



Prepared by the ADVERSE DRUG REACTIONS ADVISORY COMMITTEE (ADRAC). ADRAC is Dr Tim Mathew (Chair), Dr Paul Desmond, Dr David Isaacs, Dr Cecilie Lander, Professor Gillian Shenfield, Dr Dana Wainwright, Professor Lindon Wing.

AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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- ☆ Tendinitis and tendon rupture with fluoroquinolones
 - ☆ Olanzapine: neutropenia, convulsions and NMS
 - ☆ A gut feeling for alendronate
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Please report **all** suspected reactions to these
Drugs of Current Interest

Candesartan (Atacand)
Carvedilol (Dilatrend, Kredex)
Clopidogrel (Iscover, Plavix)
Donepezil (Aricept)
Gelatin succinylated (Gelofusine)
Montelukast (Singulair)
Naltrexone (ReVia)
Naratriptan (Naramig)
Nefazodone (Serzone)

Raloxifene (Evista)
Sildenafil (Viagra)
Tiludronate (Skelid)
Tramadol (Tramal)
Trovaflaxacin (Trovan)
Zafirlukast (Accolate)
Zanamavir (Relenza)
Zolmitriptan (Zomig)

(see back page for more details)

1. TENDINITIS AND TENDON RUPTURE WITH FLUOROQUINOLONES

ADRAC first reported tendinitis in association with the fluoroquinolone antibiotics in 1997.¹ The Committee has continued to monitor this adverse reaction, and has now received 60 reports of tendinitis, tenosynovitis and/or tendon rupture in association with these drugs. Most involved ciprofloxacin (55), but there were also reports with norfloxacin (4) and enoxacin (1).

Forty five reports described tendinitis alone, one report described tenosynovitis, and 14 reports documented tendon tear or rupture. Fifty five of the 60 reports specified the Achilles tendon, including 20 which described bilateral Achilles tendon damage. All 14 reports of tendon rupture involved the Achilles tendon. The 58 patients ranged in age from 38 to 91 (median 69) years, with no significant difference between those with tendinitis and those with tendon rupture.

The daily doses of ciprofloxacin ranged from 500 mg to 2250 mg, with 46% of patients taking 1500 mg and 46% of patients taking 1000 mg daily. For those who developed tendon rupture, 57% were taking 1500 mg daily. Time to onset varied from within 24

hours after the drug was commenced to 3 months after starting but the majority of cases of tendinitis occurred within the first week. Time to rupture was longer with a median time of 2-3 weeks. Known risk factors for these reactions include old age, renal dysfunction and concomitant corticosteroid therapy.² In the ADRAC cases, 29 reports documented concomitant corticosteroid use, and in 21 of the other 31 reports, the patients were aged 69 years or older. In the reports of tendon rupture, 12 of the 14 described either concomitant steroid use (9 cases) or old age (9 cases).

Prescribers are reminded that tendinitis and tendon rupture can be adverse reactions from the fluoroquinolones, particularly ciprofloxacin. The fluoroquinolone should be withdrawn immediately when symptoms of tendinitis appear, in order to attempt to reduce the risk of tendon rupture.

References:

1. ADRAC. The Achilles heel of fluoroquinolones. *Aust Adv Drug React Bull* 1997; 16: 7.
2. Szarfman A, Chen M, Blum MD, Pierfitte C, Gillet P, Royer RJ. More on fluoroquinolone antibiotics and tendon rupture. *N Engl J Med* 1995; 332: 193.

2. OLANZAPINE: NEUTROPENIA, CONVULSIONS AND NMS

Olanzapine (Zyprexa) is an antipsychotic agent which has been marketed in Australia since mid 1997. Since that time, ADRAC has received 327 reports of suspected adverse reactions with the drug. The product information for olanzapine indicates that the two most frequent adverse reactions in clinical trials were somnolence and weight gain which both occurred in more than 10% of patients. Reports to ADRAC show a similar trend with weight gain (29 reports) and somnolence (25) as the two most commonly reported reactions. More seriously, however, ADRAC has received reports of white cell disorders, convulsions and neuroleptic malignant syndrome.

White cell disorders are a known effect of the related drug, clozapine, and ADRAC has

received 18 reports of neutropenia in association with olanzapine. There have been no reports of agranulocytosis. Ages of the patients ranged from 23 to 67 (median: 45) years and daily doses of olanzapine ranged from 5 - 30 (median: 10) mg in the 16 patients for whom this information was available. At the time of reporting, 5 patients had recovered, 5 had not, and the outcome was unknown for the other 8. Laboratory results were available for 14 patients. These showed nadir neutrophil counts ranging from 0.8 to 1.9 (median: 1.4) cells x 10⁹/L (reference range: 2.0 - 7.5 cells x 10⁹/L).

