



AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

VOLUME 17, NUMBER 2, MAY 1998

- j Ticlopidine update
- j Protease inhibitors
- j Methotrexate — name the day
- j Interaction between miconazole oral gel and warfarin

Prepared by the ADVERSE DRUG REACTIONS ADVISORY COMMITTEE (ADRAC), a subcommittee of the Australian Drug Evaluation Committee. ADRAC is Dr Tim Mathew (Chair), Dr Paul Desmond, Dr David Isaacs, Dr Cecilie Lander, Professor Gillian Shenfield, Dr Dana Wainwright, Professor Lindon Wing.

1. TICLOPIDINE UPDATE

Ticlopidine (Ticlid) is an inhibitor of platelet aggregation used in the prevention of stroke in patients with known vascular disease who are intolerant of or unresponsive to aspirin. It is also frequently used in association with the implantation of vascular stents. In the two year period to February 1998, ADRAC has received 110 reports of suspected adverse reactions in association with ticlopidine. Most (77) implicated ticlopidine as the sole suspected drug cause of the reaction. Ages ranged from 33 to 85 (median 67) years. For the 97 reports which provided the information, onset occurred within the first month in 72% of cases with only 3 reports documenting onset after three months. The major adverse reactions are white cell disorders, and haemorrhagic reactions which may be due to thrombocytopenia or platelet dysfunction.

Agranulocytosis (19 reports) and neutropenia (17) comprised one third of the total reports on ticlopidine. These **white cell disorders** were sometimes accompanied by fever/rigors (7), pharyngitis (4), mouth ulcers (3), hepatitis (2), thrombocytopenia (3) or anaemia (2). Four of the reports of agranulocytosis were accompanied by bone marrow biopsy reports documenting maturation arrest of myeloid precursors consistent with a drug-induced aetiology. Of the 36 reports of white cell disorders, 22 patients had recovered and 14 had not recovered at the time the

reports were submitted. There were no fatalities.

In addition to the three reports of **thrombocytopenia** with a white cell disorder, there were 7 other cases of thrombocytopenia. Three were accompanied by purpura including one case which involved a rectal haemorrhage. Another case had concomitant haematuria and haemolysis. There have also been overseas reports of thrombotic thrombocytopenic purpura in association with ticlopidine. There were four other reports of **haemorrhagic effects** not related to thrombocytopenia, consisting of one report each of haemorrhagic colitis, pulmonary haemorrhage (with cardiac failure, diffuse bleeding noted at bronchoscopy), purpura, and unspecified life threatening haemorrhage (with purpura).

Prescribers should be aware that ticlopidine may be associated with blood dyscrasias, particularly neutropenia or agranulocytosis which may be of sudden onset. The product information for ticlopidine warns that the period of maximum risk is from 3 weeks to 3 months after starting therapy. Patients should be advised to report promptly any occurrence of fever, chills, sore throat and/or mouth ulcers which may indicate neutropenia or agranulocytosis. Prolonged or unusual bleeding, bruising, purpura or dark stools may indicate thrombocytopenia or platelet dysfunction. If any of these occur ticlopidine should be withdrawn immediately.

2. PROTEASE INHIBITORS

The introduction of the protease inhibitors indinavir (Crixivan), zidovudine (ZDV), zalcitabine (ZDV), zalcitabine (ZDV), zalcitabine (ZDV) and nelfinavir (Viracept) has been a significant advance in the treatment of patients with HIV/AIDS. Health professionals who treat HIV/AIDS patients would be well aware of the spectrum of adverse effects of these agents. However, their effectiveness in combination with other antiviral agents has resulted in many patients being treated in the general community and it is important for all practitioners to be aware of some of their more unusual adverse effects. Three important adverse reactions of the protease inhibitors have emerged - lipodystrophy, hyperglycaemia and nephrolithiasis.

The most common effect is the development of **lipodystrophy**. This involves a peripheral lipodystrophy with mobilisation of the lipid stores in the face, arms and legs. ADRAC has received 94 reports of this syndrome. Most (92) have involved indinavir with 4 reports implicating zidovudine and 5 with zalcitabine. In 4 reports, more than one protease

inhibitor was being used. Almost all of the reports describe facial lipodystrophy usually characterised by facial thinning or hollow cheeks. There is usually visible wasting of the arms and legs with relative central obesity. Time to onset varied from 5 days to more than a year after commencement of therapy but most reports described an onset time of 6 months or more. There is no information on recovery at this stage. It has been estimated that this syndrome may affect about 60% of patients taking protease inhibitors.¹

The possibility that protease inhibitors could be associated with **new onset diabetes mellitus, hyperglycaemia, or exacerbation of existing diabetes mellitus** was first raised last year. ADRAC has received 6 reports of hyperglycaemia, 5 reports of the development of diabetes and 3 reports of aggravation of diabetes in association with the protease inhibitors. Indinavir was a suspected drug in 11 of these reports and zalcitabine was a suspected drug in the other three cases. Time to onset varied from

one to 19 months, but usually a few months after protease inhibitor therapy commenced. Two of the 14 patients were reported as recovered after the drug was withdrawn, and of the others, 3 had been initiated with antidiabetic therapy, 3 had increased insulin requirements, 2 had made dietary modifications and the other 4 were being monitored.

Nephrolithiasis appears to be an effect of indinavir only. The product information for indinavir notes that signs and symptoms of nephrolithiasis including flank pain with or without haematuria have been reported in 3.6% of patients receiving the drug. Of the 204 reports

received by ADRAC involving indinavir, 47 have described either kidney stones, haematuria, loin/flank/kidney pain or crystalluria. Time to onset has varied from the same day the drug was started to 19 months after commencement, although two thirds of the cases have occurred in the first 3 months of use. Adequate hydration is essential to help reduce the risk of this complication.

