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ADVERSE REACTION NEWSLETTER 1999:1

**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 18, No 1, February 1999.

Allergic reactions with echinacea

The complementary medicine echinacea is derived from several species of this flowering plant and has become increasingly popular in recent years, particularly for the prophylaxis and treatment of cold and flu symptoms.

Between July 1996 and November 1998 ADRAC has received 37 reports of suspected adverse drug reactions in association with echinacea. Over half of these (21) described allergic-like effects including bronchospasm (9 reports), dyspnoea (8), urticaria (5), chest pain (4) and angioedema (3). Of the 21 patients, ages ranged from 3 to 58 (median 31) years. Twelve of 18 patients for whom medical histories were available had a history of asthma (7) and/or allergic rhinitis/conjunctivitis/hayfever (5). Echinacea was the only suspected cause in 19 of the 21 cases. Onset ranged from within 10 minutes of the first dose to "a few months", although all but two cases occurred within 3 days of starting treatment. At the time of reporting, 17 of the patients had recovered, 2 had not yet recovered and the outcome was unknown in the other 2 cases.

Update on visual field constriction with vigabatrin

In August 1997 ADRAC reported on visual field defects occurring in association with the antiepileptic drug, vigabatrin (Sabril). At that time, ADRAC had received 5 reports of this problem. To November 1998, ADRAC has received a total of 100 reports in association with vigabatrin. Of these, 43 describe visual field constriction, which was symptomatic in 30 cases. Ages of the patients involved (M: 31, F: 12) ranged from 9 to 69 years with a median of 40 years. Daily doses ranged from 0.5 to 4.5 g with a median of 2.5 g. Time to onset ranged from less than a month to over 6 years but most (38) cases had a time to onset of greater than 2 years. Only one of the patients was reported as having recovered symptomatically but this was shown to be incomplete on visual testing.

It was recently estimated that 10-20% of patients on long-term vigabatrin will develop visual field constriction.

References:

1. ADRAC. Visual field defects with vigabatrin. *Aust Adv Drug React Bull* 1997; 16: 11.
2. Appleton RE. Guideline may help in prescribing vigabatrin. *BMJ* 1998; 317: 1322

Canada

Canadian Adverse Drug Reaction Newsletter, Vol 9, No 1, January 1999

Isotretinoin: depression

Although birth defects are the most serious adverse effect of isotretinoin (Accutane™), depression has also been reported. Recently, international and domestic reports of depression, psychosis and suicidal ideation have prompted Health Canada to review the adverse reaction information for isotretinoin. Together with the manufacturer, the product monograph has been amended to strengthen warnings about depression and the possibility of suicide. Isotretinoin was approved for use in Canada in 1983 for the treatment of severe nodular and inflammatory acne, acne conglobata and recalcitrant acne unresponsive to conventional therapies. Since 1983 the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) has received 16 reports (8 since March 1998) describing depression and other reactions of a putative psychiatric nature associated with the use of isotretinoin. In 2 cases, a second drug was also reported as suspect: trimipramine (1) and fluoxetine (1). The reported reactions included depression (5), aggressive reaction (4), emotional lability (4), irritability (3), suicidal tendency (3), amnesia (2), abnormal thinking (1), aggravated depression (1), manic reaction (1) and suicide attempt (1). The median age of the patients (9 women, 7 men) was 20 (range 15 to 41) years. The time from the start of the drug therapy to the onset of the reaction varied from 1 day to 5 months. In the reports that gave dose information, all but 1 of the patients were taking 1 to 2 mg/kg daily (the recommended maximum); the remaining patient received incremental doses up to 3 mg/kg daily. In 5 cases the drug was stopped because of the adverse reaction; however, in several cases the course of therapy was completed. In the reports that indicated an outcome, 7 patients recovered, 3 recovered with residual

effects, and 1 had not yet recovered at the time of reporting. The nature of the relation between isotretinoin and the psychiatric symptoms reported has not been established. In some cases there has been evidence of a causal association (e.g., symptoms worsened with increased dose or the reaction abated when the drug was stopped). Other factors also contributed, such as the age of the patient (those 15 to 24 years old are more prone to experience major depression than the general population). It is also thought that severe acne itself may be a risk factor for depression; at least one study has demonstrated that successful treatment with oral isotretinoin therapy reduced anxiety and depression.

