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AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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

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

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

1. MATERNAL SSRI USE AND NEONATAL EFFECTS

Maternal use of SSRIs during or after pregnancy may result in adverse effects in newborn babies, due to a withdrawal effect following intra-uterine exposure, or a toxic effect from ingestion of an SSRI in breast-milk.

ADRAC has received 26 reports of neonates with symptoms attributed to **withdrawal effects** due to maternal third trimester ingestion of SSRIs (paroxetine 10, sertraline 7, fluoxetine 7, citalopram 2). The table presents the most frequently reported reactions. Other reactions included convulsions, tremor, fever and respiratory disorders (respiratory depression, apnoea, tachypnoea). Two babies had marked extensor posturing with back-arching. The usual day of onset, if reported, was the day of birth, but ranged from 0 to 4 days of age. The symptoms resolved in 2-3 days in most cases.

Table: Frequent neonatal symptoms reported in association with maternal SSRI ingestion

Symptoms	Withdrawal syndrome	Breast-milk transfer
Agitation/Jitteriness	15	4
Poor feeding	7	4
Hypotonia	7	1
Sleepiness/Lethargy	0	3
Gastrointestinal symptoms	3*	3
Total reports	26	13

* In one case the symptoms may have been from breast-milk transfer.

In addition, 13 reports have been received of neonatal adverse effects probably resulting from **breast-milk transfer** of an SSRI (sertraline 9, paroxetine 2, fluoxetine 2). There was some overlap of the symptoms resulting from drug transfer into breast-milk and from drug withdrawal (see table). However, sleepiness was reported only

with breast-milk transfer, and in two cases the baby slept for prolonged periods.

One study found that 12 (22%) of 55 neonates exposed to maternal paroxetine in the third trimester required prolonged hospitalisation for neonatal complications.¹ The most common problem was respiratory distress (9), but two neonates had hypoglycaemia and one each had bradycardia, tachycardia, jaundice and feeding problems. None had underlying pathology and all recovered following a brief period of intensive intervention. In the same study, exposure to paroxetine through breastfeeding caused symptoms in 8 (22%) of 36 infants, with alertness (6), sleepiness (1) and irritability (1).

In adult users, withdrawal effects following paroxetine appear to be more likely than following use of other SSRIs, and hence neonatal withdrawal may be more likely with paroxetine, but this is yet to be demonstrated in comparative studies.² However, paroxetine may have an advantage in breastfeeding since breast-milk transfer is proportionately lower than with fluoxetine or citalopram.³ One study in 11 infants detected sertraline in breast-milk but there were no adverse effects associated with exposure.⁴

It is probable that neonatal withdrawal effects would be minimised by using the lowest effective maternal dose, while breast-milk transfer can be treated by stopping or reducing the dose of SSRI, or by using formula milk.

References:

1. *Arch Pediatric Adolesc Med* 2002;156:1129-32.
2. *Br J Clin Pharmacol* 1996;42:757-63.
3. *Prescriber Update* No.21, June 2001:10-23.
4. *Am J Psychiatry* 1997;154:1255-60.

2. ACE INHIBITOR, DIURETIC AND NSAID: A DANGEROUS COMBINATION

The control of hypertension by ACE inhibitors and diuretics and their beneficial effects in heart failure are antagonised by NSAIDs. Concurrent use of NSAIDs and diuretics is associated with a twofold increase in the risk of hospitalisation for heart failure compared with diuretics alone.¹ Moreover, ACE inhibitors, NSAIDs and diuretics, individually or in combination, are involved in over 50% of cases of iatrogenic acute renal failure reported to ADRAC.

More specifically, the combined use of ACE

inhibitors, diuretics and NSAIDs, termed the "triple whammy", is implicated in a significant number of reports to ADRAC of drug-induced renal failure.² This effect is also seen with COX-2 inhibitors and angiotensin receptor antagonists ("sartans").³ In 2002, 28 of the 129 reports to ADRAC of acute renal failure implicated one of these combinations. Most reports to ADRAC of drug-induced renal failure relate to elderly patients, and this applies as well to renal failure associated with the triple therapy (median age 76 years). The fatality rate for ADRAC cases of renal failure with

the “triple whammy” is 10%.

The use of ACE inhibitors and angiotensin receptor antagonists is increasing, as is the use of these agents in combination products with a diuretic. Episodes of renal failure appear to be precipitated by mild stress (e.g. diarrhoea, dehydration) in a patient taking the triple combination or by the addition of a third drug (usually an NSAID) to the stable use of the other two. ADRAC suspects that the risk of acute renal failure is underestimated and the syndrome underrecognised.

