MINISTRY OF HEALTH

MANATŪ HAUORA

Prescriber Update

No. 20
February 2001

A publication of

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Prescriber Update For 2001

Future issues of this publication will be more frequent (about three times a year) and contain shorter articles. Tentative dates for 2001 are June and October.

Have Your Say

We are redefining the role of *Prescriber Update* and would value your input. If you have any comments or suggestions about the types of articles you would like to see published in *Prescriber Update,* contact the Editor (details on page 2).

Medicines In Pregnancy – Australian Handbook

The text of this reference can be found at http://www.health.gov.au:80/tga/docs/html/mip/medicine.htm and gives the categorisation of the risk of drug use in pregnancy.

Adverse Reaction Reporting

Remember to report any suspect adverse reaction of clinical concern to the Centre for Adverse Reactions Monitoring (CARM) in Dunedin. In particular, please report all adverse reactions of current concern (see page 54) and those occurring with medicines on the Intensive Medicines Monitoring Programme (see page 53). Late last year, a new adverse reaction category was added to the CARM database to cover adverse events arising from brand switching, including lack of efficacy. These can also be reported to CARM. See inside the back cover for full reporting details.

Why reporting is important

The monitoring of medicines for safety by collecting adverse reaction reports results in:

- entry of a Danger/Warning against the patient's name in the national database, as appropriate
- identification of new adverse reactions
- changes in medicine data sheets
- publication of articles in *Prescriber Update* and other medical journals
- assessment of risk factors for adverse reactions
- evaluation of risk versus benefit for medicines
- contribution to the worldwide pool of adverse reactions data through New Zealand's involvement in the WHO programme.

NECROTISING FASCIITIS ASSOCIATED WITH NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Dr Lesley Voss, FRACP, Paediatrician to Infectious Diseases Services, Starship Children's Hospital, Auckland.

This article was e-mailed to electronic Prescriber Update subscribers in October 2000.

For some time published case reports and case series have described cases of necrotising fasciitis (NF) in patients who have recently used a non-steroidal anti-inflammatory drug (NSAID), and an association has been postulated. Recently a case-control study gave further support to this postulate. The study involved 19 children with NF and varicella infection and 29 control children with serious skin and soft-tissue infection and also with varicella. The odds ratio for use of ibuprofen among those with NF was 5.0 (95% CI 1.03-26.6).

The mechanism by which NSAIDs increase the risk of NF may be by impairment of the immune response, or by masking of the symptoms of secondary infection, leading to delayed diagnosis and treatment.

Although the evidence for this association is weak due to the small number of case patients, it would be prudent to use ibuprofen with caution in children with varicella infection, particularly if there is a possibility of secondary infection.

Temporal association between NSAIDs and necrotising fasciitis in case reports

Necrotising fasciitis (NF) is a rare soft-tissue infection most frequently due to group A β-haemolytic streptococcus, although a number of other organisms have been isolated. Cases occurring in several countries over the last 10-15 years have suggested an association between this disease and the use of non-steroidal anti-inflammatory drugs (NSAIDs).[1-5] Whether this effect is due to masking of symptoms of early NF by NSAIDs, or whether the frequent use of NSAIDs for nonspecific musculo-skeletal symptoms plays a role in the pathogenesis of NF, has not been clarified.

In New Zealand, a retrospective review undertaken at Dunedin Hospital found seven cases of NF over a 4.5 year period, five of whom had received NSAIDs prior to hospitalisation.[4] The authors concluded that NSAIDs should be prescribed with caution in any patients with suspicion of infection. They also

expressed concern over whether the increased availability of NSAIDs as over-the-counter drugs results in an increase in cases of serious infection.

Case-control study: possible association between NSAIDs and NF in varicella

A case-control study conducted in Washington State and evaluating NF and ibuprofen use, investigated the use of ibuprofen and other risk factors for NF, in the setting of primary varicella.[6] There is a well recognised risk of serious secondary group A streptococcal infections complicating chickenpox.[7] Nineteen children with chickenpox and NF were compared with 29 control subjects who had serious soft-tissue infection, other than NF, complicating varicella. NF cases were five times more likely to have received ibuprofen before hospitalisation than controls (95% CI 1.03-26.6). After adjustment for group A streptococcal isolation, age, and gender, the odds ratio increased to 10.2 (95% CI 1.3-79.5). Other risk factors were also assessed including use of paracetamol, diphenhydramine, calamine lotion, pre-existing medical conditions, attendance at a day care, and duration of symptoms of secondary infection prior to hospitalisation. No significant difference was found between cases and controls for these other risk factors. A subset analysis of children with NF complicated by renal insufficiency and/or streptococcal toxic shock, markers of increased morbidity, found that these complicated cases were more likely to have used ibuprofen than were cases without complications (odds ratio 16.0; 95% CI 1.0-825.0). These cases with complicated NF also had a longer duration of symptoms associated with secondary infection before hospitalisation than those with uncomplicated disease.

A limitation of this study is the small patient numbers resulting in wide confidence intervals. This study suggests an association between ibuprofen use and the development of NF among children with varicella, and also an association between ibuprofen use and severe complications of NF.

Mechanism: impairment of immune response or masking of symptoms?

Although, the underlying mechanism of the association of NSAIDs and increased severity of streptococcal infections has not been defined, some indications that NSAIDs may alter the biological response to infection have been identified in in vitro studies. NSAIDs are cyclo-oxygenase inhibitors and may have an adverse effect on neutrophil killing and cell mediated immunity. NSAIDs interfere with the function of lymphocytes[2] and inhibit monocyte superoxide production.[8] They have also been found to augment the

production of certain cytokines such as TNF alpha, IL-1, and IL-6 which are mediators in shock.[9]

However, other studies including a randomised controlled trial have shown that ibuprofen in sepsis can improve physiologic parameters.[10] In this study of 455 patients with sepsis, although those receiving intravenous ibuprofen had reduced levels of prostacyclin and thromboxane with an improvement in some clinical parameters, there was no improvement in clinical course or subsequent outcome.[10] Use of ibuprofen for 48 hours was associated with no detected adverse effects.

It has also been suggested that the use of NSAIDs may mask the symptoms of early infection, resulting in delayed diagnosis of NF and severe disease. The Washington study, found that both cases and controls who used ibuprofen had a longer duration of secondary symptoms before hospitalisation, than cases and controls who did not receive ibuprofen.[6] The authors postulated that the use of ibuprofen contributed to partial masking of symptoms with delay in diagnosis which resulted in more severe disease.

Use ibuprofen with caution in varicella, particularly with secondary infection

In conclusion this recent case control study suggests an association between the use of ibuprofen and NF in children with primary varicella. Further studies will be required to better define the association.[11] The implications of these findings to the use of ibuprofen, and other NSAIDs, in situations where there is no varicella infection are not clear. At this time it is recommended that ibuprofen be used with caution in patients with chickenpox and particularly if soft-tissue infection is suspected.

Editor's note: Serious skin and soft-tissue infections occurring following use of the NSAIAs are adverse reactions of current concern (see page 54).

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INDICATION CHANGES FOR CISAPRIDE

Medsafe Editorial Team

This article was e-mailed to electronic Prescriber Update subscribers in November 2000.

The indications for cisapride (Prepulsid™) in New Zealand have been limited to the following:

Adults

For the treatment of:

- severe reflux oesophagitis where other treatment, including acid suppression with proton pump inhibitors, has failed; and
- gastroparesis;

where the diagnosis has been made or confirmed by a specialist physician or surgeon.

Children

Use should be restricted to children with severe gastro-oesophageal reflux, where the diagnosis has been made or confirmed by a specialist physician or surgeon.

The changes involve narrowing of the indications and placing the proviso of diagnosis by a specialist physician or surgeon on use.

The risk of rare QT-prolongation and torsade de pointes with cisapride, which is the reason for limiting the indications, can be reduced by observing the maximum recommended dose (40mg daily for adults). To further reduce the risk, cisapride is contraindicated:

- with substances which inhibit cytochrome P450 3A4;
- with other agents which prolong the QT-interval;
- in patients with predisposing factors for arrhythmia or pre-existing QT-prolongation; and
- in patients with hepatic failure.

The purpose of requiring diagnosis by a specialist is to minimise the risk to the patient by achieving careful weighing of the patient's risk of QT-prolongation with cisapride, with exclusion of patients with contraindications, and consideration of the risks and benefits of all therapies, prior to use.

Cisapride use restricted in several countries

Several countries have taken steps to restrict the use of cisapride (Prepulsid), because of the risk of QT-prolongation and death from torsade de pointes, although these events are very rare. In New Zealand, the available data, including epidemiological studies and case reports, have been reviewed by the Medicines Adverse Reactions Committee.

QT-prolongation with cisapride is rare

Two epidemiological studies have found that the risk of QT-prolongation with cisapride is very small. One study[1] used the linked databases of the Canadian Province of Saskatchewan and the United Kingdom General Practice Research Database, including a total of some 36,000 cisapride users. The rate of arrhythmia with recent cisapride use was found to be 1.1 per 1000 person-years versus 0.6 per 1000 for non-recent use. A key result of this study was the observation that the relative risk of serious arrhythmias with cisapride fell from 1.6 (95% CI 0.9-2.9) to 1.0 (0.3-3.7) when adjustment was made for predisposing factors which increase the risk (see below). This results suggests that there may be little increase in risk when predisposing factors are eliminated.

A prescription event monitoring study[2] conducted by the Drug Safety Research Unit in Southampton included 13,000 users of cisapride and found a rate of arrhythmias of 0.4 cases per 1000 patients.

Rate high in US with high maximum dosage and non-specific indications

The rate of reports of QT-prolongation with cisapride has been higher in the US than in other parts of the world, and cisapride is now available only under a special access scheme in the US. In New Zealand only one report of (non-fatal) arrhythmias with cisapride has been received. The patient was taking the interacting agents grapefruit juice and quinine. Usage differences may account for the differences in the experience of the safety of cisapride between the US and New Zealand.

- In New Zealand the maximum recommended dose is 40mg per day and in the US it is 80mg.
- In New Zealand a paediatric indication with paediatric dosage instructions is approved. Hence, there is a paediatric oral suspension with dosing pipette available. In the US there is no paediatric indication or paediatric-specific preparation.
- The adult indication in the US permits use for a broad range of conditions, but even prior to the current change the approved indication in New Zealand was quite specific.
- Cisapride is funded only on a specialist endorsement in New Zealand.

Diagnosis to be made by a specialist physician or surgeon

On the basis of these data, the indications for cisapride have been narrowed in New Zealand on the advice of the Medicines Adverse Reactions Committee, and with the agreement of the New Zealand Society of Gastroenterology. The new indications are as follows:

Adults
For the treatment of:

- severe reflux oesophagitis where other treatment, including acid suppression with proton pump inhibitors, has failed; and
- gastroparesis;

where the diagnosis has been made or confirmed by a specialist physician or surgeon.

Children
Use should be restricted to children with severe gastro-oesophageal reflux, where the diagnosis has been made or confirmed by a specialist physician or surgeon.

With the changes, the indications have been narrowed and the proviso of diagnosis of the condition by a specialist physician or surgeon has been placed on use. Note, in particular, that cisapride is no longer approved for the treatment of constipation, and mention of this indication has been deleted from the Dosage and Administration section of the data sheet.[3]

The proviso of diagnosis by a specialist physician or surgeon is to ensure that the initial prescription is preceded by careful weighing of the patient's risk of developing clinically significant QT-prolongation with cisapride against the expected benefits of this and alternative therapy, and exclusion of patients with contraindications (see below).

