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ADVERSE REACTION NEWSLETTER 1998:4

**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 4, November 1998

Nefazodone

Nefazodone (serzone) is one of the new antidepressants which was marketed in Australia in mid 1997. It is related to the SSRIs but has a dual action in that it works on both sides of the serotonin synapse. It blocks the 5HT₂-receptor and inhibits serotonin reuptake. It also has weak α_1 -adrenergic blocking activity. ADRAC has received 147 reports in association with nefazodone and the most commonly reported reactions are shown in the table.

Of particular importance are the reports of hepatic dysfunction. These developed from 3 weeks to a number of months after the drug was started. In the 8 reports in which liver function tests were provided, significant rises in alanine amino transferase (ALT) to between 473 and 3380 U/L (reference range: 0-40 U/L) and in aspartate amino transferase (AST) to between 176 and 1326 U/L (reference range: 0-40 U/L) were noted. Three patients presented with jaundice. In one of these, a liver biopsy was consistent with drug-induced hepatitis. At the time the reports were submitted, 4 patients had recovered, 2 had not recovered, and 3 were improving. The other patient, who was taking nefazodone, trifluoperazine and oxazepam developed jaundice, encephalopathy and hepatic failure and died during a liver transplant operation.

Most Commonly Reported Reactions with Nefazodone

Nausea/Vomiting	24
Abnormal Vision	20
Dizziness/Vertigo	14
Headache	14
Fatigue	10
Somnolence	10
Ataxia	10
Confusion	10
Hepatic Dysfunction	10
Tremor	9
Anxiety	7

The reports of visual disturbance highlight some unusual effects. While five of them described blurred vision, and

two others described mydriasis, the others described such curious effects as "visual lag", "thought my glasses were scratched", "light more visible and shadows and textures compelling", "cobwebs in front of the eyes" (two reports described this effect), "triple vision", "shimmering in the periphery", "trail of images", "flashing lights with tails", "multiple images", "stripe in the visual field", and "after image when turns head from side to side only at night". There was also a report of greatly decreased visual acuity

Ondansetron and chest pain

Ondansetron (Zofran) is a 5HT₃-receptor antagonist which is indicated for the prevention and treatment of nausea and vomiting induced either by cytotoxic therapy or radiotherapy, or occurring postoperatively. Since its marketing in 1991, ADRAC has received a total of 232 reports in association with the drug. Of these, 19 have described chest pain, including myocardial ischaemia (1 report) and/or myocardial infarction (2 reports) in association with ondansetron. In the 5 cases described below, the drug was given in a situation unrelated to, or not simultaneously with, chemotherapy.

In one report, a 48 year old female developed dysaesthesia, numbness, headache, nausea, left upper limb pain and chest tightness 20-30 minutes after the second ondansetron injection. A third injection the following day produced similar, but more severe symptoms. In another case, a 62 year old female was given intravenous ondansetron for nausea due to migraine and she experienced angina-like chest pain associated with ECG changes. In a third case, two weeks after maintenance chemotherapy, a 20 year old female was administered intravenous ondansetron and within a minute of starting the infusion, she developed central chest pain, shortness of breath and a dry cough.

The symptoms resolved on stopping the infusion but they recurred when the infusion was restarted. In two other cases in which ondansetron was the only suspected drug, chest pain was associated with the use of two oral doses given to control nausea and vomiting in one report, and in the other, chest tightness occurred after intravenous ondansetron.

In the other 14 cases, ondansetron was administered concurrently with chemotherapy so it is possible that one of the cytotoxic drugs was the cause of the chest pain. However, the use of ondansetron was a common link. Apart from one patient who developed a fatal myocardial infarction in association with a paclitaxel (Taxol) protocol, all the patients recovered.

There have also been literature reports of this association. In one report, 7 cases were documented and in another report, the reaction recurred on rechallenge with ondansetron. (1,2) The reports to ADRAC suggest that chest pain is a possible adverse effect of ondansetron. As the drug becomes more widely used in the treatment of post-operative and other causes of nausea and vomiting, this effect may become more apparent.

References:

1. Ballard HS, Bottino G, Bottino J. Ondansetron and chest pain. *Lancet* 1992; 340: 1107.
2. Frigerio C, Buchwalder PA, Spertini F. Ondansetron: reasons to be restrictive. *Lancet* 1996; 347: 1484-5.

Nitrates and Viagra must not be used concomitantly

Viagra is contraindicated in men for whom sexual intercourse is inadvisable due to cardiovascular risk factors.

As most readers would be aware, sildenafil citrate (Viagra) was recently marketed in Australia for the treatment of erectile dysfunction in adult males.

In the United States, where the drug has been marketed since late March, 69 patients have died after using Viagra. In the 48 patients in whom the cause of death was known, 2 had strokes and 46 had cardiovascular events. The average age of the men involved was 64 years and 12 men also took a nitrate, which is contraindicated. Fifty one of the 69 patients had one or more risk factors for cardiovascular events and 3 additional persons had coronary artery disease detected at autopsy.

In Australia, there has been one report involving the drug. It is poorly documented but describes a man who died after using the drug.

The relatively large number of reports of death is difficult to interpret as the drug is used in a group of patients with significant risk factors for cardiovascular events. Erectile dysfunction may have been caused by cardiovascular disease and sexual activity itself is a further risk factor. However, there has been a recent report from The Netherlands in which a 65 year old man without a history of cardiovascular disease had an acute myocardial infarction within an hour of taking the drug but without engaging in sexual activity.

Viagra has vasodilator properties and results in transient decreases in blood pressure that may unmask or aggravate ischaemic symptoms in men with cardiovascular disease.

