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ADVERSE REACTION NEWSLETTER 1999:3

**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

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NATIONALLY CIRCULATED INFORMATION

Australia

ADRAC Bulletin, vol 18, No 3, August 1999

Tendinitis and tendon rupture with fluoroquinolones

The Adverse Drug Reactions Advisory Committee (ADRAC) first reported tendinitis in association with the fluoroquinolone antibiotics in 1997.

The Committee has continued to monitor this adverse reaction, and has now received 60 reports of tendinitis, tenosynovitis and/or tendon rupture in association with these drugs. Most involved was ciprofloxacin (55), but there were also reports with norfloxacin (4) and enoxacin (1). Fortyfive reports described tendinitis alone, one report described tenosynovitis, and 14 reports documented tendon tear or rupture. Fifty five of the 60 reports specified the Achilles tendon, including 20 which described bilateral Achilles tendon damage. All 14 reports of tendon rupture involved the Achilles tendon. The 58 patients ranged in age from 38 to 91 (median 69) years, with no significant difference between those with tendinitis and those with tendon rupture.

The daily doses of ciprofloxacin ranged from 500 mg to 2250 mg, with 46% of patients taking 1500 mg and 46% of patients taking 1000 mg daily. For those who developed tendon rupture, 57% were taking 1500 mg daily. Time to onset varied from within 24 hours after the drug was commenced to 3 months after starting but the majority of cases of tendinitis occurred within the first week. Time to rupture was longer with a median time of 2-3 weeks. Known risk factors for these reactions include old age, renal dysfunction and concomitant corticosteroid therapy. In the ADRAC cases, 29 reports documented concomitant corticosteroid use, and in 21 of the other 31 reports, the patients were aged 69 years or older. In the reports of tendon rupture, 12 of the 14 described either concomitant steroid use (9 cases) or old age (9 cases).

The fluoroquinolone should be withdrawn immediately when symptoms of tendinitis appear, in order to attempt to reduce the risk of tendon rupture.

References:

1. ADRAC. The Achilles heel of fluoroquinolones. *Aust Adv Drug React Bull* 1997; 16: 7.
2. Szarfman A, Chen M, Blum MD, Pierfitte C, Gillet P, Royer RJ. More on fluoroquinolone antibiotics and tendon rupture. *N Engl J Med* 1995; 332: 193.

Olanzapine: neutropenia, convulsions and NMS

Olanzapine (Zyprexa) is an antipsychotic agent which has been marketed in Australia since mid 1997. Since that time, ADRAC has received 327 reports of suspected adverse reactions with the drug. The product information for olanzapine indicates that the two most frequent adverse reactions in clinical trials were somnolence and weight gain which both occurred in more than 10% of patients.

Reports to ADRAC show a similar trend with weight gain (29 reports) and somnolence (25) as the two most commonly reported reactions.

More seriously, however, ADRAC has received reports of white cell disorders, convulsions and neuroleptic malignant syndrome.

White cell disorders are a known effect of the related drug, clozapine, and ADRAC has received 18 reports of neutropenia in association with olanzapine. There have been no reports of agranulocytosis. Ages of the patients ranged from 23 to 67 (median: 45) years and daily doses of olanzapine ranged from 5 - 30 (median: 10) mg in the 16 patients for whom this information was available. At the time of reporting, 5 patients had recovered, 5 had not, and the outcome was unknown for the other 8. Laboratory results were available for 14 patients. These showed nadir Two of neutrophil counts ranging from 0.8 to 1.9 (median: 1.4) cells x 10⁹ /L (reference range: 2.0 - 7.5 cells x 10⁹ /L). There have been 15 cases of convulsions reported in slightly older patients ranging from 14 to 83 (median: 53) years. Olanzapine was taken in daily doses ranging from 2.5 to 15 (median: 10) mg and it was the only drug suspected in 12 cases. The reaction was variously described as myoclonus (3 reports), epileptic seizures (3), tonic-clonic seizures (2), seizure (2), clonus (2), night seizures, grand mal or a petit mal convulsion. Ten of the patients had pre-disposing factors such as a past history of head trauma, epilepsy or renal impairment.

