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AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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- ☆ Tramadol and serotonin syndrome
- ☆ Raloxifene and thromboembolic events
- ☆ Your reports at work — drug safety in Australia

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

Bupropion (Zyban)
Celecoxib (Celebrex)
Galantamine (Reminyl)
Gatifloxacin (Tequin)
Leflunomide (Arava)
Lercanidipine (Zanidip)
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. TRAMADOL AND SEROTONIN SYNDROME

Tramadol hydrochloride (Tramal) is a centrally acting analgesic, which although chemically unrelated to the opioids, binds to and stimulates opioid receptors. In addition, it inhibits the re-uptake of noradrenaline and serotonin. Since its marketing in Australia in late 1998, ADRAC has received 171 reports of suspected adverse reactions. Six of these reports describe the serotonin syndrome.

The commonly accepted diagnostic criteria for the serotonin syndrome were developed by Sternbach. The diagnosis requires the development of at least three of ten clinical features (see box) coincident with the addition of a new serotonergic agent to an established medication regimen or an increase in the dose of a serotonergic agent.[1]

Clinical Features of Serotonin Syndrome
- mental status changes (confusion, hypomania)
- agitation
- myoclonus
- hyperreflexia
- sweating
- shivering
- tremor
- diarrhoea
- incoordination
- fever

Four reports to ADRAC described the use of tramadol in patients who were taking antidepressants known to increase the concentration of brain serotonin. These included the selective serotonin reuptake inhibitors sertraline and citalopram, the selective monoamine oxidase inhibitor moclobemide (which releases serotonin), and a combination of the tricyclic antidepressants amitriptyline and clomipramine (serotonin reuptake inhibitors). Another report involved a patient who was taking St John's wort which is also believed to increase serotonin concentrations. The other report described the use of a relatively high daily dose (400 mg) of tramadol in an elderly male. Four of the six patients recovered after treatment while one patient required intensive care admission and had not recovered at the time the report was submitted. The outcome is unknown in another patient.

ADRAC advises that caution should be taken with the use of high doses of tramadol and with tramadol in patients taking medications known to increase brain concentrations of serotonin.

Reference:

1. Sternbach H. The serotonin syndrome. *Am J Psychiatry 1991; 148: 705-13.*

2. RALOXIFENE AND THROMBOEMBOLIC EVENTS

Raloxifene (Evista) has anti-oestrogenic effects on the breast and uterus and pro-oestrogenic effects on bone and clotting factors and has been referred to as a selective oestrogen receptor modulator. It has been marketed in Australia since 1999 and is subsidised by the PBS for treatment of established post-menopausal osteoporosis. In that time, there have been approximately 300,000 PBS prescriptions dispensed and ADRAC has received 199 reports of suspected adverse reactions with raloxifene the only suspected drug in 185 cases. Many of the commonly reported adverse effects are mild in nature and are described in the product information. These include nausea, hot flushes, headache, rashes, abdominal pain, blurred vision, pruritus and breast pain. Of most importance are the reports of deep vein thrombosis (DVT) and cerebrovascular disorders. Raloxifene is associated with an increased risk for venous thromboembolic events (VTEs) that is said to be similar to the risk associated with the use of hormone replacement therapy. The risk/benefit balance should be considered in patients with any known risk factors for VTEs.

ADRAC has received 7 reports of pulmonary embolism and 22 reports of DVT in association with raloxifene. As would be expected from the indications for the drug, all patients were females aged from 55 to 89 (median: 71) years, taking the drug for osteoporosis. The reactions occurred from a few days to 8 months after the drug was started with most cases having an onset after several months of therapy. The outcome was fatal in one patient. In addition to these cases, there were also 7 reports of stroke and 3 reports of transient ischaemic attacks.

The women described in the ADRAC reports were at an age at which such events may be more common and most of the reports did not describe any additional risk factors that may have been

present. Prescribers should be aware of the increased risk of VTEs with raloxifene, and as recommended in the product information, discontinue the drug in the event of a prolonged period of immobilisation. Prescribers should also be aware of the importance of the patient's past history, family history and other risk factors for VTEs. Raloxifene is contraindicated in patients with a past history of VTE. ADRAC recommends that patients be specifically advised of the increased risk of VTEs with all oestrogenic compounds, including raloxifene.

3. YOUR REPORTS AT WORK – DRUG SAFETY IN AUSTRALIA

…Some recent examples

Over the past year, ADRAC has seen three examples of the alertness of Australian health professionals who report adverse reactions to ADRAC. These reports can result in ADRAC recommending action to the TGA and publishing information in the Australian Adverse Drug Reactions Bulletin. The Bulletin is distributed to 58,000 Australian readers and to many other countries, which means that Australian reporters are directly contributing to worldwide drug safety.

