AUSTRALIAN
ADVERSE DRUG
REACTIONS
BULLETIN
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☆ Methotrexate misadventures
☆ Constipation — it can be severe with clozapine
☆ TTP with ticlopidine
☆ Thanks for your reports

Please report all suspected reactions to these
Drugs of Current Interest

Acamprosate (Campral) Naratriptan (Naramig)
Candesartan (Atacand) Nefazodone (Serzone)
Carvedilol (Dilatrend, Kredex) Raloxifene (Evista)
Celecoxib (Celebrex) Sildenafil (Viagra)
Clopidogrel (Iscover, Plavix) Telmisartan (Micardis/Prior)
Donepezil (Aricept) Tiludronate (Skelid)
Entacapone (Comtan) Tramadol (Tramal)
Gelatin succinylated (Gelofusine) Zafirlukast (Accolate)
Montelukast (Singulair) Zanamavir (Relenza)
Naltrexone (ReVia) Zolmitriptan (Zomig)
1. METHOTREXATE MISADVENTURES — A NEED FOR CARE AND COUNSELLING

Methotrexate is a widely used drug that carries particular risks of serious illness and death through misadventure. Three brands of methotrexate 2.5 mg tablets: Ledertrexate (Wyeth Lederle), Methoblastin (Pharmacia & Upjohn) and Methotrexate (DBL) are distributed in Australia. In addition, a 10mg tablet: Methoblastin (Pharmacia & Upjohn) is available.

Currently, all of these tablets are small and yellow.1 Although each tablet is marked with a code, this has not prevented confusion between the 2.5mg and 10mg strengths. In cases known to ADRAC in both Australia and overseas, medication errors have been due either to the dispensing of the wrong strength or the patient taking the wrong strength.2,3 The risk of misadventure is increased when a patient has supplies of both strengths, as may be needed to provide a particular dose.

A separate source of risk is the dose frequency. Quite different dosage regimens are used for the treatment of different diseases. In the treatment of some diseases such as rheumatoid arthritis and psoriasis, the patient is often told to take a dose once each week. There are instances where this dose has, instead, been taken each day or on several days each week resulting in severe unwanted effects such as neutropenia, hepatotoxicity, and bone marrow depression.4

Whenever methotrexate tablets are prescribed or dispensed, it is imperative that there be no doubt that the patient understands the strength of tablets being supplied, any changes in the strength of tablets and when the tablets are to be taken. If the tablets are to be taken once each week, it is essential for the prescriber to nominate the day and for this to be included on the label at dispensing.

References:
1. The sponsor of Methoblastin 10 mg, Pharmacia & Upjohn, is believed to be giving consideration to a change in the shape of the 10 mg tablet.

2. CONSTIPATION — IT CAN BE SEVERE WITH CLOZAPINE

Some drugs such as the narcotic analgesics are well known to cause constipation. However, the major drug causes of constipation reported to ADRAC come almost exclusively from 5 drug classes – calcium channel blockers (CCBs), NSAIDs, tricyclic antidepressants, lipid lowering drugs and SSRIs. The two most commonly reported are the CCBs verapamil (76 reports) and amlodipine (35).

Fifteen reports of constipation with clozapine have also been reported to ADRAC. Of these, 9 were described as severe with faecal impaction noted in 4 reports. While most patients recovered when clozapine was stopped, subacute bowel obstruction was reported in 2 cases and another report described rectal prolapse requiring ileostomy. The outcome in 7 cases was unknown and one patient died.1 In this case, a 47 year old male had unreported constipation which developed into severe faecal impaction. He died suddenly in hospital, probably as a result of inhalation of faecalum vomitus. This case is very similar to another published report in which a 29 year old male died after aspiration of vomitus secondary to obstruction of the transverse colon.2

Earlier this year, the Medicines Control Authority in the UK published an overview of 20 reports of reactions with clozapine suggesting gastrointestinal obstruction including 3 fatalities.3 It was speculated that reactions of this type are due to the anticholinergic properties of clozapine and may be more likely to occur in patients also taking other drugs which have anticholinergic effects.

It is important for prescribers to recognise and treat constipation in patients taking clozapine to prevent the development of more serious complications.
3. TTP WITH TICLOPIDINE

ADRAC recently received its first report of TTP (thrombotic thrombocytopenic purpura) in association with ticlopidine (Ticlid). TTP is a life-threatening syndrome of thrombocytopenia and microangiopathic haemolytic anaemia commonly associated with fluctuating neurological abnormalities, renal dysfunction, and fever. A central feature is widely disseminated platelet aggregates, which have been particularly observed in the adrenal glands, brain, heart, kidneys, and pancreas. The association of TTP with ticlopidine has been the subject of two recent publications.\(^1,2\)

In the report to ADRAC, a 56 year old female was admitted to hospital with spontaneous bruising on the arms, chest and legs after about 3 weeks use of ticlopidine for coronary stenting. Laboratory investigations showed thrombocytopenia (platelets 9 x 10\(^9\)/L [reference range: 150-400 x 10\(^9\)/L]) and declining haemoglobin (haemoglobin 88 g/L [reference range: 115-165 g/L]). There were microangiopathic red cells consistent with TTP on full blood examination. The patient’s highest recorded temperature was 38 °C and she had haematuria in addition to the spontaneous bruising. Neurological signs and symptoms included severe headaches and neck stiffness. She recovered after aggressive treatment which included plasmapheresis.

TTP is a rare and often fatal disorder with an estimated incidence of 3.7 cases per million people (0.0004%).\(^3\) Ticlopidine is one of several drugs that has been associated with the disorder and a recent estimate of the incidence amongst ticlopidine-treated patients is 0.02%.\(^2\) As mortality exceeds 20%, it is important that this complication is recognised promptly, the suspected drug ceased and treatment commenced rapidly.

Ticlopidine is likely to become more widely used because its indications have been broadened to include use in patients with coronary stents, and prescribers need to be aware of the possibility of TTP.

References:

4. THANKS FOR YOUR REPORTS

The figure shows the number of reports received by ADRAC over the past 4 financial years. There has been a steady increase over that time and this has maintained Australia’s reporting rate as one of the highest in the world. Much of this increase has come from the pharmaceutical industry and although ADRAC welcomes its support, the Committee encourages health professionals to send their reports direct to ADRAC using a blue card. ADRAC’s ability to monitor the safety of drugs is dependent on your reports.
WHAT TO REPORT? (you do not need to be certain, just suspicious!)

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 Unit

☎ 02-62328386, 02-62328387, 02-62328388, or from the website: www.health.gov.au/tga/docs/pdf/adr.pdf

Tear-out blue cards can also be found at the front of all recent editions of the "Schedule of Pharmaceutical Benefits", and at Appendix F of the "Australian Medicines Handbook".

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

Secretary: ☎ 02-62328381    Executive Secretary: ☎ 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: www.health.gov.au/tga

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