 45

Tanzania

Drug Information Bulletin Vol 10, No 1, 1998

Furazolidone withdrawal

The Pharmacy Board has announced withdrawal of all preparations containing furazolidone with effect from February, 1998.

Furazolidone is a nitrofurantoin derivative which is active against the protozoan *Giardia lamblia* and against a range of enteric bacteria including enterococci, *Escherichia coli*, *Salmonella* spp., *Shigella* spp. And *Vibrio cholerae*. The drug is bactericidal and appears to act by interfering with bacterial enzyme systems. It is used both for human beings and veterinary drugs. It has been proved to be carcinogenic, hence threatening the health of consumer.