This effect may be potentiated by administration of nitrates. In the event that a patient taking Viagra develops a cardiac ischaemic event, the time of the last dose of Viagra should be established and nitrates should be avoided for the following 24 hours. Additional adverse effects identified in clinical trials included headache, flushing, and nasal congestion, all of which are related to vasodilatation.

Other reported adverse effects were dyspepsia, abnormal vision and diarrhoea.

Reference:

1. Feenstra J, van Drie-Pierik RJHM, Laclé CF, Stricker BHCh. Acute myocardial infarction associated with sildenafil. *Lancet* 1998; 352: 957-8.

Canada

Canadian Adverse Drug Reaction Newsletter, Vol 8, No 4, October 1998

Discontinuation reactions associated with SSRIs

Withdrawal reactions following the discontinuation of tricyclic antidepressants are well known, and general guidelines recommend reducing the dose gradually. However, adverse reactions have also been identified with the discontinuation of selective serotonin reuptake inhibitors (SSRIs). The risk of SSRI discontinuation syndrome appears to be higher with SSRIs that have short half-lives (e.g., paroxetine, fluvoxamine and sertraline) and when treatment lasts 2 months or more. The CADRMP has received 26 reports of discontinuation symptoms for the 4 SSRIs marketed in Canada.

Rosenbaum and Zajecka suggested the following strategies to manage symptoms associated with the discontinuation of SSRIs:

1. Reassure the patient that symptoms are usually mild and transient. In most cases they will resolve in 7 to 14 days.
2. Gradually taper all SSRIs except fluoxetine. The final tapered dose should be less than the initial minimum therapeutic dose.
3. If acute symptoms appear during tapering or persevere despite tapering, restart the original agent and slow the rate of taper.
4. If symptoms are severe and the patient is unable to discontinue the SSRI despite tapering, consider

switching to fluoxetine (long-acting).

Discontinuation symptoms may appear when SSRI therapy is stopped or the dose is reduced.

References

1. *Drug information for the health care provider*. 18th ed. Rockville (MD): US Pharmacopeial Convention Inc.; 1998.
2. Schatzberg AF, Haddad P, Kaplan EM, Lejoyeux M, Rosenbaum JF, Young AH, et al. Serotonin reuptake inhibitor discontinuation syndrome: a hypothetical definition. *J Clin Psychiatry* 1997;58(Suppl 7):5-10.
3. Haddad P. Newer antidepressants and the discontinuation syndrome. *J Clin Psychiatry* 1997;58(Suppl 7):17-22.
4. Stahl MMS, Lindquist M, Pettersson M, Edwards IR, Sanderson JH, Taylor NFA, et al. Withdrawal reactions with selective serotonin re-uptake inhibitors as reported to the WHO system. *Eur J Clin Pharmacol* 1997;53:163-9.
5. Rosenbaum JF, Zajecka J. Clinical management of antidepressant discontinuation. *J Clin Psychiatry* 1997;58(Suppl 7):37-40.
6. Frost L, Lal S. Shock-like sensations after discontinuation of selective serotonin reuptake inhibitors [letter]. *Am J Psychiatry* 1995;152(5):810.

Croatia

Pharmaca 36; 1-2 (1-123) 1998

The Drug field (World) in the year 1997

The review presents new active substances approved in various countries during 1997. Forty seven new agents have been approved which is less than a year before when 53 have been registered. According to its usefulness they have been classified in four categories:

- "a" Significant contribution to materia medica,
- "b" Drug with certain advantages over those already approved,
- "c" Me too drugs (in a generic-chemical or clinical sense)
- "d" Drugs which should not have been approved.

For the second consecutive year no active substance was classified into the "a" category. Nine (19.5%) were classified into the "b" category: balsalazide for ulcerative colitis, anagrelide- antiplatelet/thrombocythaemia agent, faropenem-oral carbopenem, daclizumab-mono

antibody/immunosuppressive, imiquimod oral interferon stimulator for genital warts, rituximab- monoclonal antibody/lymphoma, donepezil- acetylcholinesterase inhibitor/Alzheimer disease, budipine- for Parkinson disease and glatiramer-immunomodulator for multiple sclerosis. In the "d" category (2,1%) troglitazone was classified. Thirty six (78,2%) have been classified into the "c" category.

New active substances and countries where they were approved:

Country	1992	1994	1996	1997
USA	9	7	17	16
Great Britain	5	3	7	10
Germany	2	1	6	7
Japan	14	26	8	4
Switzerland	2	1	4	2
Sweden	-	2	1	2
Denmark	-	-	3	1
France	1	1	1	1
The Netherlands	1	3	1	1
Spain	3	-	1	1

According to ATC classification agents from the N (11) group (diseases of the nervous system) dominate, followed by cardiovascular ones (8), those for systemic infections (7), cancer treatment and immunomodulators, gastrointestinal and metabolic drugs, blood and hematopoietic organs, musculoskeletal system.

Finland

Tabu, Vol 6, No 5, 1998

Severe anaphylactic shock caused by chlorhexidine

A 69-years old man with no allergy to animals, food, drugs or pollen was operated. Before the operation he received morphine, hyoscine and prilocaine without any signs of allergic reaction. Anaesthesia was induced by giving thiopental, fentanyl and rocuronium intravenously. The anaesthesia was maintained with a solution of air, oxygen and isoflurane. A nurse noticed urticaria on the patient's left side and in his groins. Hydrocortisone and cefuroxim was administrated and rocuronium was changed to pancuronium. The site of operation was disinfected with chlorhexidine solution. Short after starting the operation, the patient's systolic

blood pressure dropped to 33 mmHg and the pulse increased to 160 beats/min. Norepinephrine, epinephrine, calcium, plasma substitute and albumine was given. Due to severe tachycardia, esmolol was given. The patient had substantial swelling of the face, hands and genitals. The patient recovered quickly and allergy tests were made on natural rubber, prilocaine, methylparaben, chlorhexidine and the drugs used for the anaesthesia. Only chlorhexidine gave rise to a clear hypersensitivity reaction. All other agents came out negative.