Also of interest are the 7 reports of neuroleptic malignant syndrome (NMS). These involved 4 males and 2 females (one not stated) ranging in age from 23 to 83 (median: 65) years. Doses ranged from 5 mg to 20 mg and the onset varied from 2 days to 2 months after the drug was started. the patients had a past history of NMS with other drugs. Six of the 7 patients recovered including one who developed the syndrome on rechallenge with olanzapine.

A gut feeling for alendronate

Sodium alendronate (Fosamax) was marketed in Australia in late 1996 and since that time ADRAC has received 331 reports of suspected adverse drug reactions. Alendronate

was the only suspected drug in 91% of those reports. The reports are dominated by gastrointestinal (GI) disorders which occurred in 54% of the cases. The other major effect is on the musculoskeletal system which was mentioned in 18% of the reports.

The most important effects on the GI tract are oesophagitis and oesophageal ulceration. These were reported by ADRAC soon after the drug was marketed. 1 The Committee has now received 52 reports of oesophagitis, oesophageal ulceration or oesophageal stricture. This was confirmed endoscopically in 26 of the cases. The product information for Fosamax indicates that oesophageal ulceration occurred in 1.5% of patients in clinical studies and a similar figure has been obtained from

prescription-event monitoring. 2 other GI reactions reported to ADRAC include dyspepsia (44 reports), nausea (43), abdominal pain (37) and dysphagia (23). It is possible that some of these symptoms may also have indicated oesophageal damage. There have also been 6 reports of gastric ulceration and 2 reports of duodenal ulceration. In the 180 reports that involved the GI tract, the ages of the patients ranged from 18 to 91 (median: 71) years and all except 5 patients were aged 50 or more. 87% were female. The majority of cases were reported with a dosage of 10 mg daily with the remainder taking 40 mg daily. Time to onset varied from the same day that the drug was started to more than a year after commencement. However, 36% occurred in the first week. Only 64% were reported as recovered at the time the report was submitted and 20 reactions recurred on rechallenge.

There have also been 61 reports of musculoskeletal problems with 35 cases of muscle pain, 29 cases of joint pain and 6 cases of bone pain. In ten of these reports, muscle and joint pain occurred together. Patient characteristics were similar to those experiencing GI problems, as were dosage, time to onset, and recovery rates. The reaction recurred on rechallenge in 8 patients.

References:

1. ADRAC. Alendronate oesophagitis – are precautions effective? *Aust Adv Drug React Bull* 1997; 16: 10.
2. Mackay F, Wilton LV, Pearce G, Freemantle S, Mann RD. Alendronate and oesophageal reactions (abstract). *Pharmacoepidemiol Drug Safety* 1997; 6, Suppl 2: S20.

Canada

Canadian Adverse Drug Reaction Newsletter, Vol 9, No 3, July 1999

Acute thrombocytopenia after abciximab

(ReoPro™) therapy

Platelet- and thrombin-mediated thromboses contribute to the abrupt artery closure and acute ischemic complications that may follow percutaneous coronary intervention. Abciximab (ReoPro™), approved in Canada since 1996, is a potent antiplatelet agent that is increasingly being used to prevent ischemic complications of percutaneous coronary revascularization. Abciximab binds to the platelet glycoprotein IIb/IIIa receptor and inhibits platelet aggregation.

Thrombocytopenia (platelet count less than $100 \times 10^9/L$), including acute profound thrombocytopenia (platelet count variously defined as below $20-40 \times 10^9/L$), has been reported to occur with this agent. The mechanism of profound thrombocytopenia following abciximab therapy is not clearly understood. The risk of acute profound thrombocytopenia is estimated to be about 0.5% (95% confidence interval 0.01%-1.1%).

Review of the literature documenting abciximab-induced acute thrombocytopenia provides limited information as to the timeframe over which this adverse reaction can occur, and indicates that it generally occurs within the first 24 hours of infusion. More recently, Berkowitz and associates reported 2 cases in which baseline platelet counts were normal and acute profound thrombocytopenia was documented within 2 hours of infusion of abciximab.

Between July 29, 1997, and Mar. 18, 1999, the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) received 21 case reports of individuals experiencing adverse reactions associated with the use of abciximab. In 15 the adverse reaction was described as thrombocytopenia. One of the 15 patients died, with the cause of death attributed to intracranial bleeding; the report indicated that the baseline platelet count was normal 4 days before the start of abciximab therapy, and within 3 hours of the initial infusion of the drug, the platelet counts were reported as not countable.