References

1. Blazer DG, Kessler RC, McGonagle KA, Swartz MS. The prevalence and distribution of major depression in a national community sample: The National Comorbidity Survey. *Am J Psychiatry* 1994; 15: 979-86.
2. Lamberg L. Acne drug depression warnings highlight need for expert care. *JAMA* 1998; 279: 1057.
3. Rubinow DR, Peck GL, Squillace KM, Gantt GG. Reduced anxiety and depression in cystic acne patients after successful treatment with oral isotretinoin. *J Am Acad Dermatol* 1987; 17: 25-32.

See also information from Denmark and New Zealand below.

Low-dose ASA and serious gastrointestinal bleeding

Experts recommend low-dose ASA (75-325 mg/d) as long-term therapy in high-risk patients for the secondary prevention of cardiovascular events. The degree of risk of serious gastrointestinal (GI) bleeding from low doses of ASA, however, has not been fully characterized.

Since 1993 the CADRMP has received 19 reports of serious GI bleeding associated with ASA doses of 325 mg/d or less. Concomitant drug therapy was reported in 12 patients, but no obvious trends were seen. Most patients recovered, and no death were reported.

Patients with chronic blood loss may present with signs and symptoms of anemia (e.g., weakness, easy fatigability, pallor, chest pain or dizziness). Eight patients experienced similar symptoms; all had low hemoglobin levels and 7 experienced GI symptoms as well.

Serious GI bleeding was also reported in patients using enteric-coated ASA. Although there is evidence from endoscopic studies that the risk of GI bleeding can be reduced by the use of enteric-coated ASA other published articles indicate that this assumption may be mistaken.

In general, the GI bleeding from ASA is dose related, and

published evidence suggests that doses of 80 mg/d may be less likely to lead to major GI bleeding than doses of 325 mg/d.

In summary, patients should take long-term ASA therapy only under physician supervision to ensure that the potential benefits are assessed against individual risk factors for GI bleeding.

References

1. Kelly JP, Kaufman DW, Jurgelson JM, Sheehan J, Koff RS, Shapiro S. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. *Lancet* 1996; 348: 1413-6.
2. Slattery J, Warlow CP, Shorrock CJ, Langman MJS. Risks of gastrointestinal bleeding during secondary prevention of vascular events with aspirin - analysis of gastrointestinal bleeding during the UK-TIA trial. *Gut* 1995; 37: 509-11
3. Weil J, Colin-Jones D, Langman M, Lawson D, Logan R, Murphy M, et al. Prophylactic aspirin and risk of peptic ulcer bleeding. *BMJ* 1995; 310: 827-30.

Denmark

Ugeskrift for Læger d. 7. December 1998

Isotretinoin and depression

The Danish Medical Products Agency (MPA) has changed the labeling for isotretinoin. The new labeling includes information on the risk of depression, psychotic reactions, suicide attempt and suicide. The new labeling also states that doctors should be extra careful when subscribing isotretinoin to patients with a history of depression. The manufacturer has sent this information to all dermatologists in Denmark. However, the MPA in Denmark thinks that all physicians should be informed.

SSRIs - drug withdrawal syndrome

Data from the Danish MPA shows that the majority of the patients who use SSRIs are elderly people and women. Despite the fact that the majority are elderly people, withdrawal syndrome almost exclusively occurs in patients between 30-40 years of age. To consider the width and nature of the problem, the MPA wish to receive all reports on suspected withdrawal syndrome in connection with SSRIs.

Finland

Tabu, Vol 7, No 1, 1998

Tramadol-induced respiratory paralysis in acute renal failure

The actual patient, a 76 year-old woman suffering from juvenile rheumatoid arthritis, coronary artery disease and osteoporosis. She received medication for this. When her back pain was worsened, the tramadol dosage was increased from 100 mg to 200 mg. 200 mg was given in the evening and the day after she was apnoeic and in a state of shock. Laboratory tests showed normochromic anaemia, acute renal failure, hyponatremia and slightly raised level of creatine kinase MB-isoenzyme. By the following morning the patient had regained her orientation to place and time. No signs suggestive of cardiac infarction were found. As the clinical signs and symptoms gave suspicions of an opioid overdose, serum level of tramadol was found to be 1.1 mg/l. The therapeutic level ranges between 0.1 to 0.6 mg/l. All the patient's medications were discontinued for a while, and new medications were gradually reintroduced due to developing symptoms. Renal function was restored with fluid therapy. This case emphasizes the complex effects that the patient's age, general status and primary illness may have on drug therapy. In addition to interactions between drugs, the role of patients illnesses on drug effects should also be born in mind.

