Acne, isotretinoin and suicidality

Genitourinary symptoms with reboxetine

The multiple toxicities of amiodarone

Antidepressants in children and adolescents

Pimecrolimus, skin cancer and lymphoma

Please report all suspected reactions to these Drugs of Current Interest

Aripiprazole (Abilify)  Levetiracetam (Keppra)
Atomoxetine (Strattera)  Pimecrolimus (Elidel)
Ezetimibe (Ezetrol)  Reboxetine (Edronax)
Fenofibrate (Lipidil)  Sibutramine (Reductil)
Iron sucrose (Venofer)  Teriparatide (Fortéo)
1. ACNE, ISOTRETINOIN AND SUICIDALITY

Isotretinoin (Accure, Oratane, Roaccutane) is a retinoid derivative approved for the treatment of severe cystic acne which has not responded to other treatments including an adequate trial of antibiotics. Primarily because of this drug’s known teratogenicity, prescription of isotretinoin in Australia is restricted to specialist physicians and dermatologists.1

ADRAC has received 21 reports of patients aged 13 to 40 (median 18) years suffering suicidal ideation or making suicide attempts. In two cases fatal outcomes were documented. One of these was recently the subject of a Coroner’s investigation.

A recent formal epidemiological study which compared oral isotretinoin with other oral acne treatments found no increase in the risk of depression or suicide attributable to isotretinoin.2 Similarly, a prescription sequence symmetry study found first prescription of an antidepressant was just as likely before commencing isotretinoin as after.3 Nevertheless, it is clear that clinically significant depression may occur in patients treated with isotretinoin. If the depression is severe, it may be accompanied by suicidal ideation and, unfortunately suicide attempts. It is possible that depression in this context is caused by the severe acne and its impact on self-esteem and social function in patients who may be at an emotionally vulnerable stage of development.

Despite the lack of any established causal link between isotretinoin and depression, any patient with acne severe enough to require treatment with isotretinoin must also be considered at risk for clinical depression and its consequences including possible suicide attempts. Accordingly, when isotretinoin is prescribed, the patient and his or her family members should be alerted to this possibility and to the need for urgent re-assessment if signs of depression emerge. Patients should be encouraged to read the Consumer Medicine Information which advises those experiencing the following symptoms to stop taking isotretinoin and see their doctor:

- Feeling sad or having crying spells
- Losing interest in activities once enjoyed
- Sleeping too much or having trouble sleeping
- Changes in appetite or bodyweight
- Having trouble concentrating
- Withdrawing from friends or family
- Lacking in energy
- Feelings of worthlessness or inappropriate guilt

References

2. GENITOURINARY SYMPTOMS WITH REBOXETINE

Reboxetine (Edronax) is a selective noradrenaline reuptake inhibitor for the treatment of major depression. ADRAC has received 130 reports concerning reboxetine. Genitourinary problems, occurring within 5 weeks of commencing therapy, were described in 41 reports.

In 26 reports patients developed urinary symptoms consistent with obstruction including hesitancy, reduced urine flow, retention, and dribbling post micturition. All but 6 of the patients were male. During short-term clinical trials, urinary retention was reported in 3% of patients and impaired urination in 4.6%.1

ADRAC has also received 22 reports of male sexual dysfunction including ejaculation disorder (7 reports), erectile dysfunction (4) and pain or swelling of the testicles or external genitalia (10). Two additional reports were of increased libido in women. In short term clinical trials, abnormalities of sexual function and impotence were reported in 1.3% and 1.6% of patients, respectively.1 Testicular pain is a very unusual adverse reaction. It has also been associated with mazindol (Sanorex) an anorectic drug no longer marketed in Australia which has a similar structure to reboxetine.2

Patients prescribed reboxetine should be asked about symptoms of urinary obstruction and sexual dysfunction soon after commencing therapy.