The remaining 14 cases were reviewed to assess the rapidity of onset and the severity of thrombocytopenia. In 3 cases acute profound thrombocytopenia (platelet counts $6-40 \times 10^9/L$) was documented as occurring between 2 and 4 hours after the initiation of abciximab therapy. In 9 cases thrombocytopenia (platelet counts $5-65 \times 10^9/L$) was documented, but the onset after the start of abciximab therapy was less rapid (11 hours to 5 days). The baseline platelet counts, which were generally obtained within 72 hours before infusion of abciximab, were within normal limits in all 12 cases. Two reports did not provide sufficient detail regarding platelet monitoring to allow for assessment. The dosage regimens used in the majority of the 15 cases generally appear to be in keeping with that recommended in

the product monograph.

In conclusion, abciximab therapy is well documented in the literature to be associated with the occurrence of acute and occasionally profound thrombocytopenia within 24 hours after the start of therapy. The product monograph currently labels thrombocytopenia as a risk of therapy and recommends that platelet counts be monitored 2-4 hours after the bolus dose of abciximab. The objective of this report is to heighten physicians' awareness of the potential for acute profound thrombocytopenia to occur very rapidly after the start of abciximab therapy and to confirm the importance of monitoring the platelet count early in the course of treatment. Institution of platelet monitoring as early as 2 hours after the bolus dose may provide the greatest opportunity to diagnose, monitor and, if necessary, introduce therapy for rapidly evolving episodes of thrombocytopenia.

References:

1. Berkowitz SD, Harrington RA, Rund MM, Tchong JE. Acute profound thrombocytopenia after c7E3Fab (abciximab) therapy. *Circulation* 1997;95(4):809-13.
2. Ferrari E, Thiry M, Touati C, Gibelin P, Baudouy M. Acute profound thrombocytopenia after c7E3 Fab therapy. *Circulation* 1997;96(10):3809-10.
3. Kereiakes DJ, Essell JH, Abbottsmith CW, Boderick TM, Runyon JP. Abciximab-associated profound thrombocytopenia: therapy with immunoglobulin and platelet transfusion. *Am J Cardiol* 1996;78(10):1161-3.
4. Berkowitz SD, Sane DC, Sigmon KN, Shavender J, Harrington RA, Tchong JE, et al. Occurrence and clinical significance of thrombocytopenia in a population undergoing high-risk percutaneous coronary revascularization. *J Am Coll Cardiol* 1998;32(2):311-9.
5. ReoPro™ (abciximab); solution for intravenous injection; chimeric monoclonal antiplatelet antibody [product monograph]. Leiden [Netherlands]: Centocor; 1998. [Distributed in Canada by Eli Lilly Canada Inc.]

Hepatotoxicity associated with nefazodone (Serzone®)

Nefazodone hydrochloride (Serzone®) is an antidepressant agent that has been approved for use in Canada since Apr. 27, 1994. During postmarketing surveillance, hepatic adverse reactions such as jaundice, hepatitis, hepatic necrosis and hepatic failure have been reported in patients receiving therapeutic doses of nefazodone. On occasion, these events

resulted in liver transplantation and/or death.

Clinical manifestations of hepatic injury in patients receiving nefazodone have included the following: anorexia, fatigue, asthenia, abdominal pain, nausea, vomiting, discoloured stools, dark urine, coagulopathy, weight loss, myalgia, rash, pruritus, jaundice, ascites, confusion, asterixis, encephalopathy and hepatic coma. Laboratory evidence of hepatotoxicity has included elevated levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl-transferase and bilirubin, as well as increased prothrombin times. The majority of these events occurred within the first 9 months of treatment.

As of Mar. 18, 1999, the CADRMP has received 9 reports of symptomatic hepatic dysfunction associated with the use of nefazodone.

In addition to these 9 cases, 4 events of asymptomatic liver enzyme elevations have been reported in temporal association with nefazodone use.

References:

1. Aranda-Michel J, Koehler A, Bejarano PA, Poulos JE, Luxon BA, Khan CM, et al. Nefazodone-induced liver failure: report of three cases. *Ann Intern Med* 1999;130:285-8.
2. Nefazodone -- looks like an SSRI, but ... hepatic dysfunction ... visual disorders. *Aust Adverse Drug React Bull* 1998;14(4):14.