See also information from Sweden below

Irland

Irish Medicines Board Drug Safety Newsletter No 8, September 1998

Prepulsid (cisapride)

Cisapride has been previously associated with QT prolongation and cardiac arrhythmia due to its potential for interaction with certain drugs metabolised by the cytochrome P450 system, in particular azole anti-fungals and macrolide antibiotics.

Recently, the IMB has been made aware of reports of cardiac arrhythmia, cardiac arrest and sudden death in adults and children treated with cisapride who had not received concomitant medication and had no identifiable risk factor. The following are known risk factors for the development of cardiac arrhythmia:

1. Significant chronic obstructive pulmonary disease
2. Respiratory failure
3. Renal failure
4. Hepatic failure
5. History of/or existing cardiac disease
6. Conditions associated with QT Prolongation
7. Uncorrected electrolyte disturbances
8. Prematurity and high dosage
9. Concomitant use of azole anti-fungal agents, macrolide antibiotics, protease inhibitors and nefazadone or any drug that may prolong the QT interval.

Roaccutane (Isotretinoin)

Roaccutane is a vitamin A derivative authorised for the treatment of cystic and conglobate acne vulgaris, or in those cases of severe acne which have failed to respond to or rapidly relapse following adequate courses of accepted therapy.

Depression, psychotic symptoms and rarely suicide have

been reported with isotretinoin. Since its authorisation in 1983 the IMB has received a total of six reports of psychiatric events including one case of suicide occurring during treatment with isotretinoin.

Viagra (sildenafil)

Viagra is a new agent recently authorised in the European Union for the treatment of erectile dysfunction. Commonly reported adverse effects of viagra are headache, flushing, dyspepsia, nasal congestion and visual disturbances.

An important contraindication for taking viagra is concurrent administration of an organic nitrate. This contraindication also includes sodium nitroprusside which acts similarly as an NO donor.

Patients with a history of angina who develop anginal attacks following ingestion of sildenafil may become acutely hypotensive.

See also information from Canada above

Eltroxin (thyroxine)

Since 1997, the IMB has been notified of three patients undergoing long-term thyroid replacement therapy who inadvertently received 50 mcg in place of 100 mcg tablets, in one case leading to the development of foetal hypothyroidism.

Norway

Nytt om legemidler, Vol 21, No 6, November 1998

Paracetamol and increased effect of warfarin

In Norway, the majority of all serious adverse reactions are caused by warfarin. It is important to inform the patient of factors that may influence the blood concentration of warfarin, such as intake of food, illness and other drugs. It is well known that ASA and other non-steroidal anti-inflammatory drugs inhibit blood platelets and potentiate the anticoagulant effect of warfarin. These drugs are therefore usually not recommended as pain relievers to patients on warfarin. Paracetamol does not interact with platelets, and is therefore a suitable alternative. A recent study, however, indicates that paracetamol at doses above 2-3 g per week may potentiate the effect of warfarin, and that doses above 9-10 g per week may have a highly significant potentiating effect. Paracetamol and warfarin are both metabolized via cytochrome P450. There is therefore a

possibility that paracetamol may reduce the metabolism of warfarin via cytochrome P450. Patients should be informed that use of paracetamol may potentiate the anticoagulant effect of warfarin and require closer monitoring.

Reference:

1. Hylek EM, Heiman H, Skates SJ, Sheehan MA, Singer DE. Acetaminophen and other risk factors for excessive warfarin anticoagulation. *JAMA* 1998; 279:657-62.

Portugal

Portuguese Pharmacovigilance Bulletin, Vol 2, No 1, 1st Quarter 1998

Nucleoside Analogues: hepatic steatosis and lactic acidosis

Nucleoside-analogue-associated hepatic steatosis and lactic acidosis have been known for some years. Other nucleoside analogues, namely zalcitabine and zidovudine, have also been reported. Recently, as a result of the analysis of the first post-marketing safety data on stavudine and lamivudine, several cases of lactic acidosis and fatty liver were detected, some of which were fatal. Most cases occurred in female patients who were either obese or under concomitant therapy with other nucleoside analogues. These reactions usually manifested themselves a long time after the beginning of therapy, and were often fatal.

It was deemed necessary to include in the SPCs of all nucleoside analogues approved in the European Union Countries the following information:

1. Cases of lactic acidosis have been described, usually associated with severe hepatomegaly and hepatic steatosis in patients under therapy with nucleoside analogues.
2. a) Cases of lactic acidosis have been described in patients under therapy with nucleoside analogues, usually associated with severe hepatomegaly and hepatic steatosis.
b) Treatment with nucleoside analogues should be suspended in case of a rapid rise of aminotransferase levels, progressive hepatomegaly or metabolic/lactic acidosis of unknown aetiology.
c) Special attention should be paid when administering nucleoside analogues to patients with hepatomegaly, hepatitis or any other known risk factors for hepatic disease.

Short-acting nifedipine

The National Pharmacovigilance Centre in Portugal reevaluated the safety profile of short-acting nifedipine, from which some alterations to the Summary of Product Characteristics (SPC) resulted, as follows: Its contraindication in the case of unstable angina or recent myocardial infarction, and the ischaemic risk inducible by its use in the treatment of hypertension, are emphasised. Its use in hypertensive crises is highly inadvisable.

There seem to be no reason to support any changes in the use of long-acting formulations, especially in the treatment of hypertension.