Avoid cisapride with interacting medicines or predisposing conditions

In addition to observing the maximum daily dose and using lower doses if these are effective, the risk of QT-prolongation is reduced if cisapride is contraindicated in the following circumstances:[4]

- With use of agents inhibiting metabolism by cytochrome P450 3A4: macrolide antibiotics (erythromycin, clarithromycin, etc), azole antifungals (ketoconazole, itraconazole, fluconazole, etc), protease inhibitors (ritonavir, indinavir, etc), nefazodone and grapefruit juice.
- With use of agents which may prolong the QT-interval: quinine, terfenadine, some antiarrhythmic medicines (e.g. amiodarone, quinidine, flecainide, sotalol), tricyclic antidepressants (e.g. amitriptyline, etc) and some antipsychotic agents (phenothiazines, haloperidol, risperidone).
- In patients with a history of QT-prolongation, ventricular arrhythmia, torsade de pointes, and those with risk factors for arrhythmia, such as second or third degree atrioventricular block, clinically significant heart disease, uncorrected electrolyte disturbances and renal or respiratory failure.
- In patients with hepatic failure.

Cardiac arrhythmias with cisapride are an adverse reaction of current concern. Please report all cases to the Centre for Adverse Reactions Monitoring, PO Box 913, Dunedin.

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OMEPRAZOLE-INDUCED INTERSTITIAL NEPHRITIS

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This article was e-mailed to electronic Prescriber Update subscribers in November 2000.

Acute renal impairment due to interstitial nephritis is a rare, difficult to diagnose, complication of omeprazole, a medicine which is now widely used in New Zealand. The presenting symptoms, which are associated with elevation of plasma creatinine, commonly include rash, arthralgia, malaise, fever, nausea, lethargy and weight loss. Patients presenting with these symptoms, with no other apparent cause, should be investigated by dipstick examination and microscopy of urine and assessment of renal function. If either urinary or renal findings or both are abnormal, omeprazole should be withdrawn pending nephrology assessment. Patients usually respond rapidly to discontinuation of omeprazole, but full recovery of renal function may take 2-3 months, or, occasionally, even longer.

Interstitial nephritis is rare with omeprazole

Acute renal impairment caused by interstitial nephritis is a rare complication of treatment with omeprazole, a medicine which is now widely used in New Zealand. The first publication of a report of omeprazole-related interstitial nephritis was in 1992.[1] The New Zealand Centre for Adverse Reactions Monitoring (CARM) has received seven reports of acute renal failure due to interstitial nephritis associated with omeprazole. While omeprazole was being monitored on the Intensive Medicines Monitoring Programme (IMMP), two reports of interstitial nephritis were received from a total cohort of 22,050 patients. There were several other reports of renal failure.

Symptoms of interstitial nephritis are non-specific

Recognition of interstitial nephritis may be difficult because the symptoms of renal impairment are non-specific. The identification of disturbance in renal function can only be made by carrying out biochemical tests.

In general the presenting features described for this disorder are fever, rash and eosinophilia but these features are not always seen. An analysis of 13 published reports[2] demonstrated that patients with interstitial nephritis involving omeprazole commonly presented with malaise, fever, nausea, lethargy and weight loss. The cases reported to CARM displayed similar symptoms. In one of the CARM cases, the woman was non-specifically unwell for several months before the diagnosis was made and omeprazole discontinued. Polyuria and, in one instance, polydipsia were other presenting features.

Urine microscopy may show white cells including eosinophils, white cell casts and few red cells, but may be unremarkable.[3] Urinary eosinophils are only rarely found and require special stains for their identification. Plasma creatinine and urea concentrations will usually be elevated. The diagnosis can be confirmed by renal biopsy.

Interstitial nephritis may be caused by a medicine, an infection, or autoimmunity

Interstitial nephritis may be caused by infection, autoimmunity and glomerular disease as well as hypersensitivity to medicines.[3] A large number of medicines are reported to have caused various forms of acute interstitial nephritis. The two therapeutic groups most commonly implicated are antibacterials, and nonsteroidal anti-inflammatory agents. The medicines most commonly implicated are methicillin, penicillin, sulphonamides, co-trimoxazole, cephalosporins, rifampicin, fenoprofen, mefenamic acid, allopurinol, phenytoin and thiazides.[4] It is therefore difficult to assess the cause of interstitial nephritis in any given case. The identification of cause may be further confounded by corticosteroid therapy being initiated at the same time as the suspect medicine is withdrawn.

Interstitial nephritis with omeprazole responds to treatment withdrawal

In 13 published case reports, symptoms occurred between two weeks and six months after omeprazole was commenced.[2] In two possible cases reported to CARM, the duration of therapy was around 18 months. Doses have been within the recommended range of 20 mg or 40 mg daily. In four of the published

cases, the patients responded to withdrawal of omeprazole alone, but six other patients also received corticosteroid therapy. Some, including one of the cases reported to CARM, responded to corticosteroid therapy but did not fully recover until omeprazole was withdrawn. Initial recovery after omeprazole was withdrawn was usually rapid over a few days although full recovery of renal function took up to 2-3 months, and even longer in rare cases. There are no known reports of death as a result of this adverse reaction. In four of the published cases, renal function deteriorated again when omeprazole was reintroduced.

Investigate patients for renal function and by urine microscopy

Patients taking omeprazole, or any of the medicines listed above, who present with symptoms and signs of hypersensitivity, for example, rash, fever, eosinophilia, arthralgia, or who are non-specifically unwell should have urine microscopy and an assessment of renal function. If either or both are abnormal, omeprazole, or other possible causative agents, should be withdrawn pending nephrology assessment.

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POTENTIALLY FATAL COMPLICATIONS OF CLOZAPINE THERAPY: MYOCARDITIS, VENOUS THROMBOEMBOLISM AND CONSTIPATION

Medsafe Editorial Team

This article was e-mailed to electronic Prescriber Update subscribers in October 2000.

15 cases of myocarditis (five fatal) and eight of cardiomyopathy (one fatal) with clozapine have been reported to the Australian Adverse Drug Reactions Advisory Committee. All cases of myocarditis occurred within the first three weeks of therapy. Patients taking clozapine who present with flu-like symptoms, dyspnoea, tachycardia, chest pain and other signs and symptoms of heart failure should be investigated for myocarditis with immediate referral to a cardiac unit.

During an 11-year period six cases of pulmonary embolism (five fatal) and six of venous thrombosis were reported to the Swedish Adverse Drug Reactions Advisory Committee. During the same period only three cases of VTE were reported in association with other antipsychotic medication. Eight of the cases of VTE with clozapine occurred within the first three months of therapy.

Clozapine should be withdrawn promptly under the supervision of a psychiatrist if myocarditis or VTE develop, and alternative antipsychotic therapy should be commenced to avoid recurrence of schizophrenia.

At least five deaths from complications of bowel obstruction with clozapine have been recorded in the literature. One study found 60% of patients taking clozapine had varying degrees of constipation. Patients taking clozapine should be encouraged to exercise, take plenty of liquid and have a high fibre diet to reduce the risk of constipation. Clinicians should ask about bowel habits and give a laxative, if necessary.

Despite the range of life-threatening adverse reactions, clozapine is effective and well tolerated in many patients. One epidemiological study found that it reduced the risk of death, largely by reducing the suicide rate to a quarter of that found in past users of clozapine.

Myocarditis

The need to consider myocarditis as one cause of flu-like symptoms in those taking clozapine was discussed in the June 1995 issue of *Prescriber Update*.[1] A recent study[2] based on cases reported to the Australian Adverse Drug Reactions Advisory Committee (ADRAC) from January 1993 to March 1999 extends these concern. During the six years of the study, 8000 patients started clozapine therapy in Australia and 15 cases of myocarditis and eight of cardiomyopathy for which there was objective evidence of the diagnosis were reported.

Myocarditis risk highest in first weeks

All cases of myocarditis developed within the first 21 days (median 15 days) of initiating therapy. Five of the patients died, three with apparently no warning symptoms. In the other patients symptoms included malaise, fatigue, chest pain, palpitations, dyspnoea and fever. Six patients had peripheral blood eosinophilia; it is not clear whether all were checked. The authors commented that the time to onset of symptoms was consistent with an IgE-mediated hypersensitivity reaction, and the eosinophilia was suggestive of an acute drug reaction.

The worldwide incidence of fatal myocarditis in 1990 was estimated to be 3.3 per 10^7 people per month.[3] In this series, the rate was 5 per 8000 during the first month of clozapine. The high relative rate points to a causal relationship with clozapine.

Cardiomyopathy develops later in the course of therapy

Of the eight cases of cardiomyopathy, one patient was reported to have died, and one to have improved. The patient who died continued clozapine because of therapeutic benefit despite known cardiac dysfunction. Symptoms of cardiomyopathy included dyspnoea, tachycardia, palpitations and symptoms and signs of acute heart failure. These developed after 2-36 months (median 12 months). The authors suggested that dilated cardiomyopathy may be a more chronic form of myocarditis.

Novartis has analysed 125 reports of myocarditis with clozapine.[4] 35 of these cases were fatal. 53% occurred in the first month of therapy, and a small number (4.8%) occurred more than two years after commencement of clozapine. 70% of the patients in this series were men.

The Centre for Adverse Reactions Monitoring (CARM) has received no reports of myocarditis, but one report of fatal cardiomyopathy. For this case no data were supplied on duration of therapy or the course of the illness.

Investigate patients with flu-like symptoms, dyspnoea, tachycardia

If patients taking clozapine present with flu-like symptoms, fever, myalgia, dizziness or faintness, chest pain, dyspnoea, tachycardia or palpitations and other signs or symptoms of heart failure consideration should always be given to a diagnosis of myocarditis. Suspicion should be heightened if the symptoms develop during the first 6-8 weeks of therapy. It should be noted, however, that flu-like symptoms may also occur during the titration period as a result of clozapine's α-adrenergic properties. Patients in whom myocarditis is suspected should be referred immediately to a cardiac unit for evaluation.

A psychiatrist should supervise clozapine withdrawal

Consultation with a cardiologist and the prescribing psychiatrist is necessary to consider whether clozapine should be withdrawn pending such evaluation. If myocarditis is considered likely, withdrawal is recommended to reduce further cardiac damage. It is important to recognise that withdrawal may lead to relapse of psychosis and that clozapine may not be as effective following reinitiation as it was during initial treatment. Any withdrawal should be under the supervision of a psychiatrist with substitution of appropriate alternative therapy to avoid relapse.

Venous Thromboembolism (VTE)

Six cases of pulmonary embolism with clozapine in Swedish data

Recently a case series[5] of six cases of pulmonary embolism (PE), of which five were fatal, and six cases of venous thrombosis was published, based on reports collected by the Swedish Adverse Drug Reactions Advisory Committee (SADRAC) over an 11-year period. Each diagnosis was confirmed by necropsy, computed tomography or phlebography. In eight of the cases, the adverse reaction occurred within the first three months of clozapine therapy. Only one of the cases was taking an oral contraceptive. No information was available on the presence of factor V Leiden mutation, or other types of thrombophilia. The authors calculated an incidence of 1 case per 2000 to 6000 treated patients based on Swedish pharmacy sales for clozapine.

The evidence favours a causal relationship between clozapine and VTE

The authors of the article presenting the Swedish data[5] observed that only three cases of thromboembolism in people aged 18-60 years who were taking other antipsychotic agents were reported to SADRAC over the period of their study. They concluded that venous thromboembolism is not associated with psychoses nor is it a class effect of antipsychotics. A large study[6] of mortality

with clozapine which used American data found a death rate from pulmonary embolism of 30 per 100,000 person-years in users of clozapine aged 10-54 years, compared with no deaths in recent users. The balance of evidence points to a causal association between clozapine and venous thromboembolism, but further confirmation is required.

Possible symptoms of DVT or PE should be investigated

Patients taking clozapine who develop possible symptoms of deep vein thrombosis or pulmonary embolism should be investigated to exclude or confirm these conditions. The risk should be considered to be heightened if patients present within the first three months of therapy.

