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AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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- ☆ Rofecoxib, celecoxib and cardiovascular risk
 - ☆ Convulsions and blood dyscrasias with mirtazapine
 - ☆ Anti-epileptic drugs, pregnancy and fetal malformations
 - ☆ Hormone replacement therapy
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Please report **all** suspected reactions to these **Drugs of Current Interest**

Apomorphine (Uprima)
Esomeprazole (Nexium)
Fondaparinux (Arixtra)
Galantamine (Reminyl)
Lercanidipine (Zanidip)
Levetiracetam (Keppra)
Meloxicam (Mobic)

Pioglitazone (Actos)
Pramipexol (Sifrol)
Reboxetine (Edronax)
Rosiglitazone (Avandia)
Sibutramine (Reductil)
Tadalafil (Cialis)
Tegaserod (Zelmac)

1. ROFECOXIB, CELECOXIB AND CARDIOVASCULAR RISK

In the VIGOR study, a randomised controlled trial of the efficacy of rofecoxib in rheumatoid arthritis, the incidence of myocardial infarction was significantly greater with rofecoxib than with the comparator drug, naproxen (0.4% vs 0.1%).¹ While it was postulated that naproxen might have a cardioprotective effect, similar to that with aspirin, the result also raised the possibility that rofecoxib might be prothrombotic, leading to an elevated rate of myocardial infarction.² Two factors in the VIGOR study which may have increased the risk of cardiovascular events were the high dose of rofecoxib used (50mg daily; approved dose 12.5-25mg daily) and the exclusion of the use of aspirin by participants in the study.² Retrospective analysis indicated that aspirin for cardiovascular prophylaxis was indicated in 4% of the patients in the VIGOR study.¹ Thirty-seven percent of the myocardial infarctions occurred in this 4%.³

A recent large-scale cohort study provided support for the view that the risk of cardiovascular events with rofecoxib may be dose-related.⁴ In the study, new users of high dose rofecoxib (> 25mg daily) had a relative risk of serious coronary heart disease (CHD) of 1.93 (95% CI 1.09-3.43; p=0.024) compared with non-users of an NSAID. The study found no increased risk of CHD among users of other NSAIDs, including celecoxib, or among users of lower doses of rofecoxib, and no protective effect with naproxen.

At present the evidence for an association between rofecoxib and a risk of cardiovascular events is inconclusive and indirect. The evidence for an effect with celecoxib is even weaker.^{2,3} Reflecting

the current data, ADRAC wishes to advise prescribers of the following:

- There may be an increased risk of cardiovascular and cerebrovascular disease with rofecoxib and celecoxib.
- The increase in risk seems to be higher in those with pre-existing cardiovascular disease.
- The risk appears to be greater with rofecoxib than with celecoxib, and appears to be dose-related.
- Rofecoxib should not be used at doses exceeding the maximum approved dose (25 mg/day).
- Cardiovascular risk should be evaluated before prescribing a coxib.

Some authors have advised taking low-dose aspirin with celecoxib or rofecoxib in patients with cardiovascular risk factors.³ However, aspirin, even in low dose, has the potential to reduce the gastroprotective benefit of the coxibs.

Readers wanting a more complete presentation of the evidence and a fuller discussion of the issue should refer to the review at reference 3.

References

1. Bombardier C, Laine L, Reicin A et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;343:1520-8.
2. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* 2001;286:954-59.
3. Howes LG, Krum H. Selective cyclo-oxygenase-2 inhibitors and myocardial infarction. How strong is the link? *Drug Safety* 2002;25:829-35.
4. Ray WA, Stein CM, Daugherty JR et al. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. *Lancet* 2002;360:1071-3.

2. CONVULSIONS AND BLOOD DYSCRASIAS WITH MIRTAZAPINE

Mirtazapine (Remeron, Avanza, Mirtazon), an antidepressant, antagonises central alpha₂ adrenoceptors to cause an increase in noradrenaline and serotonin release. It is also an H₁ antagonist, causing sedation, but has little anticholinergic activity. From May 2001, when PBS subsidy commenced, to May 2003, almost 500,000 funded prescriptions were dispensed.

ADRAC has received 253 reports for mirtazapine. Common reactions reported are presented in the Table. A prescription event monitoring (PEM) study conducted in England of over 13,000 patients

taking mirtazapine found that the most frequent adverse reactions were drowsiness/sedation and malaise/lassitude (5.8% and 2.8% of patients, respectively, in the first month).¹

Potentially serious reactions reported to ADRAC are convulsions (16 reports) and blood dyscrasias (15). None of the 16 patients who experienced convulsions with mirtazapine were known to have epilepsy. Mirtazapine was the only drug taken in eight of the cases. No cases of convulsions were identified in the PEM study.