Reference:

1. Carr A, Samaras K, Burton S et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *AIDS* 1998; 12: 6927-34.

3. METHOTREXATE — NAME THE DAY

In 1994, ADRAC described two patients who developed methotrexate toxicity, one with a fatal outcome, after using excessive doses of low-dose methotrexate for treatment of rheumatoid arthritis.¹ In both of these cases, despite written instructions and verbal advice, the patients took their tablets daily instead of weekly. Recently, ADRAC received a report of another case of fatal aplastic anaemia in which an elderly female with rheumatoid arthritis took 7.5 mg of methotrexate daily instead of 7.5 mg weekly. ADRAC is now aware of 6 cases in which there is evidence that

methotrexate was taken more frequently than once a week and three of these had a fatal outcome.

For all patients being treated with weekly methotrexate, great care should be taken to give and repeat clear instructions on dosage. In particular, prescribers should **specify a particular day of the week**, preferably a day of some significance to the patient. For example, "Take two tablets each Tuesday".

Reference:

1. ADRAC. Low dose methotrexate - toxic if not taken correctly. *Med J Aust* 1994; 161: 152.

4. INTERACTION BETWEEN MICONAZOLE ORAL GEL AND WARFARIN

Drug interactions with warfarin are of major importance. Imidazole and triazole antifungal agents such as fluconazole, ketoconazole, itraconazole and miconazole are known to inhibit cytochrome P450 enzymes and potentiate the anticoagulant effect of warfarin. The interaction between warfarin and miconazole oral gel has been reported in Australia and New Zealand,^{1,2} but the receipt of 3 reports by ADRAC within the past 12 months indicates that its importance is perhaps not widely appreciated. One of these reports is described below.

An elderly female had been taking warfarin 2.5 mg daily for six years after an aortic valve replacement. During this time her international normalised ratio (INR) had been stable within the range 2.5-3.5. She was prescribed miconazole oral gel (Daktarin) which she applied four times daily, for treatment of oral thrush. After six days miconazole was stopped and five days later she presented with bruising on the arms and legs and a petechial rash on the left leg. Her INR was found to be 15.6. She was treated with fresh frozen plasma and vitamin K and her INR returned to

normal in three days.

ADRAC has received 11 reports documenting an interaction between warfarin and miconazole oral gel. They described elevations in INR to between 7.5 and 15.6. In five cases, there were no symptoms and in the other six cases, the patients presented with bruising, haematuria, or mucocutaneous bleeding.

It may be thought that as miconazole oral gel is a topically applied medication its absorption is limited. However, considerable absorption can occur through inflamed oral mucosa or from the bowel after swallowing the gel. Prescribers should counsel their patients taking long term warfarin about the possibilities of drug interactions and be aware that miconazole oral gel has this potential. Prescribers should also be aware that miconazole oral gel is available without prescription.

References:

1. Shenfield GM, Page M. Potentiation of warfarin action by miconazole oral gel. *Aust NZ J Med* 1991; 21: 928.
2. Pillans P, Woods DJ. Interaction between miconazole oral gel (Daktarin) and warfarin. *NZ Med J* 1996; 109: 346.

WHAT TO REPORT?

The Adverse Drug Reactions Advisory Committee (ADRAC) encourages the reporting of all **suspected** adverse reactions to drugs and other medicinal substances, including herbal, traditional or alternative remedies. The reporting of seemingly insignificant or common adverse reactions may highlight a widespread prescribing problem. The Committee particularly requests reports of:

*ALL suspected reactions to NEW DRUGS, especially **DRUGS OF CURRENT INTEREST**

*ALL suspected drug interactions

*Reactions to other drugs which are suspected of significantly affecting a patient's management, including reactions suspected of causing

! Death

! Danger to life

! Admission to hospital

! Prolongation of hospitalisation

! Absence from productive activity

! Increased investigational or treatment costs

! Birth defects

Reports of suspected adverse drug reactions are best made by using a prepaid reporting form ("blue card") which is available from the Adverse Drug Reactions Section

F 02-62328386, 02-62328387, 02-62328388

Tear-out blue cards can also be found at the front of all recent editions of the "Schedule of Pharmaceutical Benefits".

Further information can be found from the medical and scientific staff in the ADRAC Secretariat:

Secretary: **F** 02-62328380 Medical Officer: **F** 02-62328381

Executive Secretary: **F** 02-62328382 Fax: 02-62328392

(Problems with therapeutic devices should be reported on 1800-809361)

The Bulletin can also be found on the Internet at the TGA website: <http://www.health.gov.au/tga>

Drugs of Current Interest

Acarbose (Glucobay)

Carvedilol (Dilatrend, Kredex)

Dicloxacillin (Diclocil)

Famciclovir (Famvir)

Fluvoxamine (Luvox)

Mibefradil (Posicor)

Olanzapine (Zyprexa)

Topiramate (Topamax)

Alendronate (Fosamax)

Cilazapril (Inhibace)

Dolasetron (Anzemet)

Fexofenadine (Telfast)

Losartan potassium (Cozaar)

Nefazodone (Serzone)

Sevoflurane (Sevorane)

Valaciclovir (Valtrex)

Atorvastatin (Lipitor)

Citalopram (Cipramil)

Eformoterol (Foradile)

Fluvastatin (Lescol, Vastin)

Meropenem (Merrem)

Nicorandil (Ikorel)

Tiagabine (Gabitril)

Venlafaxine (Efexor)

ISSN 0812-3837

All correspondence to be addressed to: The Secretary, Adverse Drug Reactions Advisory Committee, PO Box 100, Woden, ACT, 2606