



Prepared by the ADVERSE DRUG REACTIONS ADVISORY COMMITTEE (ADRAC). ADRAC is Associate Professor Duncan Topliss (Chair), Dr David Isaacs, Dr Cecillie Lander, Professor John McNeil, Professor Gillian Shenfield, Dr Simone Strasser, Dr Dana Wainwright

AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

VOLUME 21, NUMBER 3, AUGUST 2002

- ☆ Patent blue V and anaphylaxis
- ☆ Quinine and profound thrombocytopenia
- ☆ Indapamide and hyponatraemia
- ☆ Epoetin alfa and pure red cell aplasia

Please report **all** suspected reactions to these **Drugs of Current Interest**

Bupropion (Zyban)
Fondaparinux (Arixtra)
Galantamine (Reminyl)
Gatifloxacin (Tequin)
Lercanidipine (Zanidip)
Meloxicam (Mobic)
Mirtazapine (Avanza, Remeron)
Moxifloxacin (Avelox)
Oxcarbazepine (Trileptal)

Pioglitazone (Actos)
Reboxetine (Edronax)
Risedronate (Actonel)
Rivastigmine (Exelon)
Rofecoxib (Vioxx)
Rosiglitazone (Avandia)
Sibutramine (Reductil)
Tegaserod (Zelmac)
Zolpidem (Stilnox)

1. PATENT BLUE V AND ANAPHYLAXIS

Patent Blue V (occasionally referred to as Sulphan Blue) is a dye used to colour lymph vessels. In lymphangiography, Patent Blue V is injected subcutaneously so it can enter the lymphatic vessels, which are then visible through the skin and can be injected with a radiological contrast agent. Patent Blue V is being increasingly used for a number of purposes including breast surgery, where it is injected into breast tissue in order to locate draining lymph nodes.

Over the years ADRAC has received 42 reports of reactions to Patent Blue V, including six reports of anaphylaxis. Five of these have been

reported since October 2000 and were in women aged 37-54 years, undergoing breast surgery. In four cases, the anaphylaxis was described as severe; two patients required admission to an Intensive Care Unit. Past exposure to Patent Blue V was generally not recorded, but is probably unlikely. One patient had a history of cold urticaria. Most recovered without sequelae.

Surgeons and anaesthetists should be aware of the potential for severe allergic reactions to Patent Blue V. The Product Information recommends testing for hypersensitivity by injecting a small volume of solution initially, then waiting a short time to see if an allergic reaction develops.

2. QUININE AND PROFOUND THROMBOCYTOPENIA

ADRAC has published 2 previous Bulletin articles about quinine and thrombocytopenia but continues to receive reports of this serious problem.^{1,2} Since 1972, ADRAC has received 571 reports of suspected adverse reactions to quinine (sulfate or bisulfate), including 198 reports of thrombocytopenia, 4 of which had a fatal outcome. Twenty of these have been received since the beginning of the year 2000. The reactions generally occurred within 3 weeks of commencing quinine although two with intermittent use had a longer time to onset. In two cases the reaction occurred soon after the first dose. Seventeen of the 20 reports documented a platelet count which ranged between 0 and $14 \times 10^9/L$ and most described hospitalisation and treatment with platelet transfusion, corticosteroids or immunoglobulin. Five reports described a positive quinine antibody test.

A recent illustrative report involved a 25 year old woman who had been taking quinine intermittently for nocturnal cramps. She had been taking about two tablets a week for 2 months. She presented with a generalised purpuric rash, and was found to have a platelet count of $5 \times 10^9/L$. Quinine was ceased, and she was hospitalised and treated with prednisolone and immunoglobulin. Her platelet count recovered to normal within a week. Drug-induced anti-platelet antibodies were detected.

Prescribers should consider the risks and likely benefits before prescribing quinine for nocturnal

cramps, and should also consider other causes of cramp (for example, salt depletion particularly in summer, electrolyte disturbance, peripheral vascular disease, motor neurone disease). Meta-analyses have found that quinine prevents on average one or two cramps per week compared to placebo, without reducing the duration or severity of cramps.³ In 1995, the American FDA withdrew the indication of nocturnal cramps from all quinine products, because of a lack of evidence of efficacy, and the Australian Medicines Handbook recommends against its use for this indication.⁴ Daytime passive stretching of the calf muscles may be effective in preventing nocturnal cramps.⁵

As illustrated in the case report above, thrombocytopenia usually recovers within a week of stopping quinine, but treatment with platelets, steroids or immunoglobulin may be required. Since quinine-induced thrombocytopenia occurs via an immune-based mechanism, patients should in future avoid all quinine-containing products, including drinks such as tonic water and bitter lemon.