Clozapine should be withdrawn immediately following a positive diagnosis or if there is a high level of suspicion. The patient's psychiatrist should supervise the discontinuation and initiation of alternative therapy.

Constipation

Five deaths from complications of gastrointestinal obstruction

Constipation is known to occur with any anticholinergic medication, particularly at high doses, but it appears that constipation with clozapine is more common than with other similar agents. Furthermore, in the literature[7,8,9] there are at least five reports of death from complications of gastrointestinal obstruction associated with clozapine. Two of the patients[7,8] were found to have died following aspiration of faeculent vomitus secondary to bowel obstruction. Neither patient was taking any other anticholinergic medication.

In one study[7] of 53 patients taking clozapine, 60% were found to have constipation. Only six of the total 53 were taking other anticholinergic medication. Most of the cases were mild, but 12% required repeated use of enemas.

The CARM database holds two reports of constipation and two of paralytic ileus with clozapine. None of these cases was fatal. In one case a man of about 45 years who had been taking clozapine for about 20 months was admitted with a pain in the left shoulder blade. He was found to have a grossly distended upper intestine. The problem was managed with daily lactulose and clozapine was continued. Delayed diagnosis is a characteristic of the cases of severe constipation with clozapine.

Exercise, plenty of liquid and high fibre diet reduce risk of constipation

Patients taking clozapine should be encouraged to exercise, take plenty of fluids and have a high fibre diet in order to reduce the risk of serious constipation.[7] Clinicians should regularly ask about bowel habits and give a laxative, if required. Slower titration of the clozapine dose on initiation of therapy may also be helpful.[7] Clozapine need not usually be withdrawn if constipation develops, but the problem requires vigilance and careful management, especially if it is serious.

Epidemiological evidence: clozapine reduces schizophrenic suicide rate

Despite a range of life-threatening adverse reactions, including agranulocytosis and diabetic ketoacidosis,[10] together with the events described here, clozapine is an important agent in the treatment of refractory schizophrenia and other psychoses, and it is well-tolerated by most patients. The epidemiological study of deaths in users and former users of clozapine by Walker et al[6] found that the rate of death was lower among current users (322 per 100,000 person-years) than among past users (696 per 100,000 person-years). The reduction in death rate during current use was largely accounted for by a reduction in suicide rate compared with past use (relative risk 0.25; 95% CI 0.10-0.30). This reduction in suicide rate is testimony to the therapeutic efficacy of clozapine.

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TICLOPIDINE, CLOPIDOGREL AND THROMBOTIC THROMBOCYTOPENIC PURPURA

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This article was e-mailed to electronic Prescriber Update subscribers in November 2000.

Ticlopidine (Ticlid™), a thienopyridine antiplatelet agent, has been shown to be associated with potentially fatal thrombotic thrombocytopenic purpura (TTP). A similar agent which is now largely replacing ticlopidine for safety reasons, clopidogrel (Plavix™), has also been associated with this adverse event, though possibly at a lower rate than ticlopidine. Because of the risk of agranulocytosis, thrombocytopenia and TTP, patients taking ticlopidine should have baseline full blood counts followed by monitoring at two-weekly intervals. Tests should continue for at least two weeks after completion of therapy. Early signs of TTP may be a skin reaction and neurological changes. Patients taking either agent should be advised of the risk of haematological reactions and advised to report any early signs. Early referral for intervention, including plasmapheresis, reduces the risk of mortality substantially.

TTP which may be fatal may occur with ticlopidine

An article published in *Prescriber Update* in February 1997[1] advised of the possibility of life threatening haematological reactions with ticlopidine (Ticlid™) that were usually reversible, although reports of some fatalities were noted. Recent evidence[2,3] indicates that thrombotic thrombocytopenic purpura (TTP) and death from this adverse reaction may occur more frequently than previously expected.

Unlike some types of thrombocytopenia, TTP is a life threatening, multi-system disease characterised by thrombocytopenia, microangiopathic haemolytic anaemia, neurological changes, renal failure and fever.[4] Idiopathic cases occur at a rate of 3.7 per year per million persons with a mortality rate for promptly treated cases ranging from 10 to 20%.[5] Its cause appears to be related to auto-antibodies against a metalloprotease that degrades von Willebrand factor.[5]

Fatality rate is reduced by plasmapheresis

Whilst no cases of TTP were reported in four published phase III clinical trials, a review by Bennett et al[3] of TTP with ticlopidine revealed 98 evaluable cases captured through post-marketing surveillance. Forty out of the total 259

reported deaths with ticlopidine were caused by TTP and 50 by thrombocytopenia. A total of 85.6% of the deaths were associated with haematological reactions. The estimated incidence of TTP with ticlopidine is 1 case per 1600 to 5000 patients treated.[5]

In the review by Bennett et al,[3] TTP had been associated with ticlopidine used following coronary artery stenting (56) and for stroke prevention (42), and 95% of cases occurred after more than two weeks of therapy. The overall TTP mortality was substantial in both groups, being greater in the stroke prevention than in the coronary artery setting (37.5% *vs* 28.6%). Death occurred in 57.9% of those patients who did not undergo plasmapheresis compared to 18.3% of those who underwent plasmapheresis.

In the CARM database, there are no reports of TTP with ticlopidine, although there are two reports of agranulocytosis and two of granulocytopenia. However, the Australian Adverse Drug Reactions Advisory Committee reported its first case of TTP in December 1999.[6]

TTP has also been associated with clopidogrel

Clopidogrel (Plavix™), another thienopyridine antiplatelet agent, was given marketing consent in New Zealand in December 1999. It is not yet on the Pharmaceutical Schedule, but it has largely replaced ticlopidine as an alternative antiplatelet agent to aspirin in patients with vascular disease. The main reason for the change is that the incidence of some major (neutropenia) and minor (nausea, skin rash) adverse reactions is lower with clopidogrel than with ticlopidine.[7]

Although TTP was not reported in any randomised clinical trials evaluating clopidogrel (around 20,000 patients), Bennett et al recently identified 11 cases during a two-year period of active surveillance,[5] and have subsequently reported identification of nine further cases.[8] Bennett et al estimated an incidence of 1 case per 15,000 clopidogrel-treated patients.[8]

In all except one case of the initial series of TTP with clopidogrel, the adverse event occurred after a treatment duration of two weeks or less.[5] All patients underwent plasmapheresis, and all except one responded. In this group more plasma exchanges (median 8) were required than in the case series of TTP with ticlopidine, and two patients relapsed more than once without re-exposure to clopidogrel and required further episodes of plasma exchange.

Advise patients of the risk of TTP and early signs

Based on this evidence practitioners need to be aware of the potential for serious life threatening haematological reactions, particularly TTP, associated with ticlopidine and possibly also clopidogrel. In the case of ticlopidine consideration should be given to limiting treatment to two weeks, whilst with clopidogrel vigilance for TTP within the first two weeks needs to be exercised.

Because of the risk of agranulocytosis, thrombocytopenia and TTP, patients taking ticlopidine should have a baseline full blood count with white cell differential and platelet counts performed prior to the start of treatment and then every two weeks during the first four months.[9] Because ticlopidine has a long plasma half-life, haematological monitoring should continue for at least two weeks after the cessation of therapy. There are no formal monitoring requirements associated with clopidogrel, but based on its recently reported potential for TTP, similar vigilance may be beneficial. However, those taking either agent should be warned of the risk of TTP and advised of the symptoms. Early signs of TTP may be a skin reaction, which may precede the onset of TTP or it may be an indication of purpura, and neurological changes. Complete blood count and creatinine level determination assist in the diagnosis.

The likelihood of the death of patients on these medications can be reduced by up to 60% if cases with a high index of suspicion are referred to a haematologist for early intervention including plasmapheresis.

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PEANUT ALLERGY

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This article was e-mailed to electronic Prescriber Update subscribers in November 2000.

Key messages:

- Pregnant women in families with atopic disease (having conditions such as hay fever, asthma or eczema), are advised to avoid peanuts and peanut products during pregnancy and breastfeeding to assist in prevention of the development of peanut allergy.
- For infants with a family history of atopic disease, it is advisable to solely breastfeed for at least six months and to delay the introduction of peanuts and peanut products until three years of age.
- The ingredient lists on food labels are one source of information about the peanut content of foods.
- The New Zealand Therapeutic Database provides lists of commercial foods available in New Zealand that do not include peanuts. This information is available on their website: www.nztd.co.nz

New Zealand situation

New Zealand has no prevalence data for peanut allergy but nut allergy is probably in the order of 1-2%.[1] The general belief amongst immunologists is that peanut allergy is increasing.[1,2,3] Peanut allergy is the most common cause of food-related anaphylaxis. In New Zealand between 1995 and 1997 out of a total 221 cases of reported food-related anaphylaxis, there were 32 hospital admissions reported as being due to peanut/nut allergy.[4]

Information for New Zealand health professionals

The Ministry of Health's Food and Nutrition Advisory Committee recently agreed that it would be useful for medical practitioners in New Zealand to receive information on peanut allergy, including the implications of a recent UK report. The purpose of this article is to provide practitioners with the most recent developments in the field. Previous information in *Prescriber Update* by Dr Penny Fitzharris, a Wellington based immunologist, discussed the possibility of prevention of peanut allergy by the avoidance of peanut products in pregnancy, during breastfeeding and in early life.[1] This advice has been confirmed in the UK report.

UK report

During 1998 in the United Kingdom, the Department of Health's Committee on the Toxicology of Chemicals in Food, Consumer Products and the Environment, produced a report to:

- **review** the available scientific literature about the association between early exposure to peanuts and peanut products and the incidence of peanut allergy in later life, and;
- **advise** on the consumption of peanuts and peanut products by pregnant and breast-feeding women, infants and young children.[5]

The Committee's work was prompted by recent publications in scientific literature suggesting that the incidence of peanut allergy was increasing. Peanut allergy can be very severe, with fatal anaphylaxis, and is a potentially serious health hazard. Due to this severity, peanut allergy prevention is an important measure. Peanut allergy is normally a life-long allergy.

Recommendations from UK report

To attempt prevention of peanut allergy, the UK report recommends the avoidance of peanuts and peanut products for the following people:

- Pregnant women who are themselves atopic (having conditions such as hay fever, asthma or eczema), or where the biological father or sibling of the unborn child is atopic;
- Breastfeeding women who are themselves atopic, or where the biological father or sibling of the breastfeeding child is atopic; and
- Children with a parent or sibling who is atopic up until until three years. It is also recommended that these children are breastfed exclusively for four to six months.

Recommendations from the New Zealand Food and Nutrition Guidelines[6]

The UK Report's recommendation about breastfeeding is in accord with the *New Zealand Food and Nutrition Guidelines for Healthy Infants and Toddlers,* which recommends solely breastfeeding children with a family history of allergy to at least six months of age. For infants, with a family history of food allergy, the introduction of solid foods should not include whole cows' milk, soy and eggs until the infant is at least one year old and peanut products until three years old (with whole peanut products being avoided until five years old).[6] For mothers who are unable to breastfeed a dairy-based formula is the

best choice. However, under the advice of a health professional, a soy-based or other infant formula may be used.[7]

Advice to the general public

For the non-atopic families, avoidance of peanuts or peanut products is not considered necessary during pregnancy or breastfeeding. For infants, who are not in the above risk categories, it is acceptable for **smooth** peanut products, such as smooth peanut butter, to be used as a weaning food at about eight to nine months, as recommended in *New Zealand Food and Nutrition Guidelines for Healthy Infants and Toddlers*. As there is the possible risk of choking it is also advised that whole peanuts are not given to children until five years of age.[6]

Advice to those with peanut allergy

For individuals with peanut allergy it is essential that all foods containing peanut products, even in minute amounts, be avoided completely. Highly peanut-sensitive individuals who have a history of systemic reaction, need to carry kits with adrenaline and antihistamines on hand for self-administration promptly at the first sign of a systemic reaction. People allergic to peanuts should avoid all tree nuts such as walnuts, almonds, hazelnuts and pecans, even if they are not sensitised to these, to minimise the risk from contamination or confusion with peanuts.[1] The reintroduction of peanuts should only be carried out when no reaction to peanut and nut products has occurred for three to five years, and under strictly supervised conditions at a specialised centre.[2]

Labelling requirements in New Zealand and Australia

Information on the likely peanut content of foods, or the content of other food allergens, is available to the consumer from two sources: food labels and the New Zealand Therapeutic Database. Currently general provisions for food labelling are required to comply with the New Zealand Food Regulations 1984 or the Australian Food Standards Code. In the New Zealand Food Regulations, the only instance in which peanuts may not be declared is if they are a minor component of a mixed ingredient added to a food. However, by about May 2002 Australia and New Zealand will have a joint standard for labelling of foods and all manufacturers should be working to a single standard. The Australia New Zealand Food Authority is awaiting final agreement on the draft Australia New Zealand Food Code.[8] There is a mandatory labelling requirement for peanuts and peanut products in the draft Code.