Contraindications:

1. Unstable angina pectoris
2. Recent acute myocardial infarction

Warnings and Special Precautions of Use:

Epidemiologic data seem to show that short-acting nifedipine used in the treatment of ischaemic heart disease may be associated with an increase in mortality and morbidity, especially when used in high doses. Therapy with short-acting nifedipine may exacerbate angina.

There is no evidence that short-acting nifedipine is of any benefit in the secondary prevention of myocardial infarction.

Therapy with short-acting nifedipine may induce a sudden decrease of blood pressure, with marked pressure fluctuation, reflex tachycardia, sympathetic stimulation and circulatory compromise of major organs.

Therapeutic Indications:

- Arterial hypertension
- Stable chronic angina and vasospastic angina

Reference:

Alderman et al., 1997, McMurray and Murdoch, 1997.

Sweden

Information from the MPA, Vol 9, No 6 October 1998

Chloramphenicol used in eyes - no evidence of causing aplastic anaemia

Since the end of the 60's the use of systemic chloramphenicol is no longer of clinical importance in Sweden. If eye drops/ointment are still in use but there are different views on the suitability due to a possible

risk for aplastic anaemia. The MPA has analysed the question and their conclusion is that there is no evidence that chloramphenicol eye drops/ointment causes aplastic anaemia. The MPA has not received any case reports where chloramphenicol eye drops/ointment was suspected of causing aplastic anaemia. Three large epidemiological case-control studies have been made on chloramphenicol and aplastic anaemia. 1,2

Study	Controls		Exp. Controls		n %	OR (95% CI)
	Cases	Exp.	Cases	n %		
IAAAS	208	2180	0 0	3 0,1 4		-(0-5,2)
Thailand	218	938	0 0	4 0,4 2		-(0-5,2)
Catalonia	145	1226	3 1,4	5 0,4		3,8 (0,8-17)
Total	571	4344	3 0,5 3	12 0,2 7		1,9 (0,5-6,8)

IAAAS: The International Agranulocytosis and Aplastic Anaemia Study.

OR: Odds ratio

Two of three exposed patients in the Catalonian study received concomitant drugs that may cause aplastic anaemia. In a worst case scenario, three cases out of 571 exposed and twelve controls out of 4344 exposed, results in an OR of 1,9 which is not statistically significant.

Reference

1. Wiholm B-E, Parsells Kelly J, Kaufman D, Issaragrisil S, Levy M, Shapiro S. The relation of aplastic anemia to use of chloramphenicol eye drops in two international case control studies. *BMJ* 1998;316:666.
2. Laporte JR, Vidal X, Ballarin E, Ibanez L. Possible association between ocular chloramphenicol and aplastic anemia - the absolute risk is very low. *CPT*. (In press 1998)

Reports in WHO file: Aplastic anaemia 4.

Lipodystrophy and HIV-proteinase inhibitors

When the HIV-proteinase inhibitors were introduced on the market, there was a breakthrough in the treatment for HIV. These drugs were shown to be very effective when used in combination with nucleoside analogues and many patients experienced a dramatic improvement of their disease. Due to the urgent need of these types of drugs,

the proteinase inhibitors were released with only poor experience from pre-studies and without any knowledge of the long term effects. After more than two years of treatment, the infection is still under control in the majority of the patients who receive combination therapy. It is common that combination therapy starts at the beginning of the infection. This means that patients with relatively good prognosis receive combination therapy against HIV.

HIV-proteinase inhibitors are known to cause redistribution of fat. This ADR is likely to be a result of a metabolic disturbance which leads to concerns about possible serious long term effects. Even though the causal relationship is not yet established, it seems like proteinase inhibitors cause effects similar to those of the metabolic syndrome when used together with nucleosides analogues. This could lead to a higher risk of cardiovascular disease. There is a marked underreporting of ADRs in association with anti-HIV drugs. Therefore there is a risk of not detecting serious long term effects in time. To sum up, it seems like all proteinase inhibitors on the market may cause redistribution of fat associated with hyperlipaemia and resistance to insulin. For patients with good prognosis, combination therapy may be postponed to reduce the risk of long term effects. The MPA and corresponding agencies within the EU are working to improve ADR supervision of anti-HIV drugs.

Information from the MPA, Vol 9, No 7 November 1998

Chlorhexidine and anaphylactic reaction

A 28-years old man received an urethral installation with chlorhexidine. He experienced a strange sensation in the body and skin tingling. Next day the treatment with chlorhexidine was repeated. Within a couple of minutes he was nauseous and had dyspnea, tachycardia and urticaria. He was treated with steroids and his condition improved. The MPA has received a total of five cases of this type of reaction with chlorhexidine.

See also information from Finland above

Triamcinolone - anaphylactic chock

A 90-year old woman, essentially healthy, was submitted to hospital for a swollen hand. Her symptoms was diagnosed as chondrocalcinosis and she received an intra-articular injection of triamcinolone. After 30 minutes the patient turned pale, was cold sweating and nauseous. She had tachycardia and urticaria and she was treated with epinephrine and clemastine. She recovered after 24 hours

and could return to her home. She had reacted with nausea and vomiting once before after a triamcinolone injection. Hypersensitivity reactions after treatment with steroids are relatively frequently reported but anaphylactic shock after intra-articular injection is very rare.

