Australian experience with pneumococcal conjugate vaccine

Warnings for high dose tricyclic antidepressants

Terbinafine and blood dyscrasias

Cholinesterase inhibitors and cardiac arrhythmias

Quinine indications — cramps deleted

Please report all suspected reactions to these Drugs of Current Interest

Aripiprazole (Abilify)
Atomoxetine (Strattera)
Ezetimibe (Ezetrol)
Levetiracetam (Keppra)

Pimecrolimus (Elidel)
Reboxetine (Edronax)
Sibutramine (Reductil)
1. AUSTRALIAN EXPERIENCE WITH PNEUMOCOCCAL CONJUGATE VACCINE

Pneumococcal conjugate vaccine was registered in February 2001 for active immunisation of infants and children from 6 weeks to 9 years of age against invasive disease, pneumonia and otitis media caused by Streptococcus pneumoniae. The vaccine is active against  S. pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F and 23F. From surveys conducted, the seven serotypes included in the vaccine will cover about 85% of invasive isolates in urban Australian children and 67% of invasive isolates in indigenous Australian children. In a clinical trial of infant immunisation, efficacy against invasive pneumococcal disease caused by vaccine serotypes of S. pneumoniae was 97% (95% CI 83-100%).

The current targeted National Childhood Pneumococcal Vaccination Program commenced in 2001. The Program provides access to free pneumococcal conjugate vaccine for children who are predisposed to high rates of pneumococcal infection or who are susceptible to high mortality should they acquire pneumococcal infection. Commencing on 1 January 2005, a new Universal Childhood Pneumococcal Vaccination Program will provide free pneumococcal conjugate vaccine for all children at 2, 4 and 6 months of age, plus catch-up vaccination in 2005 for all children under 2 years of age.

Up to March 2004, 52,000 first doses, 32,000 second doses and 20,000 third doses of pneumococcal conjugate vaccine had been administered to children under 7 years who had met the current criteria for funded vaccination.

ADRAC has received 41 reports related to pneumococcal conjugate vaccine with this vaccine being the sole suspected agent in 23 cases. The most common reactions include: pyrexia (8), injection site reaction (8), and vomiting (5). There were 2 reports of lack of efficacy. In the first case, a 2 year old child developed pneumococcal pneumonia with serotype 6B, two months after being given a single dose. In the second case, a 7 month old female who had received her third dose four months previously developed serotype 18C pneumococcal infection with bacteraemia. Both children recovered.

Reassuringly, no major or unexpected adverse events have been reported in association with the use of pneumococcal conjugate vaccine in Australian children.

References:

2. WARNINGS FOR HIGH DOSE TRICYCLIC ANTIDEPRESSANTS

The total quantity in milligrams of tricyclic antidepressant that can be obtained by patients at risk of suicide is a concern. Particularly the high dose (i.e. 50 and 75 mg) presentations of tricyclic antidepressants have been associated with some patient deaths from overdose. An overdose of dothiepin may be more likely to be fatal than overdoses of other tricyclic antidepressants.

The approved indications for the 50 mg and 75 mg tricyclic antidepressant presentations (dothiepin: Prothiaden, Dothep; doxepin: Deptran; amitriptyline: Endep; trimipramine: Surmontil) have been changed to limit use to maintenance treatment, in an attempt to reduce the risk of suicide in acutely depressed patients. The product information for these high dose products now warns about the risk of suicide by overdose. These products remain available for the treatment of major depression, but prescribers should limit prescriptions of high dose (i.e. 50 and 75 mg) tricyclic antidepressants to patients who have recovered beyond acutely depressed or suicidal phases.

Reference:
3. TERBINAFINE AND BLOOD DYSCRASIAS

Oral terbinafine (Lamisil) is indicated for onychomycosis caused by dermatophyte fungi and for tinea unresponsive to topical therapy. Haematological reactions, notably agranulocytosis, neutropenia or pancytopenia, are rare adverse effects of systemic terbinafine therapy. Onset is commonly within 4-6 weeks after commencing therapy and resolution may occur within a week if terbinafine is stopped promptly.\textsuperscript{1-6}

ADRAC has received 14 reports of these blood dyscrasias with oral terbinafine (total reports 534): agranulocytosis (7), neutropenia (5) or pancytopenia (2). The age range was 35 to 84 (median 65) years. The time to onset was 4-10 weeks, with eight patients developing the adverse reaction within five weeks of starting terbinafine. Five patients exhibited signs of infection and/or were treated with antibiotics. Recovery was documented in nine reports and occurred within a week of discontinuation of terbinafine in four of these. One patient, a 79 year old female developed agranulocytosis about 2 months after initiation of terbinafine, and died from septic shock despite treatment with granulocyte colony stimulating factor and antibiotics.

Some patients with terbinafine-associated low white cell counts have developed multisystem involvement with rash and hepatic impairment, suggestive of a drug hypersensitivity syndrome.\textsuperscript{6}

Patients taking terbinafine for longer than a month should be advised to report any symptoms of possible infection, such as fever or sore throat. Blood counts should be checked if symptoms develop.

As described in an earlier Bulletin article,\textsuperscript{7} other reactions associated with oral terbinafine reported to ADRAC include taste perversion (143 reports), abdominal pain or discomfort (23), nausea (50), hepatic dysfunction (47; including one death) and serious skin reactions (20).

References:

4. CHOLINESTERASE INHIBITORS AND CARDIAC ARRHYTHMIAS

Cholinesterase inhibitors such as donepezil (Aricept), rivastigmine (Exelon) and galantamine (Reminyl) are being used increasingly in the treatment of Alzheimer’s disease. The product information for all three drugs notes that increased cholinergic activity may have vagal effects on heart rate such as bradycardia.

The Table shows reports of cardiac arrhythmias and other effects, like syncope, which may be indicative of such problems. The larger number of reports with donepezil is almost certainly due to greater usage of this drug. Most patients recovered after the cholinesterase inhibitor was stopped or in some cases, reduced in dose. Many patients

<table>
<thead>
<tr>
<th>Cardiac arrhythmias with cholinesterase inhibitors</th>
<th>Donepezil</th>
<th>Rivastigmine</th>
<th>Galantamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>14</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Bundle branch block</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>AV block</td>
<td>5</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Syncope</td>
<td>10</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Unspecified arrhythmia</td>
<td>2</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction/cardiac arrest</td>
<td>7</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Total number of all reports</td>
<td>235</td>
<td>82</td>
<td>54</td>
</tr>
<tr>
<td>PBS prescriptions (to December 2003)</td>
<td>439,000</td>
<td>78,000</td>
<td>67,000</td>
</tr>
</tbody>
</table>
were hospitalised and in 4 cases a pacemaker was required. Four elderly patients died from suspected myocardial infarction; it is unclear whether their medication had any role in these events.

Prescribers need to be aware of the potential for cardiac arrhythmias, particularly bradycardia, with cholinesterase inhibitors. Patients with sick sinus syndrome or other supraventricular cardiac conduction conditions may be at particular risk. A pharmacodynamic interaction can also be predicted with the concomitant use of beta-blockers or calcium channel blockers.

5. QUININE INDICATIONS — CRAMPS DELETED

As a consequence of the risk of thrombocytopenia (currently 228 ADRAC reports; 6 fatal),1 quinine is no longer approved in Australia for the treatment of nocturnal cramps.

Reference:

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

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 “adverse drug reaction reporting” on the right.

Further information can be obtained from the ADRAC Secretariat:
☎ 1800 044 114 Fax: 02-6232-8392 Email: adrac@health.gov.au

ISSN 0812-3837
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