Declaration of other food allergens required by new draft Code

The draft Code will also require a number of other significant food allergens to be declared on all food labels. Those food allergens include cereals containing gluten; crustacea and their products; egg and egg products; fish and fish products; milk and milk products; nuts, sesame seeds and their products; soybeans and their products; and sulphites in concentrations of 10mg/kg or more.

New Zealand Therapeutic Database

In addition to legal labelling requirements, those consumers with food allergies may be assisted by the New Zealand Therapeutic Database, which is funded by the New Zealand Ministry of Health. This database contains information obtained from food manufacturers and distributors to enable the compilation of lists of commercial foods that are free of specific allergens. The data are available to inform health professionals and people with allergies to assist them in allergy management. Lists of foods free of the common food allergens are updated and published annually and are available on the website www.nztd.co.nz or by writing to: Mrs Alannah Steeper, NZ Therapeutic Database, Auckland Hospital, Private Bag 92024, Auckland 1.

Other Helpful Organisations

Allergy Awareness Association (PO Box 56-117, Dominion Rd, Auckland) can provide practical support to individuals and families with peanut or other allergies.

The author would like to thank a number of reviewers who provided comments on this article including: Dr John Birkbeck, Dr Jan Sinclair, Dr Rodney Ford, Dr Pat Tuohy, Dr Alison Roberts, Elizabeth Aitken, Carolyn Watts, Jane McLennan, Clare Chandler and Lyn Gillanders, and in particular Dr Penny Fitzharris.

Editor's note: The draft Australia New Zealand Food Code was gazetted on 20 December 2000 and is now called the joint Australia New Zealand Food Standards Code.

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TRAMADOL

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This article was e-mailed to electronic Prescriber Update subscribers in October 2000.

Tramadol (Tramal™) is a synthetic, centrally acting analgesic used parenterally and orally for the treatment of moderate to severe pain. It was approved in New Zealand in 1997, but it is not currently funded. Its potency is comparable to that of pethidine, but in severe pain morphine is possibly superior.

Respiratory depression and constipation are less common with tramadol and less pronounced than with other opioids. However, respiratory depression can occur, in particular, after overdose and with impaired renal function. Unlike other opioids, tramadol is not usually associated with the development of tolerance, physical dependence or psychological addiction. In clinical trials the most common adverse reactions, in decreasing frequency, were nausea, dizziness, drowsiness, tiredness, fatigue, sweating, vomiting, dry mouth and postural hypotension. Tramadol may possibly increase the risk of seizures in those with a history of epilepsy or those on medication, which lowers the seizure threshold, but it appears that tramadol does not induce idiopathic seizures except at very high doses. Tramadol is contraindicated in users of MAO inhibitors as a safety precaution and, because of the risk of serotonin syndrome, should be used with caution in combination with SSRIs.

In overdose, tramadol induces significant neurological toxicity (seizures, coma, respiratory depression), but cardiovascular toxicity is mild.

Tramadol (Tramal™) is a synthetic, centrally-acting analgesic used parenterally and orally for the treatment of moderate to severe pain. While tramadol was not granted marketing consent in New Zealand until 1997, and it is not currently listed in the Pharmaceutical Schedule, experience in other countries dates back more than 20 years. In 1998, tramadol became the most used centrally-acting analgesic worldwide; outselling morphine in dollars turned over.[1] The success of tramadol is mainly a result of its favourable side effect profile, which differs significantly from that of other opioids.

Proven efficacy in a broad range of painful conditions

Tramadol has a dose-dependent efficacy that lies between that of codeine and morphine, with a parenteral potency comparable to that of pethidine, i.e., about 10-20% of the gold standard morphine.[2] Oral bioavailability is high (85-100%) and permits easy conversion from the oral to the parenteral route and visa versa. Surprisingly, the efficacy of tramadol is not associated with the usual serious opioid side effects which can often be dose-limiting. Furthermore, unlike nonsteroidal anti-inflammatory drugs, tramadol has no serious adverse gastrointestinal effects, such as gastrointestinal bleeding. Numerous clinical trials have proven its efficacy and safety over a broad range of painful conditions, both acute and chronic; however, in severe pain morphine may be superior to tramadol.[3] It is this combination of safety with good efficacy that has made tramadol a unique addition to the analgesic armamentarium.

Dual mechanism may explain improved side effect profile

The novel way in which tramadol provides analgesia with fewer side effects may be explained by its dual mechanism of action, opioid and monoaminergic. Its major metabolite O-desmethyl tramadol (M1) has a weak affinity at μ-opioid receptors as an agonist. The monoaminergic activity comes through the two stereoisomers of tramadol itself, which act synergistically on serotonergic and noradrenergic mechanisms of pain transmission. More specifically, tramadol enhances spinal pain inhibitory pathways by inhibiting neuronal re-uptake of serotonin (5-HT) and noradrenaline (NA), and stimulating 5-HT release.[4,5] This added monoaminergic component possibly allows tramadol's efficacy to stretch over a wider range of painful pathologies than other opioids.

Constipation and respiratory depression: less likely, less pronounced

Respiratory depression with tramadol is less pronounced, and occurs less often, in comparison to equianalgesic doses of morphine.[3,6] In large clinical and

post-marketing studies including over 21,000 patients, no clinically relevant respiratory depression was reported.[7] However, respiratory depression can occur, in particular with overdose[8] (as described in children[9]) or with impaired renal function,[10] possibly due to retention of the active metabolite M1.

Another opioid side effect, which is reduced with tramadol use, is constipation.[11] Clinically this has proven to be a significant advantage with long-term therapy, but could also be beneficial in the prevention of ileus postoperatively.

Low dependence potential

The effects of long-term opioid intake on the development of tolerance, physical dependence and psychological addiction are reduced with tramadol use. In an experimental setting, it was demonstrated that even experienced opioid users could not recognise tramadol in lower doses as an opioid,[12] whereas in higher doses they could recognise it, but did not "like" it, presumably due to its tricyclic-like properties. Hence, the incidence of abuse of tramadol is low in all post-marketing surveys; the FDA reports a rate of abuse in the range of 1 in 100,000 patient exposures.[13] Furthermore, tramadol is not registered as a controlled drug in any country. However, this does not mean that its use in "at-risk" patients should be encouraged. Rare cases of withdrawal reactions after abrupt discontinuation of tramadol have also been reported.[7]

Other adverse effects: nausea, vomiting, sweating

The most common adverse events reported in clinical trials and post-marketing studies were, in decreasing order of frequency (range 7 to 1%): nausea, dizziness, drowsiness, tiredness, fatigue, sweating, vomiting, dry mouth and postural hypotension.[7] Nausea, a well-documented opioid side effect, seems to occur with an incidence comparable to that in other opioids, while vomiting is less common. The incidence of nausea varied with route and setting of administration from 3% in controlled trials of oral medication, to 21% with IV use via patient controlled analgesia (PCA) pumps in the postoperative period. Avoidance of early mobilisation after IV administration, initiation of oral treatment at low doses with gradual increase, and use of antiemetics (phenothiazines and/or 5-HT3-antagonists) can reduce the incidence and severity of this side effect.

Sweating is a side effect specific to tramadol, due to its monoaminergic effects, and it can be quite distressing to a small number of patients.[14] In rare situations, sweating may be severe enough to necessitate discontinuation.

Caution in epileptics and those on tricyclics, SSRIs, high dose opioids

The issue of possible tramadol-induced seizures has been discussed increasingly in international literature. Overall, there is no good evidence that tramadol use by itself can induce idiopathic seizures, except possibly in excessive doses.[15] However, tramadol should be used with caution in patients with a history of epilepsy and those on concomitant seizure threshold-lowering medication (e.g. tricyclics, selective serotonin re-uptake inhibitors, high dose opioids).

Tramadol contraindicated in patients on MAOIs

There are now a number of case reports, which suggest induction of a serotonin syndrome by combination of tramadol with SSRIs.[16,17] Such combinations may be used with caution. Although no reports of drug interactions with MAO inhibitors have been published, the concomitant use of MAOIs with tramadol is contraindicated as a safety precaution. Other relevant interactions between tramadol and concomitant medication have not been described. Initial reports of an interaction between tramadol and coumarins with prolongation of INR could not be confirmed.[18]

Overdosage can induce seizures and respiratory depression

In overdose, tramadol produces significant neurologic toxicity such as seizures, coma and respiratory depression, while cardiovascular toxicity seems to be limited to mild tachycardia and hypertension.[8] When seizures do occur with tramadol use, they are commonly of short duration and are easily treatable. In one reported case of a seizure, the convulsions were induced by naloxone administration.[8] Hence, although respiratory depression in overdose can be treated with the opioid antagonist, naloxone, reversal of all opioid poisoning should be conducted with low doses, repeated as clinically indicated, to avoid rebound effects including pain, hypertension, tachycardia and seizures.

Competing interests: Professor Schug has been and is involved in clinical research on tramadol, partially funded or supported by Grünenthal GmbH, Stolberg, Germany and CSL (New Zealand) Ltd., Auckland.

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DOXAZOSIN AND THE ALLHAT STUDY

Medsafe editorial team

This article was e-mailed to electronic Prescriber Update subscribers in December 2000.

Medsafe has received notification from the American National Institutes of Health that one arm of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) has been stopped early. The treatment arm containing the alpha-adrenoceptor blocker doxazosin has been found to be less effective than the diuretic chlorthalidone in reducing hypertensive heart failure. The Medicines Adverse Reactions Committee (MARC) advises that until there is better definition of this issue, it may be appropriate to avoid alpha-adrenoceptors in patients with hypertension if an alternative is available. The situation is unclear in patients with benign prostatic hypertrophy where the use of doxazosin can result in significant improvement in symptoms and quality of life.

Doxazosin arm of study stopped early

In February 2000 the doxazosin (Cardoxan™, Carduran™ and Dosan™) arm of the ALLHAT trial was stopped early. ALLHAT is a randomised, double blind, active controlled trial in the USA and Canada, which began in February 1994. This trial is comparing treatment of hypertension with a diuretic (chlorthalidone) against newer types of antihypertensives - an alpha-adrenoceptor blocker (doxazosin), an ACE inhibitor, and a calcium antagonist - in a high-risk patient group (all over 55 years with one or more cardiovascular disease (CVD) risk factors)[1].

By January 2000, a total of 9067 subjects had been randomised to the doxazosin treatment arm and another 15268 to receive chlorthalidone. The mean age was 67 years and both groups had similar demographics and CVD baseline characteristics. Median follow up was 3.3 years. At baseline there was no difference in mean blood pressure (BP) between the two groups. Doses allowed were doxazosin 2, 4, or 8mg/day or chlorthalidone 12.5, 12.5, or 25 mg/day. Certain other antihypertensives were added if BP wasn't controlled on maximal doses of the study medicines.