Ireland

Irish Medicines Board Drug Safety Newsletter, No 8, July 1999

Nimesulide (Aulin)

Nimesulide is a non-steroidal anti-inflammatory drug (NSAID) authorised in Ireland since 1995.

The potential for hepatic adverse events following exposure to nimesulide has been an ongoing concern to the Irish Medicines Board. In the light of recent reports of serious hepatic adverse events including rare cases of fatalities in patients treated worldwide with nimesulide, the IMB has amended the prescribing information as follows:

Contraindications:

Use in patients with hepatic impairment.

Use in patients with active peptic ulcer, a history of recurrent ulceration, or with gastrointestinal bleeding

Astemizole (Hismanal)

The IMB has recently been informed by the Marketing Authorisation Holder (Janssen-Cilag) of their intention to discontinue supply of astemizole (Hismanal), in Ireland. It is however, the company's intention to maintain a sufficient

supply of the product for the duration of this year's hay-fever season.

Astemizole is a non-sedating antihistamine, used for the treatment of hay fever and other allergic conditions and was authorised for use in Ireland in 1984. Like terfenadine, astemizole has been associated with prolonged of the Qtc interval and thus has the potential to induce cardiac arrhythmias, particularly if used at high doses or in conjunction with potentially interacting medicines (such as anti-arrhythmics, neuroleptics, tricyclic anti-depressants, thiazidediuretics, ketoconazole, erythromycin, clarithromycin and related macrolide antibiotics and selective serotonin reuptake inhibitors (SSRI's).

Salmeterol and eformoterol

The two long acting beta-2 agonists eformoterol (Foradil) and salmeterol (Serevent) were selected for monitoring in the Intensive Medicines Monitoring Programme (IMMP) because of concerns over the effect of regular use of beta agonists on the long term outcome of treatment of asthma. Only a short time previously an increase in death rate had been identified with fenoterol and it was found that patients using regular short acting beta agonists did not do as well as those using them on an as required basis.

Monitoring of eformoterol and salmeterol began in 1992 but usage has increased markedly in the last two years after subsidy changes. As at 31 March 1998, for cohorts of 3896 (salmeterol) and 901 (eformoterol) patients. Main indications for use were asthma CORD and combined asthma and CORD.

There have been 81 patients reported as having died while on salmeterol and 29 while on eformoterol. Most of the respiratory deaths were of end stage CORD, but there were a small number of reports of death during an acute asthma attack. The other, more commonly reported causes of death, were heart failure and myocardial infarction. Preliminary analysis does not indicate a rate of death from all causes greater than that expected in an asthmatic population.

Reference:

1. Crane J, Pearce N, Flatt A, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981-83; case-control study.
2. Sears MR, Taylor DR, Print GP, et al. Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 1990; 336: 1391-6.

New Zealand

Prescriber update, No 18, June 1999

Valvular abnormalities with dexfenfluramine and fenfluramine

Evidence now favours a causal connection between dexfenfluramine (Adifax) and fenfluramine (Ponderax) when used alone and the development of heart valve abnormalities on echocardiography. Both medicines were withdrawn in 1997. The incidence, severity and likelihood of progression of the valve abnormalities is poorly defined.

The risk appears to be minimal with use < 3 months; most abnormalities were reported as mild. The risk is presently not quantifiable, but appears to increase with duration of use.

The major consequence of concern is the development of endocarditis in the damaged valve. As a large number of patients have been exposed to these medications since Ponderax first became available in 1966, and the development of endocarditis is preventable, guidelines have been drawn up in consultation with the Cardiac Society of Australia and New Zealand:

1. Patients who took dexfenfluramine or fenfluramine for < 3 months need not be examined
2. Those who took either or both agents for 3 months should be examined by a GP for evidence of a heart murmur or other abnormal cardiac signs
3. If a murmur or other abnormality is found, or the heart cannot be examined due to obesity, refer the patient to a cardiologist for echocardiography
4. Until a cardiologist is able to advise on the risk of endocarditis, appropriate prophylactic antibiotics should be given to patients requiring dental or other surgical procedures that put them at risk of endocarditis.

Tamoxifen and venous thromboembolism

Evidence now strongly supports the suspicion that tamoxifen increases the risk of venous thromboembolism (VTE). This observation is consistent with the fact that tamoxifen has oestrogenic activity.

