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AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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- ☆ Nicorandil-associated ulceration
- ☆ Withdrawal of lumiracoxib in Australia
- ☆ Topiramate and other drugs causing glaucoma

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

Atomoxetine (Strattera)
Ezetimibe and simvastatin (Vytorin)
Moxonidine (Physiotens)
Pregabalin (Lyrica)
Ranibizumab (Lucentis)
Rosuvastatin (Crestor or Viacor)
Strontium ranelate (Protos)
Varenicline (Champix)
Ziprasidone (Zeldox)

1. Nicorandil-associated ulceration

Nicorandil (Ikorel) is a synthetic nicotine derivative, which causes arterial and venous dilatation. It is indicated for the treatment of chronic stable angina pectoris at a dose of 10-20 mg daily.

Nicorandil-associated ulceration was initially reported in the oral mucosa.[1] Subsequently, ulceration has been reported at other sites, including anal, perianal, vulvar, perivulvar, gastrointestinal and parastomal tissues, and various cutaneous sites, including the lower anterior leg, natal cleft, umbilicus and areas affected by flexural psoriasis; ulcers may occur at multiple sites.[2,3] The reaction occurs rarely, appears to be dose-related and the time to ulcer onset may be up to months after starting nicorandil. The ulcers are persistent, deep and 'punched out' in appearance, with non-specific inflammatory histology. Their pathogenesis remains unclear.

Unless nicorandil is recognised as a potential cause and the drug withdrawn, the ulcers are likely to persist despite other treatment. Conservative ulcer management is ineffective and surgery may exacerbate the tissue damage. Typically any discomfort resolves quickly after nicorandil is withdrawn, although healing may take considerably longer.

Seven of 51 reports received by the TGA for nicorandil describe ulceration. Patients were 57-88 years old, and six were female. Where stated, the daily dose was 20 mg (n=3) or 40 mg (n=2) and the time to onset of ulceration after starting nicorandil ranged from one day to many months. Six of the seven reports described tongue or mouth ulcers. One report described an 86 year old woman with an 18 month history of indurated perianal ulcer which failed to respond to conventional treatment. Healing began only after withdrawal of nicorandil, with complete resolution over several weeks.

In cases of recalcitrant ulceration, we suggest obtaining a full drug history, while considering other inflammatory or neoplastic causes. Failure to recognise nicorandil-induced ulceration can lead to substantial morbidity, inappropriate investigation and treatment, and unnecessary surgery.

References
1. Reichert S et al. Major aphthous stomatitis induced by nicorandil. Eur J Dermatol 1997; 7: 132-3.
2. Watson A et al. Nicorandil induced anal ulceration. Lancet 2002; 360: 546-7.
3. McKenna DJ et al. Nicorandil-induced leg ulceration. Br J Dermatol 2007; 156: 394-6.

2. Withdrawal of lumiracoxib in Australia

Lumiracoxib is a selective COX-2 inhibitor, which was registered in Australia in 2004 for the symptomatic relief of osteoarthritis (at 200 mg daily) and for the treatment of acute pain and pain due to primary dysmenorrhoea (400 mg daily for up to five days). Lumiracoxib was not widely used in Australia until it was included on the Pharmaceutical Benefits Schedule in July 2006.

Following the evaluation of trial data showing that the efficacy of a 100 mg daily dose was comparable to that of the 200 mg dose, a 100 mg tablet was registered for use in Australia in June 2007 for the relief of symptoms of osteoarthritis. In the 12 month period up to the end of July 2007, 567,903 prescriptions for lumiracoxib were dispensed in Australia.

In March 2007, the first Australian report of serious hepatotoxicity associated with the use of lumiracoxib was received by the TGA. Concerns about this case stimulated a priority review of the general safety profile of lumiracoxib, with a focus on hepatotoxicity.

By the time of the ADRAC meeting on 10 August, the TGA had received eight reports of serious liver injury associated with the use of lumiracoxib. There were also three reports of minor increases in liver enzymes.

All eight reports of serious liver injury involved women, aged 52-75, who had been taking lumiracoxib 200-400 mg daily for between six weeks and seven months (except in one case where the duration of use was 18 months and the dose was not stated). There were five reports of hepatic failure, including two fatalities and two liver transplants, and an additional three reports of severe jaundice or acute hepatitis without liver failure.

ADRAC was informed of a further three overseas reports of hepatic failure with lumiracoxib, all from South America. These included two women who developed hepatic failure after five days and 15 days of lumiracoxib 400 mg daily, and a 51 year old female who developed hepatic failure requiring transplantation after taking lumiracoxib 100 mg daily for four months. ADRAC also reviewed data provided by the sponsor of lumiracoxib regarding liver abnormalities seen in the clinical trial program.