Celecoxib (Celebrex) was marketed towards the end of 1999 with a great deal of media attention. It quickly generated high usage and health professionals forwarded a correspondingly high number of reports to ADRAC. ADRAC now has almost 3,000 reports in association with the drug which has allowed the establishment of a very detailed ADR profile for celecoxib. Continued reporting has confirmed the Committee's initial impression that the profile of the drug is generally similar to other NSAIDs.[1] There have now been a number of reports of gastrointestinal bleeding but they represent a lower proportion of reports than with traditional NSAIDs. Large-scale trials such as the CLASS study have confirmed that such events occur less commonly than with conventional NSAIDs.[2] Reports to ADRAC have resulted in the publication of articles concerning celecoxib's interaction with warfarin and its association with diuretics and ACE inhibitors (the "triple whammy") causing renal failure.[3,4]

The second COX-2 inhibitor **rofecoxib (Vioxx)**, was marketed more recently and has also generated a significant number of reports. A detailed ADR profile of this drug is also being developed.

Bupropion (Zyban SR) was also marketed with a great deal of media attention and has been widely utilised in a large number of patients. In the 7 months since it was listed on the PBS in February 2001, there have been 315,000 prescriptions dispensed, and ADRAC has received over 1,000 reports, again developing a comprehensive ADR profile for the drug. An article was published in the May issue of the Bulletin and has been updated on the TGA website a number of times.[5,6] As a result of reports to ADRAC, a number of changes to the product information have been recommended.

An article published in the February 2001 Bulletin alerted prescribers to the occurrence of 17 Australian cases of rhabdomyolysis in association with **cerivastatin (Lipobay)**, particularly with the concomitant use of gemfibrozil.[7] Subsequently ADRAC made a number of recommendations to the TGA including the need for a "Dear Dr" letter, a boxed warning and an additional study. Cerivastatin has since been withdrawn worldwide by the sponsor. A major driving force for the investigation of this problem in Australia was the ADRAC reports.

These few recent examples demonstrate the importance of reports to ADRAC and how they contribute to drug safety in Australia and across the globe.

… what happens to your reports?

- All reports are reviewed by a health professional within 3 working days of receipt.
- All reports are acknowledged. At this stage it is only by the use of a small acknowledgment slip but we are working on providing more individualised feedback.
- All reports are entered into the database within 2 weeks.
- Most reports (new drugs, interactions, serious and severe reactions) are reviewed by ADRAC at one of its 8 meetings each year.
- Issues of interest are published in the Bulletin or elsewhere and recommendations can be made to the

TGA for regulatory action such as changes to the PI, changes to indications, etc.

- Summarised, anonymous output from the database is freely available. Summaries for particular medicines or specified reactions can be provided. Information can be obtained by calling 1800 044114 or emailing to adrac@health.gov.au.
- Comprehensive de-identified details from Australian reports are forwarded to the WHO database at the Uppsala Monitoring Centre in Sweden. This database now holds almost 3 million case reports and provides a valuable resource for regulatory authorities and sponsors all over the world.

… what should you report?

Information on what to report is printed on the back page of each Bulletin. 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 or vaccines 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

The reporting of all **suspected** adverse reactions to drugs, vaccines and other medicinal substances, including herbal, traditional or alternative remedies is welcomed. The reporting of seemingly insignificant or common adverse reactions may highlight a widespread prescribing problem. We are particularly interested in the reporting of problems not previously described and prefer you to report directly to us, not through an intermediary.

Potential reporters are reminded that the minimum requirements for a valid report are an identifiable medicine, an identifiable reaction, an identifiable patient (initials, age, gender) and an identifiable reporter. For medicines, trade names are preferred (with AUSTL or AUSTR numbers if possible).

Remember, you do not have to be certain, just suspicious!

… how to report

Reports of suspected adverse drug reactions are best made by using a prepaid reporting form ("blue card") which accompanies this Bulletin or is available from the Adverse Drug Reactions Unit of the TGA on 02-62328386 or from: http://www.health.gov.au/tga/docs/html/adr.htm.

Tear-out blue cards can also be found in the "Schedule of Pharmaceutical Benefits", and in the "Australian Medicines Handbook". It is anticipated that by early in 2002, it will be possible to submit a report form via the website and that later in 2002, the provision for reporting to ADRAC will be built into prescribers' desktop software.

References:

1. ADRAC. Celecoxib: early Australian reporting experience. *Aust Adv Drug React Bull 2000; 19: 6-7.*
2. Silverstein FE, Faich G, Goldstein JL et al. Gastro-intestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. JAMA 2000; 284: 1247-55.
3. ADRAC. Interaction of celecoxib and warfarin. *Aust Adv Drug React Bull 2001; 20: 2.*
4. Boyd IW, Mathew TH, Thomas MC. COX-2 inhibitors and renal failure: the triple whammy revisited. *MJA 2000; 173: 274.*
5. ADRAC. Update on bupropion (Zyban SR). *Aust Adv Drug React Bull 2001; 20: 6-7.*
6. http://www.health.gov.au/tga/docs/html/zyban.htm.
7. ADRAC. Cerivastatin and rhabdomyolysis – avoid gemfibrozil. *Aust Adv Drug React Bull 2001; 20: 3.*

The Bulletin is also available on the Internet at:
http://www.health.gov.au/tga/docs/html/aadrbltn/aadrbidx.htm

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