Mirtazapine and intrahepatic cholestatic

A 49-year-old man with several episodes of depression, switched from fluoxetine to mirtazapine due to lack of effect. Shortly after this, the patient's condition improved. After four weeks of therapy, the patient became aware of oedema and his weight increased by 8 kilos. After six weeks of therapy, he also experienced abdominal pain, loss of appetite and vomiting. A few days before admission to hospital, the stools had become yellowish and the urine dark. His liver was enlarged. Drug-induced intrahepatic cholestasis was suspected on the basis of clinical findings and laboratory tests, and mirtazapine therapy was discontinued. The patient's clinical condition improved rapidly after the medication was stopped and he was fully recovered after three months.

New Zealand

Prescriber update, No 17, December 1998

Colchicine toxicity prompts dosage change

The maximum dose of colchicine in an acute attack of gout should be 6 mg (10 tablets). Colchicine should be taken at an

initial dose of 1.2 mg followed by 1 tablet every 2 hours until the gouty pain is relieved, gastrointestinal symptoms develop, or the maximum dose is reached.

In elderly patients, those who weigh less than 50 kg and those with coexisting renal or hepatic disease, alternative therapy should be used or a maximum dose of 3 mg colchicine observed. Patients with suspected overdose should be admitted to a hospital with intensive supportive facilities.

Azathioprine-Allopurinol interaction

Allopurinol and azathioprine should not be co-prescribed unless the combination cannot be avoided. Allopurinol interferes with the metabolism of azathioprine, increasing plasma levels of 6-mercaptopurine which may result in potentially fatal blood dyscrasias.

Concomitant use requires special precautions: the dose of azathioprine should be reduced to 25% of the recommended dose and the patient's blood count should be monitored assiduously.

Acute depression and isotretinoin

Isotretinoin (Roaccutane) is an extremely effective anti-acne preparation. However, in a small number of patients (less than 1%) it may be associated with symptoms of a major depressive episode.

Symptoms resolve rapidly (within 2-7 days) on discontinuation of the medicine. After a period off medication, it is worthwhile recommencing therapy at a lower dose.

Adverse reactions of current concern

A list of adverse reactions of current concern was first initiated in December 1994.

There are two reasons for this list:

1. To raise the level of awareness of these adverse reactions.
2. To evoke reports so that more information may be gathered and appropriate action taken.

The list is as follows:

Medicine	Adverse reaction	Prescriber update ref.
Alendronate	Oesophagitis	No. 16, Apr 1998
Carbamazepine	skin and haematological reactions	No. 17, Dec 1998
Colchicine	serious toxicity	No. 16, Apr 1998
Herbal medicine	all adverse reactions	No. 13, Oct 1996
Hormone replacement therapy	venous thromboembolism	No. 16, Apr 1998
NSAIDs	renal damage	No. 13, Oct 1996 & No. 16, Apr 1998

Mefloquine	neuropsychiatric reaction	No. 15, Aug 1997
Oral contraceptives	venous thromboembolism	No. 11, Feb 1996
Ticlopidine	neutropenia and thrombocytopenia	No. 17, Dec 1998 & No. 14, Feb 1997

Medsafe internet web site

<http://www.medsafe.govt.nz/Profs/Safety/pgoldreac.htm>

<http://www.medsafe.govt.nz/Profs/Safety/bee.htm>

Parenteral gold and acute vasodilatory reactions

Two acute cardiovascular reactions following sodium aurothiomalate injection (Myocrisin) have been reported to the Centre for Adverse Reactions Monitoring (CARM). Such reactions involve weakness, flushing, hypotension, tachycardia, and palpitations. Very rarely myocardial infarction and stroke may follow.

The likelihood and severity of such a reaction is increased by concomitant ACE inhibitor therapy. The frequency of this reaction with or without an ACE inhibitor is not known. Aurothiomalate should be administered to those on an ACE inhibitor only where there is ready access to emergency measures for resuscitation. The patient should be observed after administration, and any vasodilatory reaction should be treated the same as anaphylaxis. Patients who develop a vasodilatory reaction should have their medication changed.

Resensitisation to bee and wasp venom

Resensitisation to bee venom has been reported with ACE inhibitors and rarely with NSAIDs. Two well documented cases have been published, and one possible case reported to the Centre for Adverse Reactions Monitoring, of resensitisation to bee or wasp venom with a non-steroidal anti-inflammatory agent (NSAID) resulting in a serious anaphylactoid reaction. The mechanism may be the same as that which causes bronchospasm or urticaria in NSAID-sensitive individuals.

Resensitisation with an ACE inhibitor has been reported more frequently. For hypertensive patients at high risk of receiving insect stings or those undergoing desensitisation, consider alternative therapy to ACE inhibitors. Note that β -blockers are contraindicated during desensitisation programmes. If ACE inhibitors cannot be avoided and the patient is considered to be at risk of a severe vasodilatory reaction, take precautionary measures such as physical protection and/or having adrenaline on hand.

