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1. INTERACTION OF CELECOXIB AND WARFARIN

Since the introduction of celecoxib (Celebrex) to Australia in October 1999, ADRAC has received 2218 reports of suspected adverse drug reactions. Of these, there have been 21 cases describing an increase in the INR of patients on treatment with warfarin. In the 16 cases where the value of the INR was specified, it rose from a stable value of around 2.0 to a peak ranging from 4.2 to 12.2 (median: 5.3). In two other cases the INR was described as “high” and “very high”. While most of the reports did not describe complications, bleeding was reported in 6 cases. These included severe oral bleeding, intracranial haemorrhage, epistaxis and gastrointestinal haemorrhages. In most cases, the problem occurred within two weeks of the addition of celecoxib. Of the patients in whom the outcome was known, all recovered after withdrawal of celecoxib and in some cases, withholding or reducing the dose of warfarin.

In addition to these 21 cases, there have been 11 cases of bleeding in patients taking concomitant celecoxib and warfarin. These reports described purpura (3 cases), gastrointestinal haemorrhage (2), haematuria (1), haematemesis (1), melaena (1), subdural haematoma (1), unspecified haemorrhage (1) and a stroke (1). There was no reference to the INR in these reports except for one in which the INR was reported as unchanged. It is not clear in these cases whether the bleeding was the result of an interaction, an additive effect, an effect of celecoxib alone, or unrelated to the use of celecoxib.

The product information for celecoxib states that in postmarketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving celecoxib concurrently with warfarin. In the cases of increased INR and bleeding reported to ADRAC, 5 of the 26 patients in whom the age was stated were aged less than 50 years.

The product information also describes a study in healthy volunteer subjects given 2 mg to 5 mg warfarin daily in whom celecoxib had no effect on the prothrombin time. However, since warfarin is metabolised mainly by CYP2C9 and this enzyme can be inhibited by celecoxib, it is possible that in some individuals, inhibition of CYP2C9 may be significant, producing higher blood concentrations of warfarin. There have been two recent publications describing this interaction.1,2

References:

2. METFORMIN AND LACTIC ACIDOSIS — A REMINDER

At a recent ADRAC meeting, members reviewed 4 reports which described lactic acidosis in association with metformin. These reports serve as a reminder that this well-known reaction is still occurring in the community and care needs to be taken to avoid it. Lactic acidosis with metformin has considerable morbidity, and mortality has been estimated to be about 50%. A review of cases reported to the United States Food and Drug Administration indicated that 43 of 47 patients had one or more risk factors for lactic acidosis.1 These include preexisting cardiac disease or renal insufficiency, chronic pulmonary disease, severe liver disease and age over 80 years. Another risk factor is believed to be raised plasma metformin concentrations due to high dose or accumulation of the drug in the presence of impaired renal function. It is recommended that metformin be withheld 24 hours before surgery, radiological procedures with contrast or other invasive procedures.

In Australia, there have been 48 reports to ADRAC of lactic acidosis with metformin. The outcome was fatal in 15 cases. Of the 48 cases, known risk factors were identified in 35.

The product information for metformin contains the following highlighted warning:
3. CERIVASTATIN AND RHABDOMYOLYSIS — AVOID GEMFIBROZIL

Cerivastatin (Lipobay) is the fifth of the HMG-CoA reductase inhibitors (“statins”) to be marketed in Australia. Rhabdomyolysis is a known but rare effect of all the statins and is more likely to occur when a fibrate is taken concurrently. Its occurrence in association with cerivastatin appears greater than with other statins. To January 2001 ADRAC has received a total of 95 reports with cerivastatin, of which 17 (18%) have described rhabdomyolysis. This can be compared with the other statins for which the percentages range from 0.3 to 1.2%.

The 17 cases of rhabdomyolysis with cerivastatin occurred from just over a week to 18 months after the introduction of cerivastatin but most occurred in the first month of therapy. Seven of the 15 cases in which the dose was stated occurred with daily dosages of 400 µg or greater and two cases occurred shortly after the dose was increased to 800 µg daily.

Of particular interest is the fact that ten of the 17 patients were taking gemfibrozil concomitantly. The sponsor has made the concomitant use of cerivastatin and gemfibrozil a contraindication.

ADRAC wishes to alert prescribers to the possibility of rhabdomyolysis with all statins. Cerivastatin should not be used in combination with gemfibrozil.

4. SSRIs AND INCREASED INTRAOCULAR PRESSURE

From November 1972 to January 2001 ADRAC has received 92 reports of raised intraocular pressure. Since 1992, there have been 11 reports implicating selective serotonin reuptake inhibitors (SSRIs) involving sertraline (4 reports), fluoxetine (3), paroxetine (3) and citalopram (1). Ages of the patients in these reports ranged from 32 to 70 years. Onset generally occurred within 6 months of commencing the SSRI but ranged from one week to 5 years. In two cases, the SSRI may have aggravated pre-existing glaucoma. In one case, the intraocular pressures which had previously been stabilised with treatment, almost doubled. Presentations consisted of asymptomatic increases in intraocular pressures noted on routine testing (6 cases), eye pain (2 cases), and blurred vision (3 cases). At the time of reporting, 5 patients had not recovered and the outcome remained unknown for the other 6.

The major causes of raised intraocular pressure reported to ADRAC are shown in the Table with corticosteroids, antidepressants and mydriatics accounting for more than half of the reports. The association with SSRIs is less well known and is probably very uncommon although there have been several published case reports.

<table>
<thead>
<tr>
<th>Drug</th>
<th>No of Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>24</td>
</tr>
<tr>
<td>Systemic</td>
<td>13</td>
</tr>
<tr>
<td>Topical</td>
<td>6</td>
</tr>
<tr>
<td>Inhaled</td>
<td>5</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>17</td>
</tr>
<tr>
<td>SSRIs</td>
<td>11</td>
</tr>
<tr>
<td>Tricyclics</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
</tr>
<tr>
<td>Mydriatics</td>
<td>10</td>
</tr>
</tbody>
</table>

(there is another article on the back page)
5. WARNING: POTENTIAL FOR CONFUSION WITH HUMALOG

The names of the wide range of insulin products can cause confusion. The most recent example concerns the possibility for confusion between Humalog and Humalog Mix25.

Humalog is the product name for lispro insulin, a fast acting analog of human insulin. Humalog Mix25 contains 25% lispro insulin and 75% lispro insulin protamine suspension. ADRAC has been notified of a small number of instances where the similarity of the two product names has led to dispensing or transcribing errors. No serious consequences have been reported but the potential for harm is clear.

Prescribers and dispensers need to be aware of the potential for confusion. Humalog is a clear, rapidly acting insulin. Humalog Mix25 is cloudy and combines rapid with intermediate actions. The sponsor, Eli Lilly, is aware of the problem and has distributed educational material to health professionals. It also intends to soon amend the packaging of the products to help differentiate the two insulins.

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 all recent editions of the "Schedule of Pharmaceutical Benefits", and at page 19 of the 2nd edition of the "Australian Medicines Handbook".

Further information can be found from the medical and scientific staff in the ADRAC Secretariat:
Medical Officer: 📞 02-62328381 Executive Secretary: 📞 02-62328382
Fax: 02-62328392

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


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