Beware the triple whammy!
Leflunomide and peripheral neuropathy
Ezetimibe and depression – A possible signal
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Please report all suspected reactions to these Drugs of Current Interest

Atomoxetine (Strattera)
Ezetimibe (Ezetrol)
Ezetimibe/Simvastatin (Vytorin)
Fenofibrate (Lipidil)
Iron sucrose (Venofer)

Lumiracoxib (Prexige)
Moxonidine (Phylosiphens)
Pimecrolimus (Elidel)
Pregabalin (Lyrica)
Teriparatide (Forteo)
1. Beware the Triple Whammy!

ADRAC has previously warned prescribers about the ‘triple whammy’ – the combination of an ACE inhibitor (ACEI) or an angiotensin II receptor antagonist (A2RA), a diuretic and an NSAID (including a COX-2 selective NSAID), which may predispose vulnerable patients to renal failure.1,2,3 Risk factors include advanced age, pre-existing renal impairment and dehydration. In 2005, ADRAC received 21 reports of renal failure in patients who were exposed to the triple whammy. In a number of cases, precipitating factors included an acute illness, dehydration, digoxin toxicity or the recent addition of an NSAID to a patient already on an ACEI or an A2RA and a diuretic.

The National Prescribing Service (NPS) has recently released Indicators of Quality Prescribing in Australian General Practice: a manual for users, available from the NPS website (www.nps.org.au). One of the process indicators is entitled Good prescribing (avoiding the ‘triple whammy’) and reinforces the message that risk of the triple whammy should be avoided if possible and extreme caution should be taken with ACEIs or A2RAs and NSAIDs in patients with renal impairment.

It should be remembered that there are now many combination products available that contain both an ACEI or an A2RA and a diuretic.

Some of the more commonly used combinations are shown in the Table. ADRAC advises that prescribers avoid the triple whammy where possible. However, if these drugs are necessary, prescribers should be alert for situations such as illness, dehydration or initiation of an NSAID, which may predispose patients on this combination to renal failure, and advise patients to seek medical advice during such episodes.

<table>
<thead>
<tr>
<th>ACEI or A2RA/diuretic combination</th>
<th>Product name/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perindopril/indapamide</td>
<td>Coversyl Plus</td>
</tr>
<tr>
<td>Fosinopril/HCT</td>
<td>Monoplus</td>
</tr>
<tr>
<td>Enalapril/HCT</td>
<td>Renitec Plus</td>
</tr>
<tr>
<td>Quinapril/HCT</td>
<td>Accuretic</td>
</tr>
<tr>
<td>Captopril/HCT</td>
<td>Capozide; Coverex Plus</td>
</tr>
<tr>
<td>Irbesartan/HCT</td>
<td>Avapro HCT; Karvezide</td>
</tr>
<tr>
<td>Telmisartan/HCT</td>
<td>Micardis Plus; Piriton Plus</td>
</tr>
<tr>
<td>Eprosartan/HCT</td>
<td>Teveten Plus</td>
</tr>
</tbody>
</table>

HCT - hydrochlorothiazide

References:

2. Leflunomide and peripheral neuropathy

Leflunomide is a disease modifying anti-rheumatic prodrug (DMARD) with immunosuppressive properties. It has been available in Australia since 2000 for the treatment of active rheumatoid arthritis.

To date, ADRAC has received 659 reports in association with leflunomide, 30 of which described neuropathy or peripheral neuropathy. Leflunomide was the sole suspected drug in 24 of these cases. Ages ranged from 33 to 90 years. The daily dose of leflunomide was 20 mg in 24 cases, 10 mg in 1, 30 mg in 1, and not stated in the remaining cases. The time to onset (n=21) ranged from 2 weeks to 20 months.

Most reports described insidious onset of bilateral sensory changes such as numbness, hypoaesthesia, paraesthesia, or painful burning sensations affecting the feet and (in a few cases) the hands. Clinical findings variously included reduced sensation to light touch and pin prick, decreased vibration sense distally, and in one case ‘foot drop’ was noted. Decreased or absent tendon reflexes were also noted in some cases.

Nine reports included the results of nerve conduction studies which supported a diagnosis of significant length-dependent sensory or sensorimotor neuropathy. Symptoms persisted and became worse with continued use of leflunomide in several cases.

Recovery was documented after withdrawal of leflunomide in 6 patients, 3 of whom were treated with ‘cholestyramine washout’ (which reduces the
elimination half-life of the active metabolite of leflunomide from more than one week to about one day). At the time of reporting, 15 patients had not recovered and the outcome was unknown for the remaining cases.

The cases reported to ADRAC are similar to those recently described by Martin et al. The temporal association of leflunomide with peripheral neuropathy and recovery on dechallenge suggest a causal relationship. The clinical features resemble the sensory peripheral neuropathy attributable to the vasculitic component of rheumatoid disease itself. Accordingly, the association may be difficult to recognise but prescribers should consider the possible role of leflunomide in patients who complain of sensory problems in the feet because in such cases the condition is potentially reversible if the drug is ceased.

Reference:

3. **Ezetimibe and depression – A possible signal**

Ezetimibe (Ezetrol) was registered in Australia in June 2003 for treatment of hypercholesterolaemia. Since then, ADRAC has received 265 reports of suspected adverse reactions associated with the use of this drug. Twelve of the reports describe depression (9) or depressed mood (3) in patients aged 60 to 82 years. In all cases, ezetimibe was the sole suspected drug. An unusual feature was the rapid onset of symptoms - within four days in 7 of the reports and at 4-6 weeks in another 3. In one report, the symptoms resolved after the dose was reduced from 10 mg to 5 mg daily, and another report described exacerbation of pre-existing depression after the second dose. In 5 patients, symptoms abated on withdrawal of ezetimibe but recurred on rechallenge. One of these documented 2 positive rechallenges with identical time to onset and noted suicidal ideation after continued use of ezetimibe. In addition to the 5 reports of positive rechallenges 4 patients had recovered after ceasing ezetimibe and a further patient was recovering with antidepressant treatment after withdrawal of ezetimibe.

Reports of depression/depressed mood, as a proportion of total reports received, are higher for ezetimibe (4.5%) than for other hypolipidaemic agents: 3% for pravastatin (16/511) and simvastatin (86/2,784); 2.4% for atorvastatin (39/1,573) and fluvastatin (6/255); 1.9% for gemfibrozil (12/619); and for the database as a whole (1.4%).

The Ezetrol Product Information does not mention depression as a finding in clinical trials of this medicine. Further, depression occurs commonly from other causes. However, the pattern of reporting suggests a possible causal association between ezetimibe and depression, particularly in elderly patients in the early phase of treatment, where careful monitoring is advisable. ADRAC will continue to monitor reports of depression in association with ezetimibe.

Reference:

4. **Subscribe to the Bulletin on-line**

Readers can now subscribe to the Bulletin on-line. Subscribers to the ADRAC-BULLETIN email list will receive an email notifying them when the latest issue of the Australian Adverse Drug Reactions Bulletin is available on the TGA website (normally once every two months). To subscribe, visit the Bulletin section of the website at http://www.tga.gov.au/adr/aadrb.htm
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", from the Adverse Drug Reactions Unit ☎ 02-6232-8386, 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:
☎ 1800 044 114    Fax: 02-6232-8392    Email: adrac@health.gov.au

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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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