AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN
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☆ Tramadol – four years’ experience
☆ Minocycline and not so benign intracranial hypertension
☆ Acute neuropsychiatric events with celecoxib and rofecoxib
☆ Linezolid and peripheral neuropathy
☆ Kava

Please report all suspected reactions to these Drugs of Current Interest

Esomeprazole (Nexium)  Oxcarbazepine (Trileptal)
Fondaparinux (Arixtra)  Pioglitazone (Actos)
Galantamine (Reminyl)  Reboxetine (Edronax)
Gatifloxacin (Tequin)  Risedronate (Actonel)
Lercanidipine (Zanidip)  Rivastigmine (Exelon)
Meloxicam (Mobic)  Rosiglitazone (Avandia)
Mirtazapine (Avanza, Mirtazon, Remeron)  Sibutramine (Reductil)
Moxifloxacin (Avelox)  Tegaserod (Zelmac)
1. TRAMADOL – FOUR YEARS’ EXPERIENCE

Tramadol (Tramal) is a centrally acting analgesic which has been available in Australia for four years. Although chemically unrelated to the opiates, it stimulates opioid receptors and inhibits noradrenaline and serotonin uptake.

ADRAC has received 354 reports in association with tramadol. The most common reactions include nausea, vomiting, sweating, dizziness, rash, tremor and headache. The more serious adverse reactions reported are presented in Table 1.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>No. of reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion</td>
<td>36</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>30</td>
</tr>
<tr>
<td>Convulsions</td>
<td>26</td>
</tr>
<tr>
<td>Serotonin syndrome</td>
<td>20</td>
</tr>
<tr>
<td>Increase in blood pressure</td>
<td>14</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>12</td>
</tr>
<tr>
<td>Hepatic reactions</td>
<td>10</td>
</tr>
<tr>
<td>Warfarin interaction</td>
<td>5</td>
</tr>
</tbody>
</table>

For the cases of convulsions, the median time to onset was 2 (range 1-19) days. Tramadol was the only suspected drug in 11 cases, but in 14 other cases the patient was taking additional drugs which may lower the seizure threshold, including propofol, bupropion, hydrocortisone, morphine, and tricyclic anti-depressants. One patient had a history of epilepsy, and was also taking carbamazepine and phenytoin.

Tramadol may cause serotonin syndrome, particularly when it is used at high doses or in combination with other agents increasing serotonin levels. In 16 of the 20 cases, the patient was taking potentially interacting medicines including moclobemide, SSRIs, tricyclic antidepressants, sibutramine and St John’s wort.

Increases in hepatic enzymes were reported in 10 cases. One patient developed hepatic failure and died. All times to onset were short (range 1-19 days; median 9 days).

Tramadol may interact with warfarin to decrease prothrombin activity, although the mechanism is unknown. ADRAC has received five reports of this interaction. Monitoring of INR should be considered when tramadol is started in patients taking warfarin.

Although tramadol acts on opioid receptors, dependence and abuse appear to be rare. ADRAC has, however, received 11 reports of withdrawal symptoms with tramadol.

The use of tramadol has increased rapidly, with PBS dispensings of oral formulations rising from 23,000 in 2000 to 580,000 in 2001 and over 1,100,000 in 2002. Prescribers should be alert to the more serious adverse reactions, especially those of a neuropsychiatric nature.

References:
3. FDA Committee. FDC (‘Pink Sheets’) Prescription Pharmaceuticals and Biotechnology 1998;60(18):4-5

2. MINOCYCLINE AND NOT SO BENIGN INTRACRANIAL HYPERTENSION

“Benign” intracranial hypertension, also known as pseudotumour cerebri, involves a persistent rise in cerebrospinal fluid pressure. It is characterised by headache, nausea, vomiting and papilloedema with occasional sixth-nerve palsy. It is sometimes associated with drug therapy and tetracyclines are a well-recognised cause. Of the 76 cases reported to ADRAC over the past 30 years, 32 have been associated with minocycline.

