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AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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- ☆ Electrolyte disturbances with sodium picosulfate bowel cleansing products
- ☆ Amiodarone and pulmonary toxicity
- ☆ Interaction of rofecoxib with warfarin
- ☆ Seeing things with zolpidem

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

Bupropion (Zyban)
Galantamine (Reminyl)
Gatifloxacin (Tequin)
Leflunomide (Arava)
Lercanidipine (Zanidip)
Meloxicam (Mobic)
Mirtazapine (Avanza, Remeron)
Moxifloxacin (Avelox)
Oseltamivir (Tamiflu)
Oxcarbazepine (Trileptal)

Pioglitazone (Actos)
Quetiapine (Seroquel)
Risedronate (Actonel)
Rivastigmine (Exelon)
Rofecoxib (Vioxx)
Rosiglitazone (Avandia)
Tibolone (Livial)
Tramadol (Tramal)
Zolpidem (Stilnox)

1. ELECTROLYTE DISTURBANCES WITH SODIUM PICOSULFATE BOWEL CLEANSING PRODUCTS

Low volume bowel preparations for colonoscopy have become increasingly popular in recent years because of the greater comfort for patients who are not required to swallow large volumes of liquid. ADRAC has previously highlighted the risk of severe electrolyte disturbances in association with the use of oral sodium phosphate solution (Fleet Phospho-Soda Buffered Saline Laxative Mixture, Kwikprep) as a bowel preparation.¹ Since then, ADRAC has received reports in association with two other products (Picolax, Picoprep) which contain sodium picosulfate. Sodium picosulfate acts similarly to sodium phosphate in that it produces its cathartic effect by osmotic action in the gut. This results in a transfer of fluid and electrolytes across the gut to the gut lumen.

ADRAC has received 16 reports implicating sodium picosulfate products. Five described convulsions associated with hyponatraemia.

2. AMIODARONE AND PULMONARY TOXICITY

Amiodarone (Aratac, Cardinorm, Cordarone X) is an antiarrhythmic agent which is available on the PBS as a restricted benefit item for the treatment of "severe cardiac arrhythmias". ADRAC regularly receives reports of suspected adverse reactions to amiodarone; in the year 2000 there were 61 reports, and in 2001 there were 74 reports, including 5 deaths.

Since 1981, there have been 31 reports to ADRAC of deaths in association with amiodarone use, 17 of which have involved pulmonary events (pulmonary fibrosis 8, pulmonary infiltration 5, pneumonitis 2, pulmonary effusion 1, respiratory failure 1).

An illustrative case is that of an 84 year old male with a history of ischaemic heart disease, and aortic and mitral stenosis, who had a pacemaker. He had been taking amiodarone for 6 months to control tachyarrhythmias when he presented with progressive dyspnoea. A CT scan suggested pulmonary fibrosis. Amiodarone was ceased but despite treatment with pulsed methylprednisolone and high dose oral prednisolone, he died.

Although commonly insidious in onset, amiodarone-induced pulmonary toxicity may

develop rapidly. The lowest effective dose should be used, and patients should be instructed to report any dyspnoea or non-productive cough.¹ Amiodarone also has other toxicities including hepatotoxicity which can cause cirrhosis and hepatic failure, cardiovascular effects including bradycardia and tachycardia, skin reactions including photosensitivity and discolouration, neurotoxicity including ataxia and peripheral neuropathy, as well as both corneal deposits and hyper- and hypothyroidism.

Amiodarone has unique properties for the treatment of difficult cardiac arrhythmias and its use is increasing – from 150,305 PBS/RPBS prescriptions dispensed in 1995 to 360,063 in 2000.² It is particularly important for prescribers and patients to be aware of the risk of pulmonary toxicity and the presence of dyspnoea or cough should be investigated immediately.

Reference:

1. ADRAC. Electrolyte disturbances with oral phosphate bowel preparations. *Aust Adv Drug React Bull* 1997; 16: 2.

Another described syncope in a patient with both hyponatraemia and hypokalaemia. There have also been single reports of unconsciousness with hyponatraemia, metabolic alkalosis with hypokalaemia, and 4 of syncope and dehydration without documented electrolyte abnormalities.