One study, based on a sub-population of 10,000 women with breast cancer, identified 25 cases of VTE with an adequately confirmed diagnosis, and calculated a relative risk of VTE with tamoxifen use of 7.1 (95% CI 1.5-33). Another study used data from a Scottish trial of tamoxifen in the treatment of breast cancer in 1312 women. In this study the risk of VTE in users compared with non-users was higher by a factor of 2.50 (95% CI 1.11-5.56). In addition, the American Breast Cancer Prevention Study involving 13,388 women found the rate of pulmonary embolism among the tamoxifen group to be three times that in recipients of placebo (relative risk 3.01; 95% CI 1.15-9.27).

These results do not greatly affect the benefit-risk assessment for tamoxifen in the treatment of breast cancer. However, wellwomen with an elevated risk of breast cancer should not be treated with tamoxifen as a preventive measure (an unapproved indication) without an assessment of the personal risk factors for VTE.

Potentially Serious Adverse Effects of Carbamazepine: Blood Dyscrasias and Skin Rash

The Centre for Adverse Reactions Monitoring recently received 3 reports of serious adverse reactions with carbamazepine: severe cholestatic jaundice, Stevens-Johnson syndrome, and multiorgan hypersensitivity with fulminant liver failure resulting in death.

Three published incidence studies have investigated the frequency and seriousness of cutaneous or haematological reactions with carbamazepine. Rash was found to occur in around 10% of patients. Most occurred in the first 2 weeks

of treatment and were mild. In each of 2 studies one patient developed a serious reaction - erythema multiforme and Stevens-Johnson syndrome respectively.

Blood dyscrasias (moderate and severe leucopenia and 1 case of thrombocytopenia) occurred with an incidence of 2% with mild changes detected in up to 30% of patients. Most cases developed within the first month of therapy.

To reduce the risk of serious adverse effects, a blood screen and physical examination should be conducted during the first 4-6 weeks of therapy, and repeated where there are clinical reasons for concern. Carbamazepine should be withdrawn or the dose reduced if the white cell count falls below 3000/mm³ or the neutrophil count below 1000/mm³.

Clozapine and hyperglycaemia

Hyperglycaemia, sometimes leading to ketoacidosis or glycosuria, has been reported in association with clozapine. In some cases the condition has been of new onset, and in others exacerbation of pre-existing diabetes mellitus has occurred. Hyperglycaemia appears to be of early onset (2 weeks to 3 months after initiation of clozapine) and to occur without predisposing factors. Clozapine-induced hyperglycaemia may be serious leading to coma, but it is reversible on discontinuation of clozapine. In some cases continuation of clozapine is possible by controlling serum glucose levels with the use of hypoglycaemic agents. This approach may be useful in refractory schizophrenia responsive to clozapine. In those with diabetes mellitus, glucose monitoring should be conducted in conjunction with the obligatory haematological monitoring. All patients should be advised to report altered consciousness, polyuria or increased thirst.

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.

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

The list is as follows:

Medicine	Adverse reactions	Date of addition to list
Alendronate	oesophagitis	April 1998
Carbamazepine	skin and haematological reactions	December 1998
Cisapride	cardiac arrhythmias	May 1999
Clozapine	hyperglycaemia	May 1999

Colchicine	serious toxicity	April 1998
Herbal medicines	all adverse reactions	October 1996
Hormone replacement therapy	venous thromboembolism	April 1998
NSAIDs	renal damage	April 1998
Mefloquine	neuropsychiatric reactions	August 1997
Oral contraceptives	venous thromboembolism	February 1996
Ticlopidine	neutropenia and thrombocytopenia	December 1998

Singapore

Adverse Drug Reaction News, Vol 1, No 2, August 1999

Allopurinol hypersensitivity syndrome

Allopurinol hypersensitivity syndrome (AHS) is a rare but life-threatening event. The onset of hypersensitivity reactions may occur within days of starting therapy or may be delayed for several months. The mean time to onset of symptoms is 47 days after therapy is initiated. The postulated mechanism of AHS is that allopurinol may act as a haptene, and induce immune-complex nephritis, vasculitis and a polyarteritis nodosa syndrome resulting in fatality. Pruritus is an important warning syndrome and the onset of skin reaction is an indication to discontinue the drug to avoid progression to more severe reaction.