All of these 32 patients were young, ranging in age from 12 to 30 (median: 16) years, and almost all were taking long-term minocycline for acne. Most (28) were female. The time to onset ranged from two weeks to 18 months with a median of approximately 2 months. There was also one case in which the patient developed the condition one day after she was switched from doxycycline to minocycline. The majority of the cases reported to ADRAC had recovered after minocycline was withdrawn but recovery was often prolonged, taking from 2 to 12 weeks in most cases. In those cases where treatment was reported, lumbar puncture, acetazolamide and steroids were used. There were also cases where the patient had not recovered at the time the report was submitted. Some of the reports described the use of multiple lumbar punctures, one patient required “prolonged hospitalisation”, and one required a lumbo-
peritoneal shunt. In one patient, lower nasal quadrantanopia persisted after 6 months.¹

ADRAc has previously drawn attention to this association but with 3 cases reported in the past 6 months, a reminder is timely.² The possibility of drug-induced benign intracranial hypertension should be considered in any young patient presenting with persistent unexplained headache, and women taking minocycline appear to be at particular risk.

References:

3. ACUTE NEUROPSYCHIATRIC EVENTS WITH CELECOXIB AND ROFECOXIB

Acute neuropsychiatric reactions are known to occur with the non-selective NSAIDs, and are mentioned in the product information for these medicines. It appears that they may also be a class effect for the selective COX-2 inhibitors, including celecoxib (Celebrex) and rofecoxib (Vioxx).

| Table 2: More commonly reported acute neuropsychiatric reactions (Table gives number of reports of each event) |
|----------------------------------|---------------|---------------|
| Adverse event                    | Celecoxib     | Rofecoxib     |
| Confusion                        | 23            | 16            |
| Somnolence                       | 22            | 6             |
| Insomnia                         | 21            | 6             |
| Hallucination                     | 12            | 11            |
| Depression                       | 18            | 3             |
| Abnormal thinking/               |               |               |
| impaired concentration           | 15            | 4             |
| Agitation                        | 14            | 3             |
| Abnormal dreaming/               |               |               |
| nightmares                       | 10            | 3             |
| Amnesia                          | 10            | 1             |

ADRAC has received 142 (5% of total) reports of acute neuropsychiatric reactions associated with celecoxib and 49 (8%) with rofecoxib. These report numbers have been calculated after exclusion of psychiatric events which might have been associated with other events such as a hypersensitivity reaction or hyponatraemia.

As Table 2 indicates, the most common events with celecoxib are confusion, somnolence and insomnia. As a proportion of the total reports, hallucination has been reported more commonly with rofecoxib than with celecoxib.

In many cases the onset of the reaction was dramatic. The event occurred within 24 hours of the first dose in 36 cases with celecoxib and in 14 cases with rofecoxib. In 12 and 4 cases, respectively, the reaction recurred with re-exposure to the drug. In one report marked restlessness was said to occur an hour and a half after taking celecoxib on three occasions, and in another vivid dreams developed on the nights that celecoxib was taken.

Prescribers should consider warning patients of the possibility of an acute neuropsychiatric reaction when celecoxib or rofecoxib are prescribed.

4. LINEZOLID AND PERIPHERAL NEUROPATHY

Linezolid (Zyvox) is a new antibiotic indicated for the treatment of suspected or proven infections due to organisms resistant to multiple classes of antibiotics. ADRAC has received 4 reports of peripheral neuropathy in patients who had taken linezolid for 6-9 months (1 case published¹). In no case had the peripheral neuropathy resolved at the time of reporting. In the clinical trials which supported registration exposure was for no longer than 28 days. The risk of persistent peripheral neuropathy should be borne in mind when considering use beyond 28 days.

Reference:

5. KAVA

Prescribers will be aware that the Therapeutic Goods Administration (TGA) initiated a recall of medicinal products containing kava because of concerns about hepatotoxicity. Advice from the TGA about the toxicity and recall can be accessed at www.health.gov.au/tga/cm/cm.htm#kava
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

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 (see below).

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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ONLINE REPORTING


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