SPECIAL COMMUNICATIONS

Malaysia

Malaysian Adverse Drugs Reaction Advisory Committee (MADRAC)

Fulminant hepatitis and renal failure associated with the use of a herbal remedy

A 2-year old Chinese girl weighing 10kg was admitted to hospital with fulminant hepatitis and renal failure. The patient was believed to have taken a Chinese traditional remedy for fever. Based on the product brought by the parents, the remedy used was Ya-Hom Powder Five Pagodas Brand. From the history, the powder had been administered to the child three times within a period of 24 hours for fever and vomiting. Due to the patient's serious condition, cerebral resuscitation was initiated but the patient subsequently died 6 days later. The label on the packaging material of the Ya-Hom powder used stated that it contained *Magnolia officinalis*. *Magnolia officinalis* is not allowed to be used in traditional remedies registered for use in Malaysia as it has been reported to cause renal failure. However, there is a formulation of Ya Hom powder registered in Malaysia, which does not contain *Magnolia officinalis*.

REGULATORY DECISIONS

Germany

Rapid Alert dated 1 March 1999 from the Federal Institute for Drugs and Medical Devices, enclosing a communication from Hoechst Marion Roussel, 26 February 1999.

Polygeline (Haemaccel 35) - precautionary recall : hypotension

Hoechst Marion Roussel, Germany. The Federal Institute for Drugs and Medical Devices has issued a Rapid Alert enclosing a notification of a batch recall from the manufacturer of the plasma expander, polygeline (Haemaccel 35: Hoechst Marion Roussel), after an increased number of reports of hypotension.

The manufacturer is initiating a precautionary recall from the many countries throughout the world in which the product is distributed.

United Kingdom

“Dear Doctor/Pharmacist” letter,
Professor M. Rawlins, Chairman, Committee on Safety of Medicines, London, 2 December 1998

Sertindole (Serdolect), suspended: cardiac arrhythmias and sudden cardiac death.

The Committee on Safety of Medicines has informed doctors and pharmacists that the manufacturer of the limbic selective antipsychotic agent, sertindole (Serdolect: Lundbeck), has voluntarily suspended its availability from 2 December 1998. Sertindole is indicated for the treatment of schizophrenia. This suspension is due to concerns about reports of cardiac arrhythmias and sudden cardiac death associated with its use.

In the light of this information, the availability of sertindole will be suspended pending a full evaluation of its risks and benefits in collaboration with the UK Medicines Control Agency (MCA) and other European regulatory authorities.

DRUG WITHDRAWALS

Australia

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Withdrawal of tolcapone

Tolcapone (Tasmar) was registered in Australia last year and is the first of a new class of drugs for the treatment of Parkinson's disease. It acts by selective and reversible inhibition of catechol-O-methyl transferase, thus reducing the metabolism of concomitantly administered levodopa. This can lead to an improvement in symptomatic response and may allow a reduction in the daily dose of levodopa. Following overseas reports of serious and unpredictable hepatotoxicity including 3 fatalities, its registration has been withdrawn in Australia. The drug has also been suspended in Canada and Europe.

France

Agence du médicament

Survector- marketing authorisation suspension

Survector (amineptine) is an antidepressant which inhibits the reuptake of dopamine. This effect gives amineptine stimulant properties. It is indicated in “major depressive episodes (i.e. characterised)” and marketed in France since

1978. In Europe, amineptine is also registered in Portugal, Spain, Greece, Italy and Luxembourg. It is marketed in 66 other countries worldwide, in Africa, Asia and South America.

The company Servier voluntarily decided to discontinue the marketing of survector in France, because of risk of dependence. This decision has been effective since 31 January 1999.

The French medicine agency has suspended the marketing authorization of Survector at the same date.

Spain

Spanish Safety Committee

Spanish Regulatory Authorities

Survector- marketing authorisation suspension

Survector (amineptine, 100 mg tablets) is available in Spain.. Up to now five cases of abuse/dependence have been reported to the Spanish Pharmacovigilance system, since the approval of the product in 1982.

The Servier company has voluntarily decided to suspend the marketing of the drug in Spain in agreement with the Spanish Regulatory Authority on 3rd Feb 1999.

VIGIMED TOPICS

In the e-mail discussion group ‘vigimed’, maintained by the UMC for rapid exchange of information between national pharmacovigilance centres, the following topics were recently brought up:

Australia

Polygeline - hypotension

An increased frequency of reports of hypotension associated with the use of Haemaccel (polygeline plasma expander) was observed. Similar observations from other countries were requested.