Hypersensitivity reactions appear to occur more frequently in patients with renal insufficiency.

Sweden

Information from the MPA, Vol 10, No 4 August 1999

ADR reporting in Sweden 1998

The Swedish MPA receives approximately 3000 adverse reaction reports every year. 8 per cent concerns new drug substances and 46 per cent are serious adverse reactions. Several signals are under investigation or has recently been finalized. In some cases Sweden has initiated a discussion within the European Union leading to an investigation of the signal. An investigation usually leads to changed labelling and a need for more information. In some cases it has led to a withdrawal of the drug as in the case with metamizole and agranulocytosis.

Fluconazole increases the effect of warfarin

The MPA has received two case reports where pro-thrombin

level was decreased when fluconazole was added to patients on warfarin. Interaction between fluconazole and warfarin has been described several times in the literature. (1, 2) Fluconazole is a strong inhibitor of the metabolism of other drugs, especially those drugs that are metabolised via CYP 2C9.

Reference:

1. Sjöquist F. Läkemedelsinteraktioner. FASS 1999; 1417-8
2. Miners JO, Birkett DJ. Cytochrome P4502C9: an enzyme of major importance in human drug metabolism. Br J Clin Pharmacol 1998;45:525-38.

Stevens-Johnson syndrome and fluconazole

An 85-year old woman on multiple drug treatment received fluconazole due to fungal infected eczema. Shortly after she developed erythema and later on blisters over torso. When submitted to hospital she had erythema on mons pubis and groins and erosion of genital mucosa and under the breasts. The symptoms were interpreted as a suspected case of Stevens-Johnson syndrome. When fluconazole was interrupted, the skin got paler and no new blisters set in.

Dicloxacillin may cause damage of the oesophagus

A young woman was prescribed dicloxacillin due to an infected toenail. After five days she felt pain when swallowing and a feeling of something stuck in the throat. The pain increased and she had difficulties to swallow. At hospital she was treated with nystatin and sucralfate. Gastroscopy showed oesophageal ulceration.

The manufacturer has been contacted and will change the labelling to include oesophageal pain, oesophagitis and oesophageal ulceration.

Skin reactions and acamprosate

A 57-year old woman addicted to alcohol started treatment with acamprosate in March. She was already on citalopram since long. In December she went abroad. After one hour of sunbathing she developed maculo-papular exanthema over the whole body. The exanthema worsened with facial oedema and eyelid oedema. She was treated with steroids and got better. The reactions was judged to be caused by acamprosate since she had been on citalopram for a long time with no problems when sunbathing.

United Kingdom

Current Problems in Pharmacovigilance, 28 July 1999

(message)

Renal failure associated with *Aristolochia* in some Chinese Herbal Medicines.

There have been two reports recently received in the UK of patients with end-stage renal failure associated with *Aristolochia*, in Chinese herbal medicines. In both these cases the Chinese herbal medicine was used for the treatment of skin conditions. Renal failure was described in Belgium in 1993 where over 70 cases have been reported in association with a slimming product containing *Aristolochia*.

Aristolochia species are plants which have long been used in some traditional Chinese medicines.

They contain aristolochic acids, which are genotoxic carcinogens and are associated with interstitial nephropathy. There is evidence that *Aristolochia* has been a contaminant of or used mistakenly instead of other plants, in particular *Stephania* (as in the Belgian cases) and *Clematis* (as in the UK cases), which themselves are not associated with such toxicity.

In 1997 *Aristolochia* was made a Prescription Only Medicine in order to restrict its availability. In view of the serious adverse effects, the Committee on Safety of Medicines has advised that the import, sale and supply of medicinal products containing *Aristolochia* should be prohibited immediately. A banning order will come into force on 28 July 1999 and will expire at the end of October 1999. In the meantime, the Medicines Control Agency is consulting on a permanent order.

The Medicines Control Agency is sampling and testing certain Chinese herbal medicines to gain information on the extent of the problem of contamination or substitution, so that appropriate provisions in respect of such medicines can be included in a permanent banning Order.

