AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

Volume 25, Number 6, December 2006

- Drug induced pancreatitis
- Leflunomide and interstitial lung disease
- Tumour necrosis factor alpha inhibitors
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Please report all suspected reactions to these Drugs of Current Interest

Atomoxetine (Strattera)  
Ezetimibe/Simvastatin (Vytorin)  
Fenofibrate (Lipidil)  
Iron sucrose (Venofer)  
Lumiracoxib (Prexige)  
Moxonidine (Physiotens)  
Pregabalin (Lyrica)  
Teriparatide (Fortéo)
1. Drug induced pancreatitis

Gallstones and alcohol are the two most common causes of pancreatitis, but medicines are estimated to account for about 2 to 5% of cases. To date, ADRAC has received 414 such reports, implicating 695 medicines. Time to onset varied from the first day of use to many months and, in some cases, several years. Specific information about alcohol use was not provided in most of the reports. Fatal outcomes were documented in 10 of the 414 reports in this series.

Reports of pancreatitis are most frequent with azathioprine, didanosine and valproate. The drug groups more commonly implicated include antiviral agents, hypolipidaemic agents, atypical antipsychotic medicines, corticosteroids and other immunosuppressants, COX-2 inhibitors, NSAIDs, aminosalicylates (mesalazine, sulfasalazine), angiotensin II receptor antagonists, ACE inhibitors and H₂-receptor antagonists. Together, these groups (comprising slightly less than 22% of the entire ADRAC database) account for more than 60% of the reports of pancreatitis. A list of individual drugs more commonly reported is shown in the Table. Pancreatitis is listed in the Australian product information for these drugs.

<table>
<thead>
<tr>
<th>Pancreatitis: commonly reported drugs</th>
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<tbody>
<tr>
<td>azathioprine 33 lamivudine 10</td>
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<tr>
<td>didanosine 27 ezetimibe 10</td>
</tr>
<tr>
<td>valproate 28 prednisolone 9</td>
</tr>
<tr>
<td>stavudine 17 olanzapine 8</td>
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<tr>
<td>simvastatin 22 celecoxib 7</td>
</tr>
<tr>
<td>clozapine 13 mercaptopurine 7</td>
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A recent review lists these and a long list of other medicines associated with pancreatitis. A causal association has not been firmly established for many of these, but a drug-induced cause should be considered when other causes have been reasonably excluded. ‘At risk’ groups include elderly patients taking multiple medications, patients who are HIV positive, patients who have cancer and patients receiving immunomodulatory agents. There is insufficient information available on the course of the disease once the suspected drug is stopped. It would, however, seem prudent to withdraw the suspected drug(s) and prevent re-exposure.

References:

2. Leflunomide and interstitial lung disease

Leflunomide is a disease-modifying anti-rheumatic drug (DMARD) for the treatment of rheumatoid arthritis, which has been available in Australia since 2000. A recent publication described 7 Australian and 7 New Zealand reports of pneumonitis in association with leflunomide. To date, ADRAC has received 669 reports associated with the use of leflunomide, of which 142 reports involved respiratory symptoms. Twenty two reports describe one or more of the following serious reactions: pneumonitis (8), interstitial lung disease (9), lung infiltration (4), or pulmonary fibrosis (3). Although these 22 reports have used different medical terms, it is likely they have all reported the same condition, commonly called interstitial lung disease (ILD).

Among the 22 reports of ILD possibly associated with leflunomide, 16 females and 6 males were affected. Their age ranged from 52 to 84 years. Four patients died. Leflunomide was administered concomitantly with methotrexate in the majority of reports (16 out of 22) and it is difficult to identify the relative contributions of each medicine to the reaction. In 6 of these reports however, methotrexate had been used long term without problems. In the 6 reports in which methotrexate was not used, leflunomide was the only medicine suspected of causing the interstitial lung disease. Eight patients required ICU admission for intubation and ventilatory support. Objective evidence of ILD with either CT scan or biopsy was mentioned in 8 reports. The time to onset ranged from 2 weeks to 25 months but the majority of the cases had an onset of 3 to 5 months following the commencement of leflunomide.

Interstitial lung disease is a potentially fatal disorder which may occur at any time during therapy with leflunomide and with variable clinical presentation. The pulmonary status of patients should be evaluated prior to initiation of
leflunomide and patients should be closely monitored during treatment. Discontinuation of leflunomide should be considered if new onset or worsening pulmonary symptoms such as cough and dyspnoea emerge.

3. Tumour necrosis factor alpha inhibitors

Tumour necrosis factor alpha (TNFα) is a cellular protein produced by the immune system and is an important mediator of many diseases, including inflammatory arthritis and inflammatory bowel disease. Currently, three TNFα blocking agents are registered in Australia: infliximab (Remicade) - for the treatment of Crohn's disease, rheumatoid arthritis and ankylosing spondylitis; etanercept (Enbrel) - for rheumatoid arthritis, polyarticular juvenile chronic arthritis, psoriatic arthritis and ankylosing spondylitis; and adalimumab (Humira) - for rheumatoid arthritis.

While extremely effective, TNFα inhibitors are associated with several serious reactions.\(^1,2,3\) These include:

- Hypersensitivity reactions – immediately post-injection or delayed;
- Serious and life-threatening infection and sepsis;
- Recrudescence of tuberculosis and other granulomatous diseases;
- Reactivation of hepatitis B;
- Malignancy, including lymphoma;
- Haematological reactions such as pancytopenia and aplastic anaemia;
- Autoimmunity – eg, drug-induced lupus;
- CNS reactions, including demyelinating disorders and seizures;
- New-onset heart failure or worsening of advanced heart failure.

ADRAC has received 319 reports involving TNFα inhibitors since 2000. The more serious of these are: malignant melanoma (3 reports), lymphoma (5), tuberculosis (4), pneumonia/lower respiratory tract infections (23), sepsis (10), lupus or lupus-like syndrome (22) and anaphylaxis (9). According to Medicare Australia statistics, 57,846 prescriptions for the three TNFα inhibitors combined have been issued for the treatment of rheumatoid arthritis since 2000.

Given their mechanisms of action, it is possible that the use of TNFα inhibitors may predispose patients to an increased risk of malignancies or accelerate their development. A recent meta-analysis of randomised trials of infliximab or adalimumab in rheumatoid arthritis found that malignancies developed in 29/3192 (0.9%) patients treated with infliximab or adalimumab, compared with 3/1428 (0.2%) patients given placebo.\(^4\) The risk of malignancies was not different from placebo with low dose TNFα inhibitors but was 4 fold greater with high doses of infliximab or adalimumab.\(^4\) An increased risk of malignancies has also been reported for etanercept.

The Australian Product Information for these medicines advises prescribers that caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

The recent meta-analysis also showed a 2-fold increased risk of serious infections with TNFα inhibitors, regardless of dose. Patients receiving TNFα inhibitors should not receive concurrent vaccination with live vaccines and consideration should be given to screening patients for pre-existing infections, particularly hepatitis B and tuberculosis, prior to their use.\(^5\)

Reference:
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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 front of the *Schedule of Pharmaceutical Benefits* and the “Australian Medicines Handbook”, or from the Adverse Drug Reactions Unit ☎ 02-6232-8744, or from the website: http://www.tga.gov.au/adr/bluecard.pdf

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

**For further information** from the ADRAC Secretariat:
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