No difference in rates of fatal CHD and nonfatal MI

Doxazosin gave similar results to chlorthalidone for the primary endpoint of fatal coronary heart disease (CHD) and nonfatal myocardial infarction (MI),

and hence did not show superior efficacy over the diuretic. There was no difference in all-cause mortality.

Higher risk of CHF with doxazosin

However, subjects taking doxazosin had a 25% higher risk of combined CVD events (ie. CHD death, nonfatal MI, stroke, revascularisation procedures, angina, congestive heart failure (CHF), and peripheral arterial disease). This excess in CVD events for doxazosin subjects could predominantly be accounted for by a doubled risk of CHF. The other significant finding was that doxazosin was less effective in controlling systolic BP by an average of 3mmHg. The study authors extrapolated that while this value may explain the increase in risk of angina and stroke of 16% and 19%, respectively, it could not fully account for the doubling of risk for CHF.

It is important to note that the findings may apply only to high-risk patients for CVD when given doxazosin as first-line treatment for hypertension. At year three, over half of each group who were still taking their blinded medication, were taking the study medicines at maximal doses. Forty percent of the chlorthalidone group and 47% of the doxazosin group were also on second or third line agents to gain BP control. Further analysis of the data will undoubtedly follow.

This trial did not compare efficacy of doxazosin or chlorthalidone with placebo. Hence, as stated by the study authors, "it is difficult to judge whether in ALLHAT the CHF rate with doxazosin is the same as, less than, or more than would be expected without antihypertensive drug treatment."[1]

MARC recommends caution with doxazosin in hypertension

The company has provided data that has been reviewed by the Medicines Adverse Reactions Committee (MARC). The MARC advises that until there is better definition of this issue, it may be appropriate to avoid alpha-adrenoceptors in patients with hypertension if an alternative is available. The situation is unclear in patients with benign prostatic hypertrophy where the use of doxazosin can result in significant improvement in symptoms and quality of life.

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IMPORTANT NOTICE ABOUT FINGER PRICKING DEVICES

Dr Bob Boyd, Chief Advisor, Safety and Regulation, Ministry of Health and Margaret Jamieson QSM, President, Diabetes New Zealand

This article was sent as a letter to all Health Professionals/Providers, along with the following *Questions and Answers*, in November 2000.

Diabetes New Zealand and the Ministry of Health would like to remind all health professionals of the currently accepted good practice when using finger-pricking devices.

A recent survey of hospitals found that some health professionals are using a finger-pricking device which is intended for use by one person to test multiple patients, discarding only the lancet between tests. This means that some patients could have been exposed to the risk of infection from diseases such as hepatitis B.

The Ministry considers that there is an extremely small risk of transmitting Hepatitis B from these devices and that the risk of infection from other disease is negligible. The Ministry is not aware of anyone in New Zealand having contracted hepatitis B from the incorrect use of finger-pricking devices.

The Ministry is, however, aware that cross-infection from these devices has occurred overseas. Over the past ten years there have been four episodes reported worldwide of disease being transmitted through the use of individual-use devices on more than one person. Three of those episodes were in the United States of America and one in Europe.

It is understood that in each of these cases only the lancet of the finger-pricking device had been replaced, potentially allowing blood to remain in the end cap which may cause cross infection.

We would therefore like to advise all health professionals of the following.

1. It is preferable that patients/clients bring in and use their own finger pricking devices. Another alternative is to use a disposable blood sampling device (which can be used only once) such as Easy-Let Safety™, Unistik II™ and Single-let™. This list may not be exhaustive because medical devices are not currently required to be registered with the Ministry before they can be promoted and sold.

2. If a spring-loaded device is to be used, it is important that care is taken in choosing a device that is appropriate for the purpose:
    - If you are using a finger-pricking device on more than one patient, it is important that you use a device that has both a disposable lancet and plastic tip, so that any part of the device which comes into contact with the patient's skin is discarded between tests. Examples of these devices are Glucolet 2™ and Softclix Pro™.
    - It is no longer considered appropriate to depend on cleaning/disinfecting of non-disposable plastic parts to prevent cross-infection, when suitable equipment is readily available for the purpose.
    - If only one patient is using a finger-pricking device then it is appropriate they use a device that requires only the lancet to be disposed of. Examples of these devices are the B-D Lancet Device™, Glucocard Auto Lancet™, Microlet™, Medisense Precision™ and Softclix II™.
3. Due to the risk of spreading infection, the single-patient device should not be used on more than one person, even if the lancet is changed between each patient. Traces of blood can remain in the end cap and may cause cross infection.
4. This procedure may potentially transmit disease, particularly the virus infections hepatitis B, hepatitis C and HIV from contaminated equipment, gloves, hands or surfaces. Appropriate infection control procedures should be adopted. Hepatitis B is by far the most likely of these to be transmitted by cross-infection and the risk is extremely low.

What to do if concerned patients approach you

If patients approach you expressing concerns that they may have been exposed to infection through the inappropriate use of a finger pricking device, the Ministry's advice is that you:

1. advise patients that only some devices are causing concern and it is only when these are used inappropriately that there is any risk
2. reassure patients that the risk of cross-infection is extremely low
3. advise that the Ministry of Health is not recommending routine recall of patients for virus testing
4. arrange for them to have a blood test, if they remain concerned
5. encourage individual patients to continue using their own finger pricking devices as instructed and not to share them with other people.

The following *Questions and Answers* can be used to supplement this information. The Ministry would appreciate your assistance in reassuring patients as outlined above.

The Ministry of Health and Diabetes New Zealand are keen to ensure that all health professionals follow current accepted good practice so that all patients receive quality health services. We would like to thank you for your help on this matter.

FINGER PRICKING DEVICES – QUESTIONS AND ANSWERS

What is Currently Accepted Good Practice?

Current Accepted Good Practice involves the efficient and effective use of available resources to achieve quality outcomes for the patient (ref: Infection Control Standard NZS 8142:2000).

In terms of the practice regarding finger-pricking devices, health professionals are advised that it is preferable to use a single use totally disposable device when testing more than one person and to dispose of it safely after use. Alternatively they should use a device in which all parts which come in contact with the client's skin and which may become contaminated with blood are disposable and are replaced between cases to reduce the risk of transmission of infectious disease. Both lancet and plastic tip should be disposed of safely after use.

Individuals monitoring their own blood sugar levels should use their own device and not share them with others.

Has the accepted practice changed?

Yes. During the last publicity about this issue in 1998 the spokesman for the General Practitioner's Association was reported as saying that he would continue using the device designed for individual patient use to carry out monitoring in his surgery and depend on washing the plastic parts which may have got contaminated between tests. Most practitioners today, given the ready availability of the safer disposable equipment and the wider awareness of possible risk would no longer find that acceptable.

What are the finger-pricking devices used for?

These devices are used to collect a drop of blood for sampling. Most commonly they are used by people with diabetes to monitor their own blood glucose. However, they are also used in hospital clinics, when only a small amount of blood is needed to carry out the analysis. They are also used by a variety of people from individuals to health professionals in hospitals, GP surgeries, marae health services, clinics, laboratories, and rest homes.

Most finger-pricking devices resemble a ball point pen and contain a sharp, spring loaded lancet which momentarily pierces the skin.

There are two types of finger-pricking devices produced by a variety of manufacturers. There are finger-pricking devices for individual use by people such as people with diabetes who use it to collect a drop of blood to monitor their glucose level. These devices for individual use have a disposable lancet. And there are finger-pricking devices intended for use on more than one person. These have both a disposable lancet and disposable plastic tip surrounding the lancet, so that all parts, which come into contact with the patient's skin, can be discarded to minimise the risk of transmission of disease. Both lancet and plastic tip should be safely disposed of after use.

Why are Diabetes New Zealand and the Ministry of Health issuing another reminder to health professionals about this device?

In November 2000, the Ministry of Health was advised that Hutt Valley Health had used a finger-pricking device designed to be used by an individual patient on eight children, contrary to the instructions which accompanied the device. The lancet had been replaced after each use, but the plastic tip which comes into contact with the skin was not. The Ministry sent a questionnaire to hospitals to find out whether similar practices were occurring in other hospitals. The survey indicated that the use of that brand of individual use finger-pricking device on more than one patient was widespread, despite publicity two years ago from Diabetes New Zealand about accepted good practice.

How long has this been happening in New Zealand and how many people are affected?

It is difficult to determine how long the practice of using individual finger-pricking devices on more than one person has been occurring in New Zealand or how many people may be affected. However, we do know that finger-pricking devices have been available in New Zealand for at least 10 years. Devices intended for use on more than one person were introduced sometime

later, as people became more aware of the risk of transmission of disease through using individual finger-pricking devices on more than one person.

What is the risk of potential transmission of viral disease from a finger-pricking device?

Finger-pricking devices are safe when individuals are using their own device. A risk of cross-infection can only occur when the blood of an infected patient remains on the device and contaminates the sharp lancet as it pierces the skin of the next patient. This risk can be eliminated by disposing of all parts in contact with the patient's skin between tests or by using totally disposable equipment. It is no longer necessary to depend on cleaning or disinfection of the device, because the safer disposable equipment is readily available.

Advice to date suggests the risk of transmitting any infectious disease is extremely low and any risk, albeit a very small one, would relate only to Hepatitis B.

What is Hepatitis B (HBV)?

Hepatitis B is a blood borne viral infection that causes inflammation of the liver. People who live on the western side of the Pacific Ocean have relatively high rates of infection and it is particularly common in Maori, Pacific Island and Asian people, especially young men aged between 15-40 years. This infection can be passed from person to person through blood contamination. An estimated 1-2% of the New Zealand population are HBV carriers.

What are the symptoms of HBV?

- your eyes or skin may turn yellow
- you may lose your appetite
- you may have nausea, vomiting, fever, stomach or joint pain
- you may feel extremely tired and not be able to work for weeks or months.

How can you test for HBV?

You can have a blood sample tested for the presence of HBV antibodies (which represent previous infection) and for the presence of HBV (indicating current infection or carrier state).

How is HBV treated?

Hepatitis B can be prevented through immunisation or prophylactic immunoglobulin injections.

New Zealand has had a universal vaccination programme for hepatitis B since 1988. Most children over the age of 12 will be protected through immunisation. Some people who are carriers of the infection can benefit from treatment with alpha interferon.

Has anyone in New Zealand contracted Hepatitis B from use of individual finger-pricking devices on more than one person?

The Ministry is not aware of anyone in New Zealand having contracted hepatitis B from use of an individual finger pricking device on more than one person.

Have there been any problems overseas?

Over the past 10 years worldwide, there have been four episodes reported where Hepatitis B was thought to have been transmitted through use of individual finger pricking devices on more than one person. In each case only the lancet had been replaced.

If I have had a finger-pricking device used on me, which was not for my own individual use, what should I do?

The Ministry is advised that the risk of infection through use of individual finger-pricking devices on more than one person is extremely low. The Ministry is not recommending that people who have had blood tests carried out in this way should be recalled for viral blood testing. However, if people are concerned they should contact their doctor and discuss whether a blood test is appropriate for them.

Where Can the Finger-Pricking Devices be Purchased?

Finger-pricking devices can be purchased from medical wholesalers, pharmacies and Diabetes New Zealand's National Supply Scheme Office, PO Box 54, OAMARU. Ph (03) 434 8110; e-mail: info@diabetes.org.nz

SELENIUM

Medsafe Editorial Team

This article was e-mailed to electronic Prescriber Update subscribers in July 2000.