The use of *Aristolochia* contained in Chinese Herbal Medicines should be considered as a possible cause in patients presenting with unexplained renal failure and/or interstitial nephropathy. Patients who have any concern should be advised to consult their herbal practitioner as to the identity of the herbal medicines they have been prescribed. We have now been informed that, as a precaution, herbal practitioners and suppliers are suspending the use of ingredients whose Chinese names are Mu Tong and Fangji until appropriate quality checks are in place, because of the risk that they may contain *Aristolochia*.

Note from literature:

There are 350 species of *Aristolochia*, 40 species of *Stephania* and 250 species of *Clematis*.

Aristolochia clematitis drug is highly toxic. The intake of

acutely toxic doses leads to vomiting, gastroenteritis, spasms, severe kidney damage and eventually to death by kidney failure. Because of the genotoxic and cancerogenic effects of the aristolochic acids, the drug is not to be administered even in small dosages.

Adverse Drug Reaction Bulletin, No 196, June 1999

Drug-induced rhabdomyolysis

Rhabdomyolysis, the breakdown of skeletal muscle, is an important cause of acute renal failure. Many drugs can cause it. Some, like statins, appear to damage muscle directly. Others act indirectly, for example, by increasing muscle activity or by causing coma, muscle compression, and muscle necrosis. Amphetamines and opiates, respectively, are examples. Patients with malignant hyperpyrexia have genetically abnormal muscle biochemistry and develop rhabdomyolysis during anaesthesia.

SPECIAL COMMUNICATIONS

USA

FDA Medical Bulletin, summer '99 final issue

Important Drug Information

Immune Globulin Intravenous (Human) (IGIV) was first licensed in the U.S. in 1981. From 1981 to July 1998, the FDA received over 114 worldwide (approximately 83 U.S.) adverse event reports¹ for IGIV products that consisted of acute renal dysfunction (ARD). Although ARD was successfully managed in the majority of cases, 17 deaths occurred in which renal failure was possibly contributory. Of the U.S. reports, approximately 69% were associated with the use of the IGIV product manufactured by the Central Laboratory Blood Transfusion Service Swiss Red Cross (SRC) (Sandoglobulin, distributed by Novartis, and Panglobulin, distributed by the American Red Cross). Approximately 22% were associated with Gammar-P I.V./Gammar I.V., manufactured by Centeon L.L.C. The Swiss Red Cross and Centeon LLC IGIVs are the only two IGIV products licensed in the U.S. that contain sucrose as a stabilizer (1.67 and 1.0 g sucrose/g immunoglobulin, respectively). Preliminary evidence suggests that IGIV products containing sucrose may present a greater risk for acute renal failure.

In approximately four-fifths of the reported cases of IGIV-associated renal dysfunction, the patients either had some degree of pre-existing renal insufficiency and/or had a disease such as diabetes mellitus or hypertension, which frequently leads to renal impairment.

FDA recommends the following precautions be taken when administering IGIV products:

- A. Assure that patients are not volume depleted prior to the initiation of the infusion of IGIV.
- B. Exercise particular caution in the administration of IGIV in patients at increased risk for developing acute renal failure. Such patients include those with: any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, and those receiving known nephrotoxic drugs. For patients at increased risk, physician should carefully weigh the potential benefits of administering sucrose-containing IGIV products (Sandoglobulin®, Panglobulin®, and Gammar®-P I.V.) against the risks of causing renal damage.
- C. Do not exceed the recommended dose. Reduction in dose, concentration, and/or infusion rate in patients at risk of ARD has been proposed in order to reduce

the risk. Because no prospective data are presently available to identify a maximal safe dose, concentration, or infusion rate for IGIV products for patients at risk of ARD, FDA recommends that, for such patients, prescribers reconstitute/dilute and administer the product in such a manner as to produce both the minimum concentration and infusion rate 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. These correspond to a maximum infusion rate of 3 mg sucrose/kg/minute.

- D. Baseline urine output and blood urea nitrogen (BUN)/serum creatinine measurements should be assessed prior to infusion of IGIV, particularly in patients at potentially increased risk for developing acute renal failure, and again at appropriate intervals. If renal function deteriorates, discontinuation of IGIV should be considered.

References:

1. Additional literature reports were under review at time of printing.
2. Seven Renal Adverse Event Reports (4 international and 3 U.S. cases) were associated with unspecified IGIV products.