References:

1. ADRAC. Cinchona alkaloids – the bite's as bad as the bark! *Aust Adv Drug React Bull* 1988; December.
2. ADRAC. Quinine, cramps and cricket. *Aust Adv Drug React Bull* 1991; 10: August.
3. Anonymous. Quinine and cramp. *Prescr Internat* 2000; 9: 154-7.
4. Australian Medicines Handbook, 3rd edition, Adelaide: AMH: 2002. p. 585
5. Daniell HW. Simple cure for nocturnal leg cramps. *N Engl J Med* 1979; 301: 216.

3. INDAPAMIDE AND HYPONATRAEMIA

An article was recently published describing the Australian experience of hyponatraemia in association with the non-thiazide diuretic, indapamide.¹ In the 30 year history of reporting to ADRAC, indapamide, which was marketed in the mid 1980s, is the most commonly reported cause of hyponatraemia with 164 reports.

Of these 164 reports, 68 also described hypokalaemia. Over half (92) of the reports described accompanying symptoms including confusion, nausea, vomiting, dizziness, anorexia, malaise, fatigue, syncope, somnolence and convulsions. Most patients (88%) were 65 years or over and 82% were female. Many of the reports (129) documented a serum sodium concentration and in 75 cases, the concentration was ≤ 120 mmol/L.

Despite the fact that hyponatraemia can complicate treatment with any diuretic

medication, ADRAC continues to receive reports of the association. In the first 5 months of 2002, there have been 18 reports. It should also be noted that indapamide is present in combination with perindopril (Coversyl Plus). Although Coversyl Plus contains only 1.25 mg of indapamide compared with the standard 2.5 mg tablet, there have been 5 reports of hyponatraemia associated with this product in the first 5 months of the year. ADRAC recommends that indapamide should be used cautiously and changes in conscious or mental state should prompt measurement of serum sodium concentration.

Reference:

1. Chapman MD, Hanrahan R, McEwen J, Marley JE. Hyponatraemia and hypokalaemia due to indapamide. *MJA* 2002 176: 219-221.

4. EPOETIN ALFA AND PURE RED CELL APLASIA

Pure red cell aplasia (PRCA) is a rare adverse effect of epoetin alfa, which has recently been highlighted in an article and subsequent letter in the literature.^{1,2} The condition results from the development of antierythropoietin antibodies, resulting in transfusion-dependent anaemia. PRCA has been reported only after chronic use of epoetin in patients with renal failure. In a series of 82 cases reported by the FDA, PRCA developed after the use of epoetin alfa from 1 month to 5 years (median: 7 months).

ADRAC has received 12 reports of PRCA associated with epoetin alfa (Eprex) use. The ages of the patients ranged from 28 to 76, and duration of epoetin use, where known, was from 4 to 13 months.

Antierythropoietin antibodies which develop in this condition cross-react with all other erythropoietin products, including darbepoetin (Aranesp) which has been available in Australia since November, 2001. Experience with this product is limited, specifically it is not known whether PRCA will develop in association with darbepoetin as the only agent used.

The sponsor of Eprex has recently issued a 'Dear Healthcare Professional' letter, recommending

that Eprex be given by the intravenous route where feasible, as this is thought to reduce the risk of antibody formation.

In patients with worsening anaemia, other causes (eg, iron, folate, or Vitamin B12 deficiency; aluminium intoxication; infection or inflammation; blood loss or haemolysis) should be excluded. If PRCA is suspected it should be confirmed with antibody testing and/or bone marrow examination. Epoetin alfa should be discontinued, and patients should not be switched to another erythropoietin. PRCA may respond to immunosuppressive therapy, spontaneous resolution has occurred occasionally.

Please report all cases of suspected PRCA to ADRAC. Antibody testing can be arranged through Janssen Cilag – phone 1300 369 949.

References:

1. Casadevall N, Nataf J, Viron B et al. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. *N Engl J Med* 2002; 346: 469-75.
2. Gershon SK, Lukshenburg H, Coté TR, Braun MM and others. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. *N Engl J Med* 2002; 346: 1584-86.

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, or from the website: <http://www.health.gov.au/tga/adr/index.htm>

Tear-out blue cards can also be found at the front of the "Schedule of Pharmaceutical Benefits" and the "Australian Medicines Handbook".

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



1800 044 114

Fax: 02-62328392

Email: adrac@health.gov.au

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

The Bulletin is also available on the Internet at: <http://www.health.gov.au/tga/adr/aadrb.htm>

ISSN 0812-3837

☆ The Adverse Drug Reactions Unit has a revamped website. Login at:
<http://www.health.gov.au/tga/adr/index.htm>

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