Low volume sodium phosphate and sodium picosulfate products can cause marked dehydration, hyponatraemia, other electrolyte abnormalities and associated complications. Infants, the elderly, the frail and those with congestive heart failure or compromised renal function are particularly at risk. Alternative less concentrated bowel cleansing preparations should be used in these patients.

References:

1. Kanji Z, Sunderji R, Gin K. Amiodarone-induced pulmonary toxicity. *Pharmacotherapy* 1999; 19: 1463-6.
2. Health Insurance Commission. Pharmaceutical Benefit Schedule Item Statistics [cited 2001 Jan 3]. Available from: URL: http://www.hic.gov.au/statistics/dyn_pbs/forms/pbs_tab1.shtml.

3. INTERACTION OF ROFECOXIB WITH WARFARIN

ADRAC has previously published a report on the interaction between celecoxib and warfarin¹; it appears that rofecoxib (Vioxx) and warfarin may also sometimes interact to a clinically significant extent.

ADRAC has received 416 reports of suspected adverse reactions to rofecoxib since its marketing in Australia in late 2000. Of these, 8 described an increase in the INR in patients taking warfarin. In 6 of those reports, INR values were given, ranging from 3.8 to 11.8. In half of the reports, the timing of the reaction relative to the date of commencing rofecoxib was accurately described; this varied from 1 to 6 weeks. Five of the 8 reports did not describe haemorrhagic complications, however bleeding was reported in 2 cases (epistaxis and rectal haemorrhage) and anaemia (haemoglobin 87 g/L) in one case. Five patients were hospitalised, and 2 received treatment with intravenous vitamin K.

A further report described a patient taking both rofecoxib and warfarin, who died after a cerebral

haemorrhage, although in this case the INR was stable (1.7 – 2.5) throughout.

A recently-published study showed that rofecoxib 25 mg daily for 21 days added to a stable warfarin regime increased INR by an average of 8%.² Celecoxib and warfarin are both metabolised by the enzyme CYP2C9, which may provide an explanation for the interaction of those two drugs. A mechanism for the interaction of rofecoxib and warfarin is unknown.

ADRAC recommends that, in patients taking warfarin, increased monitoring of INR should be conducted when rofecoxib treatment is started, stopped or the dose changed.

References:

1. ADRAC. Interaction of celecoxib and warfarin. *Aust Adv Drug React Bull* 2001; 20: 2.
2. Schwartz JI, Bugianesi KJ, Ebel DL et al. The effect of rofecoxib on the pharmacodynamics and pharmacokinetics of warfarin. *Clin Pharmacol Ther* 2000; 68: 626-36.

4. SEEING THINGS WITH ZOLPIDEM

Zolpidem (Stilnox) was marketed in Australia in late 2000 for the short term treatment of insomnia. It is structurally unrelated to the benzodiazepines, but has a similar pharmacological action. In 2001, ADRAC received 72 reports describing 170 reactions in association with zolpidem as shown in Table 1.

Of these 72 reports, 56 described one or more neurological or psychiatric reactions, especially visual hallucinations, confusion, depression and amnesia. Most reactions occurred with a daily dose of 10 mg and 70% occurred after the first dose. Most of the 15 reports of hallucinations occurred within a few hours, often soon after the drug was taken. Half of the reports of amnesia described a total loss of memory for events immediately after the drug was taken, although two described poor memory in subsequent days. The onset of confusion and depression was sometimes apparent within hours of taking the drug but in most cases occurred the following day.

Prescribers should be alert to the fact that zolpidem may be associated with distressing neurological or psychiatric reactions.

Adverse Reaction	Number of Occurrences
Visual hallucinations	15
Nausea	9
Confusion	8
Depression	7
Amnesia	6
Dizziness	6
Headache	6
Somnolence	6
Depersonalisation	5
Agitation	4
Anxiety	4
Somnambulism	4
Vomiting	4

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, 87, 88, or from the website: <http://www.health.gov.au/tga/docs/html/adr.htm>

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

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

 62328180 (1800 044114)

 adrac@health.gov.au

 ADRAC, PO Box 100, Woden, ACT, 2606

Fax: 02-62328392

(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/docs/html/aadrbltn/aadrbdx.htm>

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