Table: Common reactions reported to ADRAC with mirtazapine

Reactions	Number of reports	Reactions	Number of reports
oedema	33	nightmares	14
anxiety/ agitation	24	increased weight	14
myalgia/ arthralgia	24	diarrhoea	11
sedation	23	nausea/ vomiting	11
skin reactions	20	hepatic reactions	10
blood dyscrasias	15	hallucination	9
convulsions	16	serotonin syndrome	4
hyperkinesia	15		
dizziness	15		

The blood dyscrasias reported were neutropenia (8; one case also had thrombocytopenia), thrombocyt-

openia (6), lymphopenia (1) and pancytopenia (1). Two patients had fever with neutropenia. The time to onset was ≤ 2 months in 8 out of the 11 reports where this information was provided. Mirtazapine was the only suspected drug in nine of the blood dyscrasia reports. The PEM study found two cases of blood dyscrasias: neutropenia (identified following a history of sore throat) and agranulocytosis.

Health professionals should be alert for signs of blood dyscrasias (fever, sore throat, petechiae etc.) in users of mirtazapine.

Reference:

1. Biswas PN, Wilton LV, Shakir SAW. The pharmacovigilance of mirtazapine: results of a prescription event monitoring study on 13 555 patients in England. *J Psychopharmacology* 2003;17:121-6.

3. ANTI-EPILEPTIC DRUGS, PREGNANCY AND FETAL MALFORMATIONS

For some decades, an association has been recognised between maternal epilepsy and an increased risk of fetal malformation. Inadequately controlled epilepsy is associated with dangers to mother and fetus, but anti-epileptic drugs (AEDs) might cause adverse consequences in the fetus.¹ ADRAC receives occasional reports of fetal malformations (FMs) associated with the use of AEDs in pregnancy. However, for many of these reported malformations, there are few published prospective data in human pregnancy indicating whether the AEDs involved increase the risk above background. To address this lack, prospective Pregnancy Registers have been established in North America, Europe, UK and Australia.

Analysis of the 40-month data from the ongoing Australian Pregnancy Register for Women on Antiepileptic Medication has yielded important and clinically relevant information.² Out of 403 pregnancy outcomes for women taking AEDs, 87.8% resulted in a healthy live birth, and 6.5% had a FM. (The remainder had spontaneous abortions or premature death in utero.) The FM rate was significantly greater in pregnancies exposed to valproate in the first trimester (16.0%) compared with those exposed to all other AEDs (2.4%)($p < 0.01$). Furthermore, the mean daily dose of valproate was significantly higher in those with FMs than in those without FMs (1975mg vs 1128mg, $p < 0.01$).

A recently published, prospective Finnish study of 970 pregnancy outcomes in women with epilepsy

also found an association between the use of valproate in pregnancy and FM (odds ratio 4.1; 95% CI 1.6-11; control group: pregnancies in women with epilepsy not using AEDs in the first trimester).³ Increased risks were also seen with carbamazepine (2.5; 1.0-6.0) and oxcarbazepine (10.6; 1.1-106), and with low serum folate concentration in early pregnancy (5.8; 1.3-27). In this study the rate of major FMs with AED exposure was 3.8% versus 0.8% in the non-exposed group ($p = 0.02$).

Prescribers should review the medication of women on AEDs in pre-pregnancy planning. Treatment should aim to maximise seizure control while minimising the risk of FM. Folic acid supplementation prior to conception and during the first trimester is desirable in all pregnancies, especially in those women taking AEDs.

The Australian Pregnancy Register for Women on Antiepileptic Medication provides an observational, prospective, longitudinal study. Currently pregnant women taking AEDs (for epilepsy or other purposes) can be registered by phoning 1800-069-722. The data obtained by this Register will help to guide management principles in this group of at-risk women in the future.

References:

1. ADEC. Anticonvulsants/antiepileptics. In *Prescribing Medicines in Pregnancy*. 4th Edn. 1999:17-9.
2. Vajda F, O'Brien T, Hitchcock, Graham J, Cook M, Lander C, Eadie M. Critical Relationship between

sodium valproate dose and human teratogenicity. Abstract presented at the meeting of the Australian Association of Neurologists, May 2003.

3. Kaaja E, Kaaja R, Hiilesmaa V. Major malformations in offspring of women with epilepsy. *Neurology* 2003, 50:575-9

4. HORMONE REPLACEMENT THERAPY

The statement of the TGA's Expert Advisory Committee on Hormone Replacement Therapy (7 Aug 2003) is published on the TGA's web site at <http://www.tga.gov.au/medianav.htm>. The statement covers the results of the US Women's Health Initiative Study and the UK Million Women Study in relation to the effects of HRT in

increasing the risk of heart attack, stroke, venous thromboembolism, breast cancer and dementia. The Expert Committee recommends that HRT should not be used for long-term disease prevention, but that short-term treatment for symptoms of menopause is still an appropriate treatment option.

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.tga.gov.au/adr/bluecard.pdf> Tear-out blue cards can also be found at the front of the "Schedule of Pharmaceutical Benefits" and the "Australian Medicines Handbook". Reports can also be submitted electronically, by going to the TGA website (<http://www.tga.gov.au>) and clicking on "adverse drug reaction reporting" (at right).

Further information can be obtained 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)

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The Bulletin is also available on the Internet at: <http://www.tga.gov.au/adr/aadrb.htm> (with full references).

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