At the August meeting, it was known that a 100 mg dose of lumiracoxib had been registered recently in Australia. However, the Committee was concerned there was insufficient evidence for an adequate margin of safety with the 100 mg daily dose because of the possibility that the hepatotoxicity of lumiracoxib may be idiosyncratic; that lower doses may be hepatotoxic in specific populations such as the elderly, low-weight individuals, or those with other underlying disease; or that the 100 mg daily dose may be exceeded by patients seeking more pain relief. ADRAC also considered that the apparent rate of severe liver injury with lumiracoxib appeared greater than for other marketed non-steroidal anti-inflammatory drugs.

After the above review and advice from ADRAC that the risks of lumiracoxib outweighed its benefits, the TGA acted immediately to cancel the registration of all forms of lumiracoxib in Australia, on the grounds that failure to cancel the registration would create an imminent risk of death, serious illness or serious injury. Following the cancellation, the TGA advised that all patients should stop taking lumiracoxib immediately, and should be assessed by their doctor for any evidence of liver damage (see the TGA website at www.tga.gov.au/alerts/prexige.htm)

3. Topiramate and glaucoma

Topiramate is an antiepileptic indicated for either monotherapy or add-on therapy in adults and in children aged two years and over; and for the prophylaxis of migraine in adults. It has an authority required PBS listing for the treatment of epilepsy, and was recently PBS-listed as a third-line agent for the prophylaxis of migraine.

Topiramate has been rarely associated with the development of angle-closure glaucoma. To date, TGA has received 11 reports of glaucoma associated with the use of topiramate out of 175 total reports for the drug, involving nine females and two males with a median age of 36 (range, 22-47) years. Time to onset was within the first month of treatment in four reports, within the second month in two reports, and not stated in five reports. Five patients had recovered at the time of reporting, three had not yet recovered, and recovery status was unknown in the other three.

Although all of these cases have involved adults, a literature report has described bilateral angle-closure glaucoma presenting as headache, nausea, and fatigue in a five year old girl 10 days after starting topiramate.[1]

A published review of reports of ocular reactions to topiramate included 86 cases of acute glaucoma, 83 of which were bilateral.[2] In this series, time to onset was one to 49 days after starting topiramate, with 85% of cases occurring in the first two weeks of treatment. Permanent vision loss was described in seven reports. Topiramate was also associated with a number of other ocular adverse effects, including acute myopia, suprachoroidal effusions, periorbital oedema, and scleritis.[2]

A number of drugs have been associated with angle-closure glaucoma. The drugs most-commonly reported to TGA are topiramate (11 reports), sertraline (10), tropicamide (7), venlafaxine (6) and ipratropium bromide (5).

Management of topiramate-induced glaucoma involves immediate cessation of topiramate and urgent medical treatment of the glaucoma as required. A number of mechanisms have been proposed for this reaction, but because pupillary block is not involved, pilocarpine and iridotomy are generally ineffective. Permanent vision loss can occur if the condition is not managed appropriately.[3]

Of note is that migraine itself may cause eye pain and it is important that non-migraine causes should be considered in patients treated with topiramate for migraine, who present with eye pain.

(*References over page*)

References

1. Lin J, Fosnot J and Edmond J. Bilateral angle closure glaucoma in a child receiving oral topiramate. *Journal of American Association for Pediatric Ophthalmology and Strabismus* [JAAPOS] 2003; 7: 66-68.
2. Fraunfelder FW *et al.* Topiramate-associated acute, bilateral, secondary acute-angle closure glaucoma. *Ophthalmology* 2004 Jan;111(1):109-11.
3. Levy *et al*. Topiramate-induced bilateral angle-closure glaucoma. *Can J Ophthalmol* 2006; 41: 221-225.

WHAT TO REPORT? (you do not need to be certain, just suspicious!)

ADRAC encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, OTC medicines, herbal, traditional or alternative remedies. ADRAC particularly requests reports of:

*ALL suspected reactions to **new drugs** (see **drugs of current interest,** front page**)**
*ALL suspected drug interactions
*Suspected reactions causing
- •Death
- •Admission to hospital or prolongation of hospitalisation
- •Increased investigations or treatment
- •Birth defects

For blue cards
Reports of suspected adverse drug reactions are best made by using a prepaid reporting form ("blue card") which is available from the website: <http://www.tga.gov.au/adr/bluecard.pdf > or from the Adverse Drug Reactions Unit ☎ 02-6232-8744;

Reports can also be submitted electronically, by going to the TGA website <http://www.tga.gov.au> and clicking on “report problems” on the left.

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The Bulletin is also available on the Internet at: **<http://www.tga.gov.au/adr/aadrb.htm>**

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