Sertraline and phenytoin - possible interaction

A woman was treated with sertraline due to a depression. She also received phenytoin for epilepsy, warfarin for frequent thrombosis in legs, furosemide, diazepam, codeine and paracetamol. After two weeks treatment with sertraline, she was submitted to hospital due to dizziness, nystagmus and ataxia. The serum concentration of phenytoin was controlled and was found to be 239 µmol per litre. The latest value, taken less than a year before, was 60 µmol per litre. Recommended therapeutic level is 40-80 µmol per litre. The patient's condition improved when phenytoin was replaced with carbamazepine. Both warfarin and phenytoin are mainly metabolized via CYP2C9 and sertraline is thought to be a weak inhibitor of this enzyme. No increased effect of warfarin had been noticed during the three weeks before the discovery of the high level of phenytoin, but after withdrawal of sertraline and warfarin the prothrombin time increased significantly. A contributory cause may have been carbamazepine.

Does calcium carbonate inhibit absorption of anticoagulantia?

It is known that calcium carbonate inhibits uptake of several drugs. The MPA has received one report of a possible interaction with dicoumarol and calcium carbonate. An elderly woman had taken dicoumarol during a longer period. Besides dicoumarol she took oxazepam, dextropropoxyphene, paracetamol, codeine, lactulose, furosemide, amiloride and estriol. A short time after Calcichew-D3 (calcium carbonate and vitamin D3) was added, the prothrombin time increased but returned to normal when the drug was terminated. The MPA has not found any published studies with humans that describes interaction between calcium carbonate and anticoagulantia. The MPA requests urgently that doctors should report similar observations that may indicate a possible interaction between calcium carbonate and dicoumarol or warfarin.

Severe low back pain after injection with streptokinase

Six cases of acute, severe lower back pain in patients treated with streptokinase have been reported to the MPA. Connection with other drugs could not be established and none of the patients had any known allergy. The patients had to interrupt the treatment and they needed more analgesics than usual. The underlying mechanism is not known, but scientists have been speculating that an allergic reaction or an ischemic released pain could be the cause. These reports are the first ones on this matter that the MPA has received.

United Kingdom

Current Problems in Pharmacovigilance Vol 24, August 1998

Cisapride (Prepulsid): Risk of arrhythmias

Cisapride is a prokinetic drug authorised in adults for motility disorders of the upper gastrointestinal tract such as reflux oesophagitis. In 1996, the MCA alerted prescribers to an interaction between cisapride and other drugs metabolised by the cytochrome P450 3A4 liver enzyme system.¹ By inhibiting the metabolism of cisapride, these interactions lead to raised cisapride blood levels which may cause QT-interval prolongation and ventricular arrhythmias. Recent experimental evidence suggests that therapeutic concentrations of cisapride have direct electrophysiological effects on the heart.²

Serious cardiac arrhythmias (ventricular tachycardia, ventricular fibrillation, torsades de pointes) and cases of sudden death have been reported in patients taking cisapride. Many of these patients were taking drugs suspected to increase cisapride blood levels by inhibiting its metabolism. However, in some patients taking cisapride these reactions have occurred in the absence of interacting drugs. Most of these patients had pre-existing cardiac conditions which may have predisposed them to arrhythmias. Cisapride should therefore not be used in the following circumstances:

- with CYP3A4 inhibiting drugs including macrolide antibiotics (e.g. erythromycin, clarithromycin), azole antifungals (e.g. fluconazole, itraconazole, ketoconazole), protease inhibitors (e.g. ritonavir, indinavir) and nefazadone
- with other drugs known to prolong the QT interval such as quinine, halofantrine, terfenadine, astemizole, some anti-arrhythmic drugs (e.g. amiodarone, quinidine) certain antidepressants (e.g. amitriptyline)

and some antipsychotic agents (phenothiazines and sertindole).

- by patients with a personal or family history of QT interval prolongation.
- by patients with a previous history of ventricular arrhythmia or torsades de pointes.
- by patients with risk factors for arrhythmia such as those with second or third degree atrioventricular block, clinically significant heart disease, uncorrected electrolyte disturbances (potassium/magnesium), renal or respiratory failure.

Cisapride is frequently used in children, particularly for the treatment of infantile gastro-oesophageal reflux. Concern about such use has increased because of recent reports of QT interval prolongation in neonates treated with cisapride.³ The pharmacokinetics of cisapride in premature neonates are unpredictable and may lead to potentially cardiotoxic blood levels. Cisapride is, therefore, specifically contra-indicated in premature infants (gestational age less than 36 weeks) for up to 3 months after birth. Furthermore, in children up to the age of 12 years, there are insufficient data to support the use of cisapride.

References

1. CSM/MCA. *Current Problems in Pharmacovigilance* 1996; 22: 1.
2. Drolet B et al. *Circulation* 1998; 97: 204-210.
3. Bernadini S et al. *Arch. Dis. Child.* 1997; 77(3): F241-F243.

Isotretinoin (Roaccutane)

Roaccutane is an oral preparation of isotretinoin a derivative of Vitamin A. It was authorised in the UK in 1982 for the treatment of severe acne which has failed to respond to conventional antibiotic treatment. Since 1982 we have received 841 suspected adverse drug reaction (ADR) reports for Roaccutane describing 1349 reactions.

Frequently reported reactions were:

1. skin disorders (18% of total) e.g. rash, dry skin and photosensitivity.
2. musculoskeletal disorders (11%) e.g. myalgia and arthralgia.
3. gastrointestinal disorders (10%) e.g. cheilitis, abdominal pain and dry mouth.
4. eye disorders (7%) e.g. conjunctivitis, dry eyes and blurred vision.

5. neurological disorders (7%) e.g. migraine and convulsions.

Roaccutane is a teratogen and is therefore contra-indicated in a woman of childbearing potential unless she meets the following criteria:

- Has severe disfiguring cystic acne resistant standard therapy.
- Pregnancy is excluded before starting therapy with Roaccutane and a negative pregnancy test obtained within two weeks prior to therapy.
- Therapy is started only on the second or third day of the next menstrual cycle.