Misadministration of topical bovin thrombin

It has been submitted from the FDA for publication in Adverse Reaction Newsletter 1999 and Signal a drug safety issue concerning fatal and serious, but non-fatal events resulting from misadministration of topical bovine thrombin products through the vascular route. This manuscript is entitled Misadministration of Topical Bovine Thrombin.

The Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA) has received reports through MedWatch of three fatalities and one serious, but not-fatal adverse event following the improper administration of Thrombin, Topical (bovine origin) U.S.P. by several inappropriate routes.

The first report was received in April, 1987. A physician injected Thrombostat (Thrombin, topical) directly into the splenic tissue of a 61-year old patient with a perforated colon. The patient developed immediate anaphylactic-like shock and died 1 hour later. The second serious, but non-fatal report was received in October, 1996. A surgeon mistakenly administered 3,000 units of Thrombin-JMI into the catheter of a 69-year old patient with renal failure, who

was being prepared for hemodialysis. The patient developed severe hypotension, bradycardia, and respiratory failure, requiring intubation and assisted respiration. The patient recovered a week later. He also developed pulmonary emboli. The patient was released from the hospital a week later with hypertensive medications and Coumadin. The third incident occurred in April, 1998. A physician in Japan administered 10,000 units of Thrombostat into a nasogastric tube for the treatment of bleeding gastric ulcers in a 67-year old patient. The patient had immediate, generalized convulsions, and went into shock. He later developed acute renal failure, disseminated intravascular coagulation and cerebral thrombosis and died from these complications two months later. The last and most recent incident occurred in December, 1998. A surgeon administered 10,000 units of ThromboGen through a dialysis access site, causing excessive blood clotting and death to a 61-year old woman with end stage renal disease.

As a result of these reports, FDA has recommended that GenTrac, Inc. provide a more prominent as well as consistent display to its carton labelings of the words "FOR TOPICAL USE ONLY- DO NOT INJECT". FDA also suggested that similar language be added to the Warnings section of the package insert. GenTrac has agreed to take action in accordance with the Agency's recommendations. In addition, FDA intends to highlight the risks associated with misadministration of topical thrombin products through communications with the medical community.

Thrombin, topical (bovine origin) U.S.P. is indicated as an aid to hemostasis wherever oozing blood from capillaries and small venules is accessible. The first topical bovine thrombin product licensed in the U.S. was Thrombostat (Parke-Davis, 1943). Since then, two other U.S. topical thrombin products have been licensed and are manufactured by GenTrac, Inc.- ThromboGen (1986) and Thrombin-JMI (1995). GenTrac, Inc is currently the only licensed manufacturer that distributes topical bovin thrombin products in the U.S. While Parke-Davis continues to produce its product, it is distributed only in eight foreign countries.

REGULATORY DECISIONS

Ireland

Irish Medicines Board Drug Safety Newsletter, No 8, July 1999

Terfenadine

(Triludan, Terfenor, Terfenadine)

Terfenadine is a non-sedating antihistamine which has been authorised in Ireland for over 17 years. It was available as an "over the counter" medicine from 1987 - 1997. In 1997, its status was changed to a prescription only medicine following evaluation of its potential to induce cardiac arrhythmias, particularly when used in combination with other medicinal products (including ketoconazole, itraconazole and related imidazole anti-fungal agents, erythromycin, clarithromycin and related macrolide antibiotics).

This was the subject of a formal referral, on safety grounds to the EU Committee for Proprietary Medicinal Products (CPMP). The IMB in association with the CPMP undertook an extensive review of the safety of terfenadine and other non-sedating antihistamines. The review, which was completed towards the end of 1998, concluded that the risk/benefit profile of the 120 mg product was unfavourable and as a result, this product was withdrawn from all EU markets.

A positive CPMP Opinion was issued in respect of the 60 mg product which remains available on the Irish market as a prescription only medicine for the symptomatic relief of allergic rhinitis and conjunctivitis and of allergic skin disorders.

Spain

Immunoglobulin - intravenous

The Spanish Medicines Agency has received 2 case reports of hepatitis-C that are suspected to be in connection with the use of endobulin (Immuno Globulin Intravenous; MAH: Baxter-Immuno).

The AGEMED has taken the decision, as a precautionary measure, to put on hold all samples of this pharmaceutical product available in Spain, until further information is provided by the MAH. This measure will be put into action from 29th July 1999.