(See also under Regulatory Decisions, Germany above)

Malaysia

Pethidine - cardiac arrest

A case of maternal death from cardiac arrest was reported to be associated with the use of pethidine injection. Information on underlying risk factors was requested.

It was suggested that pethidine is prone to give rise to a

combination of hypotension, pulmonary hypertension, hypovolaemia and histamine release.

LITERATURE REFERENCES

Netherlands

Y M Pinto, I C van Gelder, M Heeringa, H J G M Crijns
The Lancet Vol 353, March 20, 1999

QT prolongation and life-threatening arrhythmias associated with fexofenadine

For clinicians treating patients with suspected or known QTc prolongation and ventricular arrhythmias, it is important to be aware of rare but life-threatening arrhythmogenic properties of some antihistamines. Fexofenadine, a histamine H1-receptor antagonist used for the treatment of seasonal allergic rhinitis, was approved by the FDA in December, 1996, with its main advantage being its proposed lack of effect on Qtc time. Fexofenadine is the primary active derivative of terfenadine. Terfenadine was withdrawn because of its association with cardiac arrhythmias mainly in conjunction with macrolide antibiotics and antifungal medication. These adverse effects of terfenadine were known for several years but it was only withdrawn after the approval of Fexofenadine, which was reported not to cause cardiotoxic reactions. The mechanism of the drug-induced polymorphic ventricular tachycardia is not clear, but is thought to be related to an excessive delay of repolarisation producing marked Qtc prolongation. Use of this drug is steadily increasing since it is often used to replace its predecessor terfenadine, which was among the most frequently prescribed drugs in the United States. Pharmacoepidemiological studies are needed before a more definitive risk-benefit analysis can be made.

References

1. Marhan A, Wagstaff Aj. Fexofenadine. *Drugs* 1998; **55**: 269-74.
2. Product Information: Allegra (R), Fexofenadine. Hoechst Marion Rousell, Inc, Kansas City, MO, 1997.
3. Eosle RL. Cardiac actions of antihistamines. *Annu Rev Pharmacol Toxicol* 1996; **36**: 233-52.
4. Simons FE, Bergma NJ, Watson WT, Simons KJ. The clinical pharmacology of Fexofenadine in children. *J Allergy Clin Immunol* 1996; **98**: 1062-64.
5. Faber TS, Zehender M, Just H. Drug-induced torsade de pointes. Incidence, management and prevention. *Drug Saf* 1994; **11**: 463-78.

Daan Lansdorp, MD. The Netherlands Pharmacovigilance Foundation Lareb,
Br J Clin Pharmacol, 47, 223-230 (1999)

Potentiation of acenocoumarol during vaginal administration of miconazole

Miconazole, an antifungal imidazole derivative, decreases the transformation of lanesterol to ergosterol by competitive inhibition of the CYP P450 enzyme lanesterol-14 - demethylase, which in turn causes impairment of the fungal cellular membrane. Because of inhibition also of hepatic CYP P450 enzymes, parenteral miconazole administration decreases the clearance of several other drugs, for example amphotericin, astemizole, cisapride, cyclosporine, phenytoin, terfenadine and coumarin anticoagulants. Since appreciable amounts of miconazole are absorbed in the gut, interactions may also occur after taking miconazole tablets. In addition, several case reports have shown that oral application of miconazole can also potentiate coumarin anticoagulants. In contrast, the topical administration of miconazole, i.e. on the skin or vagina, is considered not to interact with coumarin derivatives.

Reference

1. Stockley IH. Drug interaction, 4th edition. London: The Pharmaceutical Press 1996.

New Zealand

Peter W. Beggs et al.
Br J Clin Pharmacol, 47, 99-104 (1998)

A comparison of the use, effectiveness and safety of bezafibrate, gemfibrozil and simvastatin in normal clinical practice using the New Zealand Intensive Medicines Monitoring Programme (IMMP)

In normal clinical practice in New Zealand gemfibrozil appears less effective and more frequently causes adverse effects leading to withdrawal of treatment, than either bezafibrate or simvastatin.

Portugal

Cad. Saúde Pública, Rio de Janeiro, 14(4): 725-733, 1998

The pharmacovigilance system in Portugal

The safety profile of a drug is not a static concept. It progresses and can change on the basis of scientific data gathering before and after it is marketed. Therefore, it is now considered fundamental that all countries have the capacity

to continuously monitor the safety of medicines authorized for sale. Based on the resulting and appropriate data, this allows them to alter the previously authorized conditions for use of a given drug as a public health safeguard.