Effective contraception must be practised for at least four weeks before treatment, during the treatment period and for at least four weeks following its cessation.

Lipodystrophy in HIV positive patients treated with protease inhibitors

In clinical trials, the protease inhibitor ritonavir (Norvir) was shown to cause hyperlipidaemia. Since marketing, spontaneous reporting of suspected ADRs has shown that hyperlipidaemia also occurs with the other protease inhibitors; indinavir (Crixivan), saquinavir (Invirase) and nelfinavir (Viracept). Spontaneous reporting has also demonstrated that protease inhibitors can be associated with the development of glucose intolerance and diabetes mellitus¹. More recently, reports have suggested that protease inhibitors may cause peripheral lipodystrophy, increased abdominal fat, buffalo humps and breast hypertrophy². It has been suggested that this group of reactions, as well as hyperlipidaemia and diabetes mellitus, comprise a syndrome caused by protease inhibitors³.

Although protease inhibitors are a likely factor in this syndrome, a number of literature reports as well as 2 of the 33 UK cases of lipodystrophy reported to the MCA/CSM occurred in HIV positive patients treated with a combination of other antiretroviral drugs (excluding protease inhibitors).

Many questions remain unanswered, including:

1. the frequency and pathophysiology of these reactions³;
2. the exact relationship between lipodystrophy, hyperlipidaemia and insulin resistance;

3. whether these reactions are reversible;
4. their long term consequences such as the risk of ischaemic heart disease.

Despite these important ADRs, combination antiretroviral therapy, including a protease inhibitor, is proven to delay the progression of HIV infection and is of benefit in the majority of patients.

References

1. MCA/CSM. *Current Problems in Pharmacovigilance* 1997; 23:10
2. Carr A, et al. *AIDS* 1998; 12: F51 - F58.
3. Carr A, et al. *Lancet* 1998; 351: 1881 - 1883

Meloxicam: Gastrointestinal and skin reactions

Meloxicam (Mobic) is a non-steroidal anti-inflammatory drug which is indicated for osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. It has been marketed in the UK since September 1996. By the beginning of June 1998, approximately one million prescriptions had been dispensed for meloxicam in the UK.

By 19 June 1998, a total of 773 reports describing 1,339 suspected adverse drug reactions (ADRs) for meloxicam had been received from the UK. The most frequently reported reactions are gastrointestinal, dermatological, neurological (mostly headache), cardiovascular (oedema and palpitations), dizziness, flushing and fatigue.

Forty one percent of all ADRs were gastrointestinal, of which 18% were gastrointestinal perforation, ulceration and/ or bleeding. Although most patients recovered after meloxicam was withdrawn and/or after treatment was instituted, 5 patients died.

Alendronate sodium (Fosamax) with oesophageal reactions

Alendronate sodium (Fosamax) is an amino-bisphosphonate used for the treatment of osteoporosis in post-menopausal women.

July 1998, Medicines Control Agency had received 97 UK reports of oesophageal reactions, one of which was fatal.

Recommendations:

1. Alendronate sodium has very low bio-availability and needs to be taken at least 30 minutes prior to breakfast.
2. The tablet may lodge in the oesophagus and is irritant to the oesophageal mucosa; it should not be chewed or sucked; it should be taken with a full

glass of water and the patient should remain upright for at least 30 minutes afterwards. Use of alendronate sodium is contra-indicated in patients who are unable to sit upright or stand for 30 minutes.

3. Caution is required if the patient is also taking NSAIDs.

Around 1-2% of patients taking alendronate sodium may experience oesophageal reactions, even when following the dosing instructions. Patient should stop taking alendronate sodium if oesophageal symptoms occur.

Reference:

MCA/CSM. *Current Problems in Pharmacovigilance*, 1996; 22, 5.

Leukotriene antagonists: a new class of asthma treatment

Cysteinyl leukotrienes are arachidonic acid-derived inflammatory mediators which are potent constrictors of bronchial smooth muscle. In addition, they attract human eosinophils and cause airway oedema, mucus hypersecretion and reduced mucociliary clearance. Montelukast (Singulair), first marketed in February 1998, and zafirlukast (Accolate), first marketed in July 1998, are competitive cysteinyl leukotriene type 1 receptor antagonists. By blocking the leukotriene receptors, both drugs can improve respiratory function and symptoms in patients with asthma. Both montelukast and zafirlukast should be taken regularly to produce clinical benefit.

Importantly:

1. treatment with these drugs does not allow a reduction in existing corticosteroid treatment.
2. leukotriene antagonists are not indicated for the treatment of acute asthma attacks, however, for patients already on therapy, they may be continued during an acute attack.

Zafirlukast

Zafirlukast is contra-indicated in patients with hepatic impairment or moderate to severe renal impairment and, due to a lack of clinical data, in children under the age of 12. Elevations in serum transaminases can occur during treatment with zafirlukast and liver function tests should be performed in patients who develop symptoms of liver dysfunction. At doses greater than 20mg twice daily, significant hepatotoxicity may occur. The most common adverse reactions in clinical trials

were headache and nausea. Zafirlukast may also cause vomiting, diarrhoea, abdominal pain and hypersensitivity reactions including urticaria, angioedema and rashes. Zafirlukast inhibits the hepatic cytochrome P450 2C9. Due to an interaction with warfarin, the prothrombin time should be closely monitored if these drugs are co-administered. Zafirlukast also interacts with theophylline, terfenadine, aspirin and erythromycin but the clinical significance of these interactions is not known.