3. SERIOUS GASTROINTESTINAL EFFECTS WITH CELECOXIB AND ROFECOXIB

ADRAC has received a significant number of reports of peptic ulcer (with and without perforation or haemorrhage) and of gastrointestinal (GI) haemorrhage with celecoxib (Celebrex) and rofecoxib (Vioxx)(see table).

Many of the patients with peptic ulcer had known risk factors: they were aged ≥ 60 years (73% for celecoxib vs 97% for rofecoxib), they had a history of peptic ulcer (18% vs 0%) or they were taking other medication which increased their risk (45% vs 81%). However, 16 of those who developed peptic ulcer with celecoxib (none with rofecoxib) were aged < 60 years and had no stated risk factors. In five of these cases the ulcer was diagnosed within 4 weeks of initiation of celecoxib. In nine of the 16 cases, the diagnosis was confirmed by endoscopy, radiology, or during surgery.

Table: Reports of peptic ulcer or GI haemorrhage with celecoxib and rofecoxib

	Celecoxib	Rofecoxib
PBS prescriptions May 2000 to Dec 2002	9.3 million	4.3 million
Total reports	3315	637
Total peptic ulcers	101	31
with risk factors	84	31
without risk factors	16	-
Total GI haemorrhage	250	56
with risk factors	234	51
without risk factors	16	5

Of the reports of GI haemorrhagic events (in the absence of a diagnosis of peptic ulcer), 16 cases with celecoxib and five with rofecoxib involved

4. TRAVACALM – YOUR REPORTS MAKE A DIFFERENCE !

In the second week of January 2003, ADRAC received 5 reports of adverse reactions associated with the use of the over-the-counter travel sickness

ADRAC wishes to remind prescribers that the combination of ACE inhibitors (or angiotensin receptor antagonists), diuretics and NSAIDs (including COX-2 inhibitors) should be avoided if possible, and great care should be taken with ACE inhibitors and NSAIDs in patients with renal impairment.

References:

1. *Arch Intern Med* 1998;158:1108-12.
2. *MJA* 2000; 172:184-5.
3. *MJA* 2000; 173:274 (corr. *MJA* 2000; 173:504).

patients aged < 60 years, with no stated history of GI ulcer and no concurrent use of another NSAID. Those reports mentioning alcohol as a possible factor were excluded. For these 21 cases, time to onset ranged from 1 day to 8 months (median 13 days). In four cases the reaction occurred after a single dose, and in one of these cases the patient’s haematemesis recurred following a single dose a week later.

Initial results from clinical trials indicated a rate of upper GI ulceration with celecoxib or rofecoxib of around 2 per 100 patient-years during 6-9 months’ treatment, significantly lower than with the nonselective NSAIDs.^{1,2} However, while a pivotal study suggested that there may be a long-term advantage of rofecoxib over the nonselective NSAIDs for upper GI ulceration,¹ results after 12 months’ usage of celecoxib indicated similar rates of ulcer complications to diclofenac and ibuprofen.³ The differences between celecoxib and rofecoxib apparent in the ADRAC data may reflect the differences seen in the clinical trials and/or they may relate to differences between the populations of users. Whatever the absolute rates of peptic ulcer may be with celecoxib and rofecoxib, the serious events reported to ADRAC suggest that selective COX-2 inhibitors should be treated with similar caution to other NSAIDs.

References:

1. *N Engl J Med* 2000;343:1520-8.
2. *JAMA* 2000;284:1247-55.
3. *BMJ* 2002;324:1287-8.

tablet, Travacalm Original (containing hyoscine hydrobromide 0.2mg, dimenhydrinate 50mg, caffeine 20mg). The reports described combinat-

-ions of hallucinations, confusion, ataxia, and blurred vision. It was recognised that hyoscine poisoning would account for this pattern of reactions.

After discussions with the owner of the registration licence, the implicated batches of Travacalm Original were urgently recalled on 21 January. Concurrent laboratory testing at the TGA revealed that the hyoscine content of the tablets ranged from none to seven times the dose stated on the label.

ADRAC had not received any reports for Travacalm in the preceding four years, but subsequently received 124 reports by the end of May 2003. In some cases the adverse reactions

lasted up to several days after a single dose, and 24 patients were hospitalised.

The responsible batches of Travacalm were manufactured by Pan Pharmaceuticals, Australia's largest manufacturer of complementary and over-the-counter medicines. The Travacalm reports received in January 2003 and the subsequent evaluation of the cause triggered an investigation of the entire operations of the company by the TGA. Widespread inadequacies in manufacturing processes were identified, and as a result all products (over 1500 medicines) made by Pan over the past 12 months were recalled, and the company's manufacturing licence was suspended for 6 months.

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