References
1. Edronax, Australian Product Information, Pharmacia Australia Pty Ltd. 1 Sep 2004
3. THE MULTIPLE TOXICITIES OF AMIODARONE

Amiodarone is an antiarrhythmic agent which is approved for the treatment of “severe tachyarrhythmias unresponsive to other therapy.” It is available as a restricted benefit on the PBS. Use has increased rapidly in recent years from 150,000 prescriptions in 1995 to about 430,000 prescriptions/year in 2002-2004.1

Long term amiodarone has a very long half-life (up to 110 days) and accumulates in adipose tissue and in highly perfused organs (lung, bone marrow, adrenals, liver, pancreas, heart, spleen and kidney), potentially causing serious adverse reactions in these and other body systems as indicated in the Table.2 With its long half-life adverse reactions may become manifest after discontinuation.

Table: Adverse reactions reported to ADRAC with amiodarone

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>No. of reports (deaths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid disorders</td>
<td>212 (8)</td>
</tr>
<tr>
<td>Respiratory disorders</td>
<td>195 (24)</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>94 (4)</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>81 (8)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>34 (1)</td>
</tr>
<tr>
<td>Muscle disorders</td>
<td>29</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>28</td>
</tr>
<tr>
<td>Corneal changes</td>
<td>27</td>
</tr>
<tr>
<td>Haematological disorders</td>
<td>18</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>809 (46)</strong></td>
</tr>
</tbody>
</table>

Because of the frequency of fatal outcome, the most dangerous effect of amiodarone is its pulmonary toxicity, reviewed by ADRAC in 2002.3 Fatal outcomes are typically associated with pneumonitis progressing to pulmonary fibrosis and respiratory failure. Although commonly insidious in onset, amiodarone-induced pulmonary toxicity may also develop rapidly as in a recently reported case. An elderly male taking metoprolol, candesartan, aspirin, atorvastatin and risedronate was prescribed amiodarone 200mg daily for atrial fibrillation and after 6 months developed fatal respiratory failure secondary to pneumonitis. The risk of pulmonary adverse effects increases with increasing cumulative dose, but is also present at low dose over short durations, especially in elderly patients and those with pre-existing lung disease.4,5 The prognosis is usually good if the drug is stopped early.4

Amiodarone has unique properties for the treatment of difficult cardiac arrhythmias. Whereas long-term therapy for life-threatening ventricular arrhythmias may be necessary, not all patients initiated on amiodarone for acute atrial arrhythmias require continuing treatment. If amiodarone is used chronically, the lowest effective dose should be prescribed. Patients should be informed of the warning symptoms of amiodarone toxicity and told to seek medical attention promptly should they occur.

Lung function should be monitored including 6-monthly chest x-ray, and the development of dyspnoea or cough should be investigated immediately.2,5 Monitoring of ECG, liver function and thyroid function 6-monthly is also recommended.2 Hyperthyroidism can present abruptly as weight loss, myopathy and worsening arrhythmia. Annual eye examination is also recommended. Nearly all patients develop corneal deposits, which are usually benign, but other more serious eye effects may occur.

References

4. ANTIDEPRESSANTS IN CHILDREN AND ADOLESCENTS

The joint clinical guidance on the use of antidepressant medications in children and adolescents by the Royal Australian and New Zealand College of Psychiatrists, the Royal Australasian College of Physicians and the Royal Australian College of General Practitioners has now been released and is available at [http://www.ranzcp.org/publicarea/pracguid.asp](http://www.ranzcp.org/publicarea/pracguid.asp)

5. PIMECROLIMUS, SKIN CANCER AND LYMPHOMA

The US FDA has received 10 reports of cancer-related events, skin cancer and lymphomas, in children and adults who have used pimecrolimus (Elidel) cream. It is not known whether there is a causal relationship in these cases, and the long term safety of Elidel is unknown. Elidel is indicated as short-term or as second-line intermittent long-term treatment of atopic dermatitis (eczema). ADRAC advises applying only enough Elidel to control symptoms and using for as short a period as possible. Long-term use should be intermittent not continuous to