Selenium is an essential trace element. Although concentrations in New Zealand soils are low, there is no indication that this has resulted in any detrimental effects on the health of New Zealanders. With current levels of animal and poultry supplementation of selenium and consumption of imported plant foods, especially wheat and legumes, it appears that intake of selenium by most New Zealanders is at or around recommended levels, as indicated by the 1997 National Nutrition Survey and the 1997/98 New Zealand Total Diet Survey. The current recommended daily intake in the US for adults is 55µg.

Some New Zealanders take selenium supplements with the intention of reducing the oxidative damage of free radicals. The daily dose recommended on the label of these supplements is usually 50-200µg. The Dietary Supplements Regulations 1985 require supplements to have a maximum adult dose of 150µg/day. The maximum safe daily intake is 400µg.

Symptoms of selenium toxicity include a garlicky odour in the breath, fatigue, gastrointestinal symptoms, transverse lines on the nails, alopecia, and peripheral neuropathy. Treatment is by supportive care. There is no known effective antidote. Symptomatic recovery may be quite rapid, occurring within two weeks in one case.

Selenium is an essential trace element

Selenium is an essential trace element, used in particular in the glutathione peroxidase enzyme system which protects intracellular structures against oxidative damage. In foods it is present largely as the amino acids selenomethionine and selenocysteine, in which it replaces the usual sulphur atom.

Most New Zealand diets have low but sufficient levels of selenium

A deficiency of selenium in an area of China has resulted in an endemic form of cardiomyopathy, called Keshan disease. Selenium has low concentrations

in most New Zealand soils, but there has been little indication that the low intake has resulted in any detrimental effects on the health of New Zealanders. The disease patterns for coronary artery disease, hypertension and cancer are similar to those in Western countries with far higher selenium intakes.[1]

An evaluation of selenium requirements completed in 2000 by the US Institute of Medicine revised the American recommended adult intake to 55µg/day, the level at which the enzymes with antioxidant functions are at maximum activity.[2] A recent study[3] conducted in New Zealand estimated that a suitable minimum intake for New Zealanders, achievable without use of supplements, is 39µg/day. At this level plasma glutathione peroxidase is at two-thirds of maximal activity which was thought to be sufficient by the WHO/IAEA/FAO Expert Committee.[4]

The 1997 New Zealand National Nutrition Survey,[5] based on recall of food consumed during the previous day, calculated a mean daily selenium for men aged ≥ 15 years of 60µg/day and for women aged ≥ 15 years of 44µg/day. The 1997/98 Total Diet Survey[6] examined selenium intake in two groups of men (young male 19-24 years and adult male > 25 years) and two groups of women (adult female > 25 years and lacto-ovo vegetarian female 19-40 years) using simulated diets. Estimated intakes for both groups of men were in excess of the US recommendation, while the estimated intakes for the women coincided with the US recommended level, 55µg/day. The intake calculated in the National Nutrition Survey is considered to be a more representative indication of dietary intake of selenium by New Zealanders.

The intake of selenium by New Zealanders has increased since the earlier Total Diet Surveys in 1982 and 1987/88.[6] To prevent animal diseases, farm animals are drenched with selenium-enriched products and the meal fed to poultry has selenium added. Generally bread made in the South Island is lower in selenium than bread made in the North. Since deregulation of the grain industry much North Island bread has a significant proportion of imported, largely Australian wheat which is selenium-rich. But South Island bread is made predominantly with wheat grown locally in low-selenium soils. Current practices need to continue for the selenium intake of New Zealanders to remain around recommended levels.

Meats, eggs, dairy products and bread are the main sources of selenium in New Zealand diets.[6] Kidney, liver and seafood, and for the vegetarian, imported legumes are rich in selenium.

Some New Zealanders take selenium supplements

Some people use selenium supplements as a prophylactic against cancer and cardiovascular disease, but its value for either purpose is not well established.[4,7] One placebo-controlled study of patients with a history of basal cell or squamous cell carcinomas of the skin found a significantly lower rate of total cancer incidence among the group taking selenium.[8] These results need to be confirmed by further large scale long term studies.[8,9]

The dose recommended on the label of selenium supplements is usually 50-200µg daily. The Dietary Supplements Regulations 1985 require selenium supplements to be manufactured and labelled so that the recommended daily dose is no more than 150µg.

A maximum safe daily dietary intake has been estimated at 400µg.[2,4] At an intake of 750-850µg functional signs of toxicity can be expected.[4] In an American publication, the normal range in serum is said to be 0.84-1.3 µmol/L,[10] but what is regarded as 'normal' will vary from country to country and region to region.

Symptoms of toxicity: garlicky breath, alopecia, peripheral neuropathy

Selenium, like arsenic, inactivates the sulphhydral groups of amino acids. Toxicity has been associated with a garlicky odour in the breath (caused by methylated selenium), fatigue, gastrointestinal disturbances, transverse lines on the nails, alopecia and peripheral neuropathy. Treatment involves discontinuation of the source of excessive intake and supportive care. There is no known antidote or suitable chelator.

In a published[11] case of selenium poisoning, the patient took 10 tablets a day for two weeks following a loading dose of a supplement containing an unknown amount of selenium. During this time he developed diarrhoea, worsening fatigue, a tingling sensation in the extremities and became completely bald. Two weeks after discontinuing the supplement he had a serum selenium level of 8.26µmol/L and appeared healthy with regrowth of hair and normal neurological examination.

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INTERACTIONS WITH ST. JOHN'S WORT (HYPERICUM PERFORATUM) PREPARATIONS

Medsafe Editorial Team

This article, and a consumer leaflet, were posted to general practitioners, selected specialists, community and hospital pharmacies, and complementary healthcare practitioners and retailers on 31 March 2000. Also e-mailed to electronic Prescriber Update subscribers in April 2000.

Complementary healthcare products containing St John's wort are available through direct marketing and from pharmacies, health food shops, supermarkets and complementary healthcare practitioners. They are used for a variety of conditions including the symptoms of depression. A number of clinical trials published in peer reviewed journals have commented favourably on the safety and efficacy of products containing standardised extracts of this botanical substance.

A recently published study[1] found a clinically significant reduction in serum levels of indinavir, a protease inhibitor used to treat HIV infection, when it was used with a St John's wort preparation. A second article[2] described two cases of heart transplant rejection in patients taking St John's wort with cyclosporin. There had previously been individual reports suggesting interactions with other medicines may be occurring. There have, however, been no reported deaths associated with use of St John's wort.

Why do St John's wort preparations interact with other medicines?

It appears that St John's wort preparations may interact with medicines either by increasing the rate of their metabolism or increasing levels of neurotransmitters. The effect on metabolism appears to occur by induction of certain cytochrome P450 isoenzymes in the liver and gut (particularly CYP 3A4, but also 1A2 and 2C9) reducing the blood levels and effectiveness of some medicines.

Many medicines, including carbamazepine and phenytoin, are potent enzyme inducers which act at the CYP 3A4 site. Several naturally occurring substances including grapefruit juice, red wine and broccoli have also been found to have effects on these enzyme systems.[3]

St John's wort may also increase the levels in the brain of the neurotransmitter serotonin by an additive or potentiating effect on other medicines. Medicines which may interact with St John's wort in this way include the selective serotonin reuptake inhibitor (SSRI) antidepressants (e.g. fluoxetine, paroxetine), other antidepressants affecting serotonin levels (e.g. nefazodone), and some migraine treatments (e.g. sumatriptan, naratriptan). These additive interactions may result in a variety of symptoms such as mental state changes, autonomic dysfunction (sweating, increased blood pressure) and motor effects consistent with increased serotonin.

Which medicines interact with St John's wort?

The following table lists medicines for which there is varying degrees of evidence of a possible interaction with St John's wort. For some (e.g. cyclosporin, warfarin, indinavir, carbamazepine) the loss of clinical effectiveness is potentially serious. The table gives an indication of the nature and strength of the evidence of interaction, describes the effect of an interaction should it occur, and provides advice on the management of patients. For some of the medicines listed there is at present no more than a theoretical possibility of interaction.

The table is not exhaustive, but it covers the information available to date. Other medicines not included in this list therefore may also interact with St John's wort preparations. In general, the following medicines are not likely to interact with St John's wort preparations:

- topical medicines with limited systemic absorption (inhalers, skin creams and ointments, eye and ear drops, enemas etc.)
- non-psychotropic medicines which are principally renally excreted.

How should patients be managed?

The levels of active ingredients within products containing St John's wort may vary from batch to batch and from one preparation to another. The degree of interaction with prescribed medicines may also vary. Hence, for some conditions the table advises discontinuing St John's wort. For these patients, in light of the currently available information, it is not advisable to attempt to stabilise them on suitable doses of a St John's wort preparation and the medication treating the condition.

When patients stop taking St John's wort preparations, the loss of enzyme induction may result in increased blood levels of interacting medicines possibly leading to toxicity. Any toxicity may take several days to present.

Those who need to stop St John's wort should have the management of their depression reviewed.

Reporting suspected interactions

Medical practitioners and pharmacists are asked to report suspected interactions, and adverse reactions, to St John's wort to the Centre for Adverse Reactions Monitoring, PO Box 913, Dunedin. Copies of the reporting form can be obtained from the Centre at the above address or can be downloaded from Medsafe's web site: www.medsafe.govt.nz/Profs/adverse.htm

Medicines interacting with St John's Wort (SJW)

Patients taking these medicines should not start taking St John's wort preparations without seeking medical advice:

Medicine	Evidence base	Evidence and effect of interaction	Suggested management of patients already taking St John's wort preparations
HIV protease inhibitors (indinavir, nelfinavir, ritonavir, saquinavir)	Strong	A clinical study has demonstrated reduced blood levels with possible loss of HIV suppression.	Measure HIV RNA viral load and stop SJW. Review management of depression.
Immunosuppressants (cyclosporin, tacrolimus)	Strong	Case reports have demonstrated reduced blood levels with transplant rejection.	Check cyclosporin or tacrolimus blood levels and stop SJW. Levels may increase on stopping SJW. The dose of immunosuppressant may need adjusting. Review management of depression.
HIV non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine, delavirdine)	Theoretical	Reduced blood levels with possible loss of HIV suppression is theoretically possible.	Measure HIV RNA viral load and stop SJW. Review management of depression.
Warfarin	Moderate	Case reports of reduced anticoagulant effect and need for increased warfarin dose have been reported.	Check INR and stop SJW. Monitor INR closely as this may rise on stopping SJW. The dose of warfarin may need adjusting. Review management of depression.

Medicine	Evidence base	Evidence and effect of interaction	Suggested management of patients already taking St John's wort preparations
Anticonvulsants (carbamazepine, phenobarbitone, phenytoin)	Theoretical	Reduced blood levels with risk of seizures theoretically possible.	Check anticonvulsant levels and stop SJW. Anticonvulsant levels may increase on stopping SJW. The dose of anticonvulsant may need adjusting. Review management of depression.
Digoxin	Moderate	Isolated case reports of reduced blood levels have been reported. Theoretical loss of control of heart rhythm or heart failure.	Check digoxin levels and stop SJW. Digoxin levels may increase on stopping SJW. The dose of digoxin may need adjusting. Review management of depression.
SSRIs and related antidepressants (citalopram, fluoxetine , fluvoxamine, paroxetine, sertraline, nefazodone)	Moderate	Small numbers of case reports of increased serotonergic effects have been reported.	Weigh the benefits of continuing SJW against possible adverse effects. Review management of depression.
Triptans (sumatriptan, naratriptan, rizatriptan, zolmitriptan)	Weak	Increased serotonergic effects with increased chance of adverse reactions theoretically possible.	Weigh the benefits of continuing SJW against possible adverse effects. Review management of depression.