Montelukast

Montelukast is metabolised by the hepatic cytochrome P450 CYP3A4 and co-administration of inducers of this enzyme (such as phenytoin, phenobarbitone and rifampicin) result in a marked reduction in its plasma levels. The most common adverse reactions in clinical trials were headache and abdominal pain. Other adverse reactions observed in clinical trials included; nausea, diarrhoea, gastro-enteritis, influenza, pharyngitis, sinusitis, cough, nasal congestion, dizziness, fatigue and insomnia.

USA

FDA MedWatch News, November 16, 1998

Tasmar (tolcapone), drug warning

Additional product labeling:

Because of the risk of potentially fatal, acute fulminant liver failure, Tasmar (tolcapone) should ordinarily be used in patients with Parkinson's disease on l-dopa/carbidopa who are experiencing symptom fluctuations and are not responding satisfactorily to or are not appropriate candidates for other adjunctive therapies

Because of the risk of liver injury and because Tasmar, when it is effective, provides an observable symptomatic benefit, the patient who fails to show substantial clinical benefit within 3 weeks of initiation of treatment, should be withdrawn from Tasmar.

Tasmar therapy should not be initiated if the patient exhibits clinical evidence of liver disease or two SGPT/ALT or SGOT/AST values greater than the upper limit of normal. Patients with severe dyskinesia or dystonia should be treated with caution.

Patients who develop evidence of hepatocellular injury while on Tasmar and are withdrawn from the drug for any reason may be at increased risk for liver injury if Tasmar is reintroduced. Accordingly, such patients should

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not ordinarily be considered for re-treatment.

Cases of severe hepatocellular injury, including fulminant liver failure resulting in death, have been reported in post-marketing use. As of October 1998, 3 cases of fatal fulminant hepatic failure have been reported from approximately 60,000 patients providing about 40,000 patient years of worldwide use. This incidence may be 10- to 100-fold higher than the background incidence in the general population. Underreporting of cases may lead to significant underestimation of the increased risk associated with the use of Tasmar.

Immune Globulin Intravenous (Human) (IGIV), with acute renal failure

Since IGIVs were first introduced in 1981, the Food and Drug Administration (FDA) has received over 114 worldwide adverse event reports of renal dysfunction and/or acute renal failure associated with the administration of these products. Although acute renal failure was successfully managed in the majority of cases, deaths were reported in 17 patients worldwide. Many of the patients who died had serious underlying conditions.

In an effort to reduce the risk of acute renal failure, FDA recommends that the following precautions be taken when considering administration of IGIV products:

1. Assure that patients are adequately hydrated prior to the initiation of the infusion of IGIV.
2. Exercise particular caution in the administration of IGIV products in patients at increased risk for developing acute renal failure. Such patients include, but are not limited to, those with: any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, concomitant nephrotoxic drugs.
3. Do not exceed the recommended dose. Reduction in dose, concentration, and/or rate of administration in patients at risk of acute renal failure has been proposed in order to reduce the risk of acute renal failure. Because no prospective data are presently available to identify a maximal safe dose, concentration, or rate of infusion for IGIV products for patients at risk of acute renal failure, FDA recommends that, for such patients,

prescribers reconstitute/dilute the product in such a manner as to produce both the minimum concentration and rate of infusion practicable. For sucrose-containing IGIVs, a maximum infusion rate of 3 mg sucrose/kg/minute (2 mg Ig/kg/min for Sandoglobulin and Panglobulin; 3 mg Ig/kg/min for Gammar-P I.V) should not be exceeded.

4. Renal function, including urine output and blood urea nitrogen (BUN)/serum creatinine, should be assessed prior to infusion of IGIV, particularly in patients judged to have a potential increased risk for developing acute renal failure, and again at appropriate intervals. If renal function deteriorates, discontinuation of the product should be considered.

SPECIAL COMMUNICATIONS

South Africa

The Medicines Control Council

Chlormezanone- Withdrawal

Chlormezanone has been available in several analgesic combination products in South Africa and is used extensively as an over-the-counter painkiller. Paracetamol-chlormezanone combination products have been used for generalised pain associated with tension such as tension headache, low back pain, painful muscle spasm, pre-menstrual tension, painful menstruation, reduction of muscle spasms and reduction of fever. As the risk-benefit profile of chlormezanone-containing products is considered to be unacceptable, the Medicines Control Council has decided to withdraw the registration of all chlormezanone-containing products from South Africa.

Sri Lanka

The Drug Evaluation Subcommittee (DESC)

Alert about intramuscular diclofenac

The Drug Evaluation Subcommittee (DESC) has received reports of severe pain, muscle necrosis, abscesses,

necrotising fasciitis and death with the use of intramuscular diclofenac. Therefore DESC made the following recommendations.

1. Prescribers should very carefully consider the risk/benefit when using intramuscular diclofenac. It should not be used for trivial conditions, nor used when oral administration would be adequate.
2. Serious adverse reactions are less with rectal administration.
3. Intramuscular diclofenac should be given only by deep intramuscular injection into the upper outer quadrant of the buttock. The maximum number of injections is two per day for 2 days.
4. Prescribers should refer to the Product information leaflet that comes with the vials for full information before administering intramuscular diclofenac.

United Kingdom

EMA Press release, 17 November 1998

Tasmar (tolcapone)

Tasmar is indicated for the adjunctive treatment of Parkinson's disease and is available in the European Union in the form of 100 mg and 200 mg film-coated tablets. On 12 November 1998 the EMA's scientific committee, the CPMP, adopted an Opinion recommending the suspension of the marketing authorisation for Tasmar due to increasing concerns over reports of severe hepatotoxicity, three with a fatal outcome.