There have been 15 cases of convulsions reported in slightly older patients ranging from 14 to 83 (median: 53) years. Olanzapine was taken in daily doses ranging from 2.5 to 15

(median: 10) mg and it was the only drug suspected in 12 cases. The reaction was variously described as myoclonus (3 reports), epileptic seizures (3), tonic-clonic seizures (2), seizure (2), clonus (2), night seizures, grand mal or a petit mal convulsion. Ten of the patients had pre-disposing factors such as a past history of head trauma, epilepsy or renal impairment.

Also of interest are the 7 reports of neuroleptic malignant syndrome (NMS). These involved 4 males and 2 females (one not stated) ranging

in age from 23 to 83 (median: 65) years. Doses ranged from 5 mg to 20 mg and the onset varied from 2 days to 2 months after the drug was started. Two of the patients had a past history of NMS with other drugs. Six of the 7 patients recovered including one who developed the syndrome on rechallenge with olanzapine.

Prescribers should be aware that white cell disorders, seizures and NMS can all occur in association with olanzapine.

3. A GUT FEELING FOR ALENDRONATE

Sodium alendronate (Fosamax) was marketed in Australia in late 1996 and since that time ADRAC has received 331 reports of suspected adverse drug reactions. Alendronate was the only suspected drug in 91% of those reports. The reports are dominated by gastrointestinal (GI) disorders which occurred in 54% of the cases. The other major effect is on the musculoskeletal system which was mentioned in 18% of the reports.

The most important effects on the GI tract are oesophagitis and oesophageal ulceration. These were reported by ADRAC soon after the drug was marketed.¹ The Committee has now received 52 reports of oesophagitis, oesophageal ulceration or oesophageal stricture. This was confirmed endoscopically in 26 of the cases. The product information for Fosamax indicates that oesophageal ulceration occurred in 1.5% of patients in clinical studies and a similar figure has been obtained from prescription-event monitoring.² Other GI reactions reported to ADRAC include dyspepsia (44 reports), nausea (43), abdominal pain (37) and dysphagia (23). It is possible that some of these symptoms may also have indicated oesophageal damage. There have also been 6 reports of gastric ulceration and 2 reports of duodenal ulceration. In the 180 reports that involved the GI tract, the ages of the patients ranged from 18 to 91 (median: 71) years and all except 5 patients were aged 50 or more. 87% were female. The majority of cases

were reported with a dosage of 10 mg daily with the remainder taking 40 mg daily. Time to onset varied from the same day that the drug was started to more than a year after commencement. However, 36% occurred in the first week. Only 64% were reported as recovered at the time the report was submitted and 20 reactions recurred on rechallenge.

There have also been 61 reports of musculoskeletal problems with 35 cases of muscle pain, 29 cases of joint pain and 6 cases of bone pain. In ten of these reports, muscle and joint pain occurred together. Patient characteristics were similar to those experiencing GI problems, as were dosage, time to onset, and recovery rates. The reaction recurred on rechallenge in 8 patients.

Prescribers are reminded that gastrointestinal and musculoskeletal disorders are significant adverse effects of alendronate. The reports to ADRAC have included a small number of reports where oesophageal damage has occurred despite adherence to dosage instructions, but it remains important for patients to follow these instructions closely.

References:

1. ADRAC. Alendronate oesophagitis – are precautions effective? *Aust Adv Drug React Bull* 1997; 16: 10.
2. Mackay F, Wilton LV, Pearce G, Freemantle S, Mann RD. Alendronate and oesophageal reactions (abstract). *Pharmacoepidemiol Drug Safety* 1997; 6, Suppl 2: S20.

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 Section

 02-62328386, 02-62328387, 02-62328388, or from the website: www.health.gov.au/tga/adr.pdf

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

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

Secretary:  02-62328381 Executive Secretary:  02-62328382

Fax: 02-62328392

(Problems with therapeutic devices should be reported on 1800-809361)

The Bulletin can also be found on the Internet at the TGA website: www.health.gov.au/tga

Drugs of Current Interest

The Committee maintains a list of drugs for which reporting of all reactions - mild or serious, previously described or unexpected - is encouraged. Most of the drugs on the list have been registered in Australia recently and intensified reporting is helpful in showing whether post-marketing experience reflects the clinical trial experience on which registration was based. The Committee updates the list regularly.

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