Medicine	Evidence base	Evidence and effect of interaction	Suggested management of patients already taking St John's wort preparations
Oral contraceptives	Weak	Small numbers of case reports of breakthrough bleeding, contraceptive failure theoretically possible but no case reports of contraceptive failure have been reported.	Weigh the benefits of continuing SJW against theoretical possibility of reduced contraceptive efficacy. Review management of depression.
Theophylline	Theoretical	Reduced blood levels and loss of bronchodilator effect theoretically possible.	Check theophylline levels and review use of SJW. Weigh the benefits of continuing SJW against possible adverse effects. Theophylline levels may increase on stopping SJW. The dose of theophylline may need adjusting. Review management of depression.

Note: Other medicines not included in this list may also interact with St John's wort.

The SJW consumer information leaflet is available on the website (www.medsafe.govt.nz/Consumers/medicine/sjw.htm), or it can be ordered from ph 04-496-2277, fax 03-479-0979, email pubs@moh.govt.nz or post an order to the Ministry of Health, C/- Wickliffe Ltd. PO Box 932, Dunedin.

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UPDATE ON VALVULAR ABNORMALITIES WITH DEXFENFLURAMINE AND FENFLURAMINE

Medsafe Editorial Team

This article was e-mailed to electronic Prescriber Update subscribers in July 2000.

In June 1999, Medsafe issued an alert on valvular abnormalities with dexfenfluramine and fenfluramine. The alert advised that those who at any time in the past had received either agent for ≥ 3 months should be investigated for valvular abnormalities.

Since release of this advice, the Accident Compensation Corporation (ACC) has received > 400 claims for investigation. Two claims of medical mishap due to valvular damage associated with use of dexfenfluramine or fenfluramine have been accepted. The Centre for Adverse Reactions Monitoring has received 8 reports of abnormalities, possibly associated with use of fenfluramines. In 2 cases there were some echocardiographic or histological features consistent with those described in the literature for these agents. One of these patients required valve replacement and the other had evidence of disease more than 20 years after exposure to fenfluramine.

Recent evidence suggests that those with mild disease may improve after withdrawal of fenfluramine, and that the incidence of valvular abnormalities may be dependent on the duration of treatment.

Individuals who have received dexfenfluramine or fenfluramine for ≥ 3 months at any time in the past and who have not yet been investigated should be evaluated for evidence of heart murmur or other abnormal cardiac signs, and referred to a cardiologist for echocardiography if any abnormality is identified. Until a cardiologist is able to advise on the risk

of endocarditis, appropriate prophylactic antibiotics should be given to those requiring dental or surgical procedures putting them at risk of endocarditis. General practitioners should fill out an ACC claim for medical misadventure to cover the cost of investigation, detailing the patient's exposure to the medication.

ACC has received > 400 claims for investigation for valvular disorders

In June 1999, Medsafe issued an alert[1] about heart valve abnormalities occurring in association with the anorexiants, dexfenfluramine (Adifax™) and fenfluramine (Ponderax™). Dexfenfluramine and fenfluramine were removed from the market worldwide in September 1997, but there was a possibility that people who had taken either agent in the past for ≥ 3 months may have symptomatic or asymptomatic valvular abnormalities. Those with any abnormality are at risk of endocarditis when undergoing dental and certain surgical procedures unless appropriate antibiotic prophylaxis is administered.

The alert recommended that all those who had taken dexfenfluramine or fenfluramine in the past for ≥ 3 months should be examined for evidence of a heart murmur or abnormal cardiac signs. Those in whom an abnormality has been detected should be referred to a cardiologist for further investigation including echocardiography.

The ACC made an undertaking before publication of the alert to cover the cost of the visits to general practitioners and cardiologists for investigation. At the time the advice was issued, Medsafe estimated that more than 25,000 people may have used dexfenfluramine or fenfluramine, but it had no information on duration of use.

At the beginning of June 2000, ACC had received 435 claims for visits to general practitioners in former users of either anorexiant.[2] The ACC did not have data on the number of cases who required investigation by a cardiologist, but it advised that 80% of claims were for more than $100. In addition, two cases of medical mishap for valvular heart disease occurring as a result of administration of dexfenfluramine or fenfluramine had been accepted and three cases were being processed.

CARM has received eight reports of valvular disorders with fenfluramines

By the middle of March 2000, the Centre for Adverse Reactions Monitoring (CARM) had received eight reports of valvular disorders in individuals who

had taken fenfluramine or dexfenfluramine. All cases were reported following the alert and for all the causal association with use of these agents was thought to be possible. However, four were of valvular stenosis which has not been described in the published cases, one appeared to be a result of rheumatic heart disease and one was not sufficiently well documented to permit detailed analysis. The remaining two cases were more consistent with what has been described in the literature.[3] In both cases the patient had taken fenfluramine for more than a year in the 1970s and a heart murmur was diagnosed 1-4 years after commencing therapy. A full physical examination of one patient two years prior to use of fenfluramine had found no abnormalities. In one case an echocardiogram taken in 1995 showed thickened aortic valve leaflets and mild aortic incompetence. The other case required aortic valve replacement in 1997. The valve was thickened with 5mm fibrotic walls, and in the opinion of the surgeon, the damage had not been caused by rheumatic fever or other infection. Histologically the valve was too fibrotic to make a specific diagnosis, but there were some features in keeping with a fenfluramine effect.

Improvement may follow withdrawal in mild disease

Since release of the Medsafe advice, further studies have been published on heart valve abnormalities with dexfenfluramine and fenfluramine. Unfortunately, most have been very small, and suffered from the fact that it is not ethical to conduct a well-controlled prospective randomised trial to examine the issue.

One such study[4] involved 19 recipients of fenfluramine and phentermine and 11 recipients of placebo who had been treated as part of a randomised trial which was terminated when dexfenfluramine and fenfluramine were removed from the market. Active treatment had been for 8-73 weeks (mean 41). Echocardiography at the end of treatment revealed that five of those who had received active treatment (*vs* 1 placebo recipient) had mild aortic regurgitation, and met published criteria for drug-related valvular disease. Follow-up echocardiography six months later showed improvement in all five cases, with three no longer meeting the criteria. This study provides the best evidence to date that recovery or improvement may follow valvular damage by fenfluramines at least in some patients.

Incidence appears to be related to treatment duration

A further study[5] involved individuals from 25 centres in the United States treated with dexfenfluramine (479) or fenfluramine and phentermine (455) and untreated matched controls (539). The mean duration of therapy for the

dexfenfluramine group was 6.0 (1-18) months and for the fenfluramine and phentermine group it was 11.9 (1-63) months. Significantly, increased rates of aortic regurgitation were found in the treated groups: 8.9% for dexfenfluramine, 13.7% for fenfluramine and phentermine and 4.1% for placebo. There was no increase in the respective rates in those who had been treated for ≤ 3 months, but treatment with fenfluramine and phentermine for > 18 months was associated with a rate of 21%. Only nine of the treated cases were of moderate or moderate to severe disease compared with 95 cases of mild disease. The physical findings and prevalence of serious cardiac events were not significantly different between the three groups. Considering all grades, there was no significant difference in the prevalence of mitral regurgitation between the three groups, but the treated groups had significantly higher rates of mild mitral regurgitation.

Serious valvular damage appears to be rare

This study is the first[6] to provide data to support the suspicion that the incidence of heart valve disease may be dependent on treatment duration. It is also reassuring because severe disease was uncommon and physical findings and number of serious cardiac events did not differ significantly between the placebo group and the treated groups.

To date controlled studies have largely found only mild cases of valvular damage. Severe cases and/or those with long term consequences, such as those described in the original case series[3] and seen in the two CARM reports highlighted in this article appear to be extremely rare.

Those treated ≥ 3 months should be investigated for valvular disorders

The advice issued in June 1999 still stands and should be observed.

- Patients who took dexfenfluramine or fenfluramine for < 3 months need not be examined.
- Those who took either or both agents for ≥ 3 months should be examined by a general practitioner for evidence of a heart murmur or other abnormal cardiac signs.
- 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.

- 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.
- Practitioners should send an adverse reaction report for valve abnormalities requiring antibiotic prophylaxis in patients exposed to these medicines to CARM.

At the time of initial assessment, general practitioners should fill out a claim form clearly labelled "medical misadventure" which details the patient's exposure to the medication. The ACC will make a minimum contribution of $26 towards the cost of the initial visit. The patient should forward the claim to ACC (The Special Claims Unit, PO Box 1426, Wellington) to seek prior approval before proceeding with further investigations, such as echocardiography.

A fuller version of this advice is in the article in *Prescriber Update* no.18, June 1999, and can be found on the Medsafe web site at www.medsafe.govt.nz/Profs/PUarticles/diet.htm. A consumer information leaflet is also available on the web site (www.medsafe.govt.nz/Consumers/medicine/diet.htm), or it can be ordered from ph 04-496-2277, fax 03-479-0979, email pubs@moh.govt.nz or post an order to the Ministry of Health, C/- Wickliffe Ltd. PO Box 932, Dunedin.

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The following medicines are currently being monitored:

Medicine	Proprietary name	Indication/Action
Celecoxib	Celebrex	COX-2 inhibitor (selective NSAIA)
Copper IUCD *(follow-up only)*	Multiload Cu 375	IUCD
Eformoterol	Foradil/Oxis	potent long-acting β2-agonist
Entacapone	Comtan	Parkinson's disease – adjunctive treatment only
Levonorgestrel intrauterine system	Mirena	progestogen-releasing intrauterine system
Montelukast	Singulair	anti-asthmatic/leukotriene inhibitor
Nefazodone	Serzone	antidepressant /5HT2 blocker
Olanzapine	Zyprexa	atypical antipsychotic
Quetiapine	Seroquel	atypical antipsychotic
Rofecoxib	Vioxx	COX-2 inhibitor (selective NSAIA)
Salmeterol	Serevent	potent long-acting β2-agonist
Tolcapone	Tasmar	Parkinson's disease – adjunctive treatment only
Zafirlukast	Accolate	anti-asthmatic/leukotriene inhibitor *(not currently marketed)*

Please report all cases of adverse events occurring with IMMP medicines to the Centre for Adverse Reactions Monitoring (CARM), PO Box 913, Dunedin. The reporting form enclosed can be used or it can be downloaded from the Medsafe website: www.medsafe.govt.nz/Profs/adverse.htm

Recent Additions

Celecoxib (Celebrex™) **and Rofecoxib** (Vioxx™)

As COX-1 sparing NSAIAs or selective COX-2 inhibitors, celecoxib and rofecoxib do not interfere with the function of gastrointestinal mucosa to the

same degree as non-selective NSAIAs, and are thought not to cause gastrointestinal ulceration or haemorrhage.

Entacapone (Comtan™)

Like tolcapone, entacapone is a reversible catechol-O-methyl transferase (COMT) inhibitor used in the treatment of Parkinson's disease concomitantly with levodopa/benserazide or levodopa/carbidopa. It acts by increasing the bioavailability of levodopa and prolonging the duration of response.

Zafirlukast (Accolate™)

Zafirlukast, like montelukast, is a leukotriene inhibitor. Leukotriene production and receptor occupation are factors in the pathophysiology of asthma. More specifically, as a leukotriene inhibitor, montelukast interferes with contractile activity of airways smooth muscle and has antiinflammatory activity. It is an oral therapy approved for the prophylaxis and treatment of asthma, but it should not be used as rescue medication.

ADVERSE REACTIONS OF CURRENT CONCERN

CARM
CENTRE FOR ADVERSE REACTIONS MONITORING

The purpose of the Medicines Adverse Reactions Committee's (MARC) list of Adverse Reactions of Current Concern is twofold: to raise the level of awareness of these adverse reactions and to evoke reports so that more information may be gathered and appropriate action taken. The current list is below, with the latest additions in bold.