EMA Press release, 23 November 1998

Entacapone (comtess/comtan)

Entacapone is a catechol-o-methyl transferase (COMT) inhibitor, indicated for the adjunctive treatment of Parkinson's disease and is available in the form of 200 mg film-coated tablets. The most recent safety information indicate that entacapone does not appear to be hepatotoxic. However, rare reports of clinically significant increases in liver enzymes have been reported. Information for patients

1. Comtess/Comtan must not be used if you have a history of Neuroleptic Malignant Syndrome and/or non-traumatic rhabdomyolysis (rare form of muscle disorder)

2. If you need to stop taking Comtess/Comtan, please consult your doctor. Withdrawal of Comtess/Comtan treatment may have to be done gradually and your other antiparkinsonian therapy may need to be adjusted to prevent the worsening of your parkinsonian symptoms or unwanted side effects (e.g., rigidity, shakiness, agitation, confusion, fever).

Information for Prescribers

- a) Entacapone is not recommended for patients with a previous history of NMS and/or non-traumatic rhabdomyolysis.
- b) Rhabdomyolysis secondary to severe dyskinesias or NMS has also been observed rarely in patients with Parkinson's disease, although it has not been reported during entacapone treatment.
- c) NMS, including rhabdomyolysis and hyperthermia is characterised by motor symptoms (rigidity, myoclonus, tremor), mental status changes (e.g., agitation, confusion, coma), hyperthermia, autonomic dysfunction (tachycardia, labile blood pressure) and elevated serum creatine phosphokinase (CPK) which may be a consequence of rhabdomyolysis.
- d) NMS has been reported rarely in Parkinson's disease patients when other dopaminergic medications were withdrawn abruptly, prescribers should exercise caution when discontinuing entacapone treatment. Withdrawal should proceed slowly, and if signs and/or symptoms occur despite a slow withdrawal of entacapone, an increase in levodopa dosage may be necessary.

EMA Press release, 27 November 1998

Mabthera (rituximab)

Mabthera is authorised for the treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.

Information for patients:

1. If you are treated with mabthera, reactions like breathing difficulties, fever, chills, rash, and reduction in blood pressure may occur.
2. Because the possible reduction in blood pressure at the beginning of the treatment, patients taking medicines for high blood pressure may be advised by their doctors to stop taking them 12 hours prior to mabthera infusion. If you have a history of heart

disease (i.e. angina pectoris, cardiac arrhythmias, or congestive heart failure), or a history of breathing problems, your doctor will take special care of you during therapy with mabthera.

3. Your doctor will give you a medicine to prevent or reduce pain and/or fever and allergy before each infusion of mabthera.
4. Some severe reactions, in particular severe breathing difficulties, have been fatal. Tell your doctor immediately if you experience any difficulty in breathing.

Information for Prescribers:

- a). Mabthera infusions should be administered in a hospital environment where oncologist/haematologist is available.
- b) Patients with a high number of circulating malignant cells or high tumour burden, who may be at higher risk of especially severe cytokine release syndrome, should only be treated with extreme caution and when other therapeutic alternatives have been exhausted.

These patients should be very closely monitored throughout the first infusion.

- c) Severe cytokine release syndrome has been reported for several patients, and is characterised by severe dyspnea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features of tumour lysis syndrome such as hyperuricemia, hyperkalemia, hypocalcemia, acute renal failure, elevated LDH and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or edema visible on a chest x-ray.
- d) If a patient develops severe cytokine release syndrome, the infusion should be interrupted immediately.
- e) Premedication consisting of an anti-pyretic and an antihistaminic, should always be administered before each infusion of mabthera.
- f) Approximately 50% of patients treated with mabthera experience infusion-related adverse reactions, including cytokine release syndrome. These are accompanied by hypotension and bronchospasm in approximately 10% of patients. These symptoms are usually reversible with interruption of mabthera infusion and

administration of an anti-pyretic, and an antihistaminic.

- g) Angina pectoris, or cardiac arrhythmias have occurred in patients treated with mabthera.

USA

FDA MedWatch and the manufacturer Pfizer Inc. November 24, 1998

Viagra (sildenafil citrate)

New warnings and information in the product labeling for Viagra (sildenafil).

Information added to the labeling includes:

Postmarketing cardiovascular events: The revised labeling addresses postmarketing reports of heart attacks, sudden cardiac deaths, and hypertension.

Risk of sexual activity: Sexual activity in patients with preexisting cardiovascular disease carries a potential cardiac risk. Pfizer, therefore, advises doctors that treatments for impotence, including Viagra, generally should not be used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status.

Vasodilatory effects (effects on blood pressure): Physicians should consider whether their patients with heart disease could be affected by transient decreases in blood pressure, especially in combination with sexual activity.

Patients who were not studied in clinical trials: Several groups of patients were not studied in the clinical trials for Viagra. These include those who:

- a) suffered a heart attack, stroke, or life-threatening arrhythmia within the previous six months.
- b) had significant hypotension or hypertension,
- c) had a history of cardiac failure or coronary artery disease causing unstable angina, and
- d) had retinitis pigmentosa, an eye disorder.

Prolonged erections or priapism: The labeling now includes a warning about the rare occurrence of painful, prolonged erections (longer than four hours).

DRUG WITHDRAWALS

Peru

Digimed alert No 07 - 98

Ebrotidina - Market withdrawal

The Ministry of Health of Peru inform the health professionals, institutions of health care and the consumers that the marketing authorization of the drugs containing ebrotidina, a antiulcer H2-receptors blocker, as been cancelled and these products withdrawal from the market in this country.

The reason is serious hepatic adverse drug reactions reported to the Spanish Pharmacovigilance System, specially during long term treatment and associated with NSAID drugs.

Ebrotidine is marketed in Peru under the brandname of Ebrocit, in 400mg tablets, produced by *Laboratorios Ferrer S.A.*, from Spain.