Medicine	Adverse reactions	Prescriber Update reference
Cisapride	cardiac arrhythmias	No.18, Jun 1999 & No.14, Feb 1997
Clozapine	hyperglycaemia	No.18, Jun 1999
Diane-35™	**venous thromboembolism**	**This issue**
Herbal medicines	all adverse reactions	No.13, Oct 1996
Hormone replacement therapy	venous thromboembolism	No.16, Apr 1998

Medicine	Adverse reactions	Prescriber Update reference
Nefazodone	hepatic reactions	No.19, Feb 2000
NSAIAs	**serious soft-tissue infection**	**This issue**
Oral contraceptives	venous thromboembolism	No.11, Feb 1996
Ticlopidine	neutropenia and thrombocytopenia	No.17, Dec 1998 & No.14, Feb 1997

Please report all cases of adverse reactions of current concern to the Centre for Adverse Reactions Monitoring (CARM), PO Box 913, Dunedin. The reporting form enclosed can be used or it can be downloaded from the Medsafe website: www.medsafe.govt.nz/Profs/adverse.htm

Recent Additions

Diane-35™ and venous thromboembolism

CARM now holds nine reports of pulmonary embolism (one of which is poorly documented and may be a duplicate) and three of deep vein thrombosis with Diane-35. None of these cases was fatal, but the recently published New Zealand study by Parkin, Skegg et al[2] included two cases of fatal pulmonary embolism with Diane-35.

Currently data relevant to the association of Diane-35 with venous thromboembolism are very sparse.[3,4] While evidence to date is for a risk similar to that with the third generation oral contraceptives, these results may be subject to bias because of the small number of cases and controls in each of the studies. In addition, as Diane-35 is indicated for oral contraception in women with androgenic conditions and for the polycystic ovary syndrome, it may be inappropriate to compare directly the rates because of the differences in indication and patient groups.

NSAIAs and any serious soft-tissue infection

Recently the MARC has considered studies[1] finding an association between use of NSAIAs during a viral infection and the subsequent development of necrotising fasciitis. The evidence for an association is not strong but it raises several questions:

- Is there an association between use of NSAIAs and necrotising fasciitis regardless of the condition for which the NSAIA is used?
- Do NSAIAs increase the risk of other serious soft-tissue infections besides necrotising fasciitis?

- Does the association with serious skin and soft-tissue infections apply to all or only some NSAIAs?

Hence, any serious soft-tissue infection following use of an NSAIA has been added to the list of adverse reactions of current concern. The objective is to collect more information about local experience, while the MARC also continues to survey the international literature for new case-control studies and other material examining the possible association. See also the article on necrotising fasciitis and non-steroidal anti-inflammatory drugs in this issue (page 4).

Recent Deletions

Alendronate and oesophagitis

CARM has received a total of three reports of oesophagitis with alendronate, one of these reports was received in May 1998, the month following inclusion on the list. None has been received since. Oesophagitis with alendronate is a topical effect and is more likely to occur if the instructions for administration of the medicine are not strictly adhered to.[5,6]

Carbamazepine and skin and haematological reactions

At the end of 1999, a total of 206 skin reactions (59% of total reports with carbamazepine) and 58 haematological reactions (17%) with carbamazepine had been reported to CARM. 25 of the skin reactions and 12 of the haematological reactions were reported in the period 1997 to 1999.

Serious skin reactions occurring with carbamazepine include Stevens Johnson syndrome and toxic epidermal necrolysis. The more serious cases that have been reported have been multisystem hypersensitivity reactions. In two recent cases both skin and haematological reactions were present. In each case the patient recovered without sequelae. The presence of hepatic involvement may be indicative of a more serious hypersensitivity reaction. In one such case the patient died following the development of fulminant liver failure, and in another it took six months for liver function to return to normal.

Most rashes and blood dyscrasias occur within 30 days of commencement of carbamazepine. Hence, extra vigilance for these events is warranted during the first 4-6 weeks of therapy.[7,8]

Colchicine and serious toxicity

Serious toxicity with colchicine became an adverse reaction of current concern in April 1998, following the death of a patient taking colchicine for an acute attack of gout.[9,10] Since this time, CARM has received four reports involving serious toxicity with colchicine. In two cases colchicine was taken at 1.2mg daily and deterioration in liver function was noted about three weeks and six months, respectively, after commencing colchicine. The patient whose therapy lasted longer also had alopecia and peripheral nephropathy. The third patient, a 48-year-old man, developed vomiting and diarrhoea leading to significant hyponatraemia the day following ingestion of 4.8mg for acute gout. In the fourth case an overdose of 40 x 0.6mg tablets was taken by a 64-year-old man being treated with colchicine for gout. Within 48 hours he developed diarrhoea and vomiting. Multisystem involvement followed, and his platelets fell to a low of 46 x 10^9/L, 4-7 days post-ingestion. The patient recovered.

NSAIAs and renal damage

From the commencement of the New Zealand adverse reactions reporting programme in 1965 to December 1999, 123 cases of renal damage with NSAIAs were reported. The NSAIAs associated with > 4 reports are acetylsalicylic acid or aspirin (19), diclofenac (52), naproxen (8), fenoprofen (5; fenoprofen is no longer available), piroxicam (6) and sulindac (9). Seven cases of renal damage with oral NSAIAs were reported from April 1998 to December 1999. In four cases the duration of treatment was two weeks or less. All except one were taking diclofenac, and four were taking no other medication besides an NSAIA (one of these was taking diclofenac and ibuprofen). None died but three patients had not recovered at the time of reporting and for one of these this was about 25 days after withdrawal of the medication.

Mefloquine and neuropsychiatric reactions

Because of international concern and several New Zealand cases, neuropsychiatric reactions with mefloquine were included in the list in August 1997. CARM has received 34 reports of adverse reactions to mefloquine since 1993, and 28 of these were of neuropsychiatric reactions. Of the 11 cases reported between August 1997 and December 1999, all except two were apparently taking no other medication. It is notable that six were recorded as not having recovered at the time of reporting. Symptoms have included depression, panic attacks, severe psychiatric episodes with behavioural disorder, acute mania, disassociation with reality and convulsions.

Updates on Current Listings

Cisapride and cardiac arrhythmias

Cardiac arrhythmias with cisapride were included with the adverse reactions of current concern in June 1999. Since then, because of deaths from QT-prolongation, several countries have withdrawn cisapride from the market or restricted its use. New Zealand, along with Australia, has decided to continue its availability with a modification in the indications (see article on page 7).

During the time that cisapride has been available in New Zealand, CARM has received only one report (in September 1999) of cardiac arrhythmias (supraventricular tachycardia). The patient was a 62-year-old woman who was taking grapefruit juice and quinine, both of which may have contributed to the reaction, the first by inhibiting metabolism and the second by an additive effect on QT-interval. Cisapride should be avoided in patients with hepatic failure, a history of QT-prolongation or other risk factors for QT-prolongation, or with the use of other agents which may prolong the QT-interval (e.g. some antiarrhythmics and tricyclic antidepressants), or those inhibiting metabolism by cytochrome P450 3A4 (e.g. macrolide antibiotics and azole antifungals).[12]

Clozapine and hyperglycaemia

CARM has received one report of hyperglycaemia with clozapine. The patient who was obese had mildly raised blood glucose after two weeks of clozapine therapy. Clozapine was continued, but details were not provided of any measures to control glucose levels. It is recognised that clozapine can usually be continued in patients developing hyperglycaemia or reduced glucose control with pre-existing diabetes mellitis provided measures are implemented to reduce glucose levels.[13]

Adverse reactions associated with herbal medicines

From January 1992 to December 1999, 122 reports of adverse reactions occurring in association with complementary therapies have been received. For most alternative therapies insufficient is known about the product's pharmacology or adverse reactions profile to be able to assign causality with confidence. Some exceptions are those cases where a positive rechallenge has occurred or the reaction was a hypersensitivity reaction with rapid onset, and no other apparent cause such as concomitant medication.

Interactions between prescription medicines and St John's wort, usually resulting in loss of potency of the prescription medicine, are well-recognised (see article on page 42). Six cases have been reported to CARM. Three cases involved intermenstrual bleeding with an oral contraceptive. In one case the contraceptive was the progestogen-only product, Femulen, for which there is

no known pharmacological basis for an interaction. In the other two cases the patient was taking Microgynon 30. St John's wort is thought to increase the rate of metabolism of oestrogens with resulting lowered contraceptive efficacy. Two other cases involved interaction with warfarin with an increase in potency resulting in a rise in INR in patients whose INR had been stable previously. These cases are at variance with published reports in which a decrease in potency was observed,[14] and with the understanding of the mechanism of the St John's wort interaction. The sixth case involved a possible mild serotonin syndrome in a patient taking St John's wort along with clomipramine.

Hormone replacement therapy and venous thromboembolism

Since 1989, six cases of pulmonary embolism and five of deep vein thrombosis with hormone replacement therapies have been reported to CARM. Death was the outcome in one case of pulmonary embolism which occurred with deep vein thrombosis. Three of the women were reported to have predisposing conditions.

Hormone replacement therapy increases the risk of venous thromboembolism by a factor of > 4 in the first year of use. The relative risk (an increase of 2-4 times compared with non-users) is similar to that with oral contraceptives, but the incidence of venous thromboembolism increases with age.[15]

Oral contraceptives and venous thromboembolism

From 1987 to 30 June 2000, CARM received 30 reports (nine fatal) of pulmonary embolism with third generation oral contraceptives (OC) and one report with a second generation pill. Even despite the now low use of third generation OCs, with two users of second generation pills for every user of a third generation OC, the third generation OCs continue to dominate in the reporting of pulmonary embolism.

The balance of evidence continues to be in favour of there being about twice the risk of venous thromboembolism with third generation compared with second generation OCs.[16] Further, a recent study[2] of deaths from pulmonary embolism in New Zealand women aged 15-49 years found a death rate of 2 women per year in users of oral contraceptives, or 1 death per 100,000 woman-years.

Ticlopidine and neutropenia and thrombocytopenia

Up to September 2000, four reports of blood dyscrasias, two each of agranulocytosis and granulocytopenia, had been reported to CARM. In three cases the reaction developed up to 10 days after completion of a course of ticlopidine. In two of these cases the course was for only two weeks of therapy.

White cell count fell as low as 0.8 x 10^9/L in one case. All four patients recovered fully. Two were treated with granulocyte colony stimulating factor and antibiotics.

Since neutropenia and thrombocytopenia with ticlopidine were included on the list of adverse reactions of current concern in December 1998, thrombotic thrombocytopenic purpura has become a recognised adverse reaction of ticlopidine.[17] This reaction is frequently fatal but chances of survival are improved if the patient is treated with phasmapheresis. See article on page 19.

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CARM
CENTRE FOR ADVERSE REACTIONS MONITORING

ADVERSE REACTION REPORTING GUIDELINES

Please do not hesitate to report *any suspect reaction of clinical concern*. The following general guidelines apply.

Report adverse reactions to:

- All medicines
- Vaccines
- "Over-the-counter" (OTC) medicines
- Herbal, traditional and alternative remedies

Report adverse **reactions** and **interactions** that are:

- **serious**
- **adverse reactions of current concern**[1]

Report all adverse reactions to **new medicines** and **all** events to **IMMP medicines**.[2]

Report serious allergic reactions so that a danger or warning can be entered against the patient's name in the national health database.

If in doubt, report.

To report: Use the pre-addressed postage paid adverse reactions card supplied with *Prescriber Update* or *New Ethicals Catalogue.*

Or: Download the form from www.medsafe.govt.nz/profs.htm

Mail the report to: The Medical Assessor
Centre for Adverse Reactions Monitoring
PO Box 913, Dunedin

Or fax it to: (03) 477 0509

Phone: (03) 479 7247

Email: carmnz@stonebow.otago.ac.nz

1. The list of adverse reactions of current concern is on page 54.
2. The list of medicines in the Intensive Medicines Monitoring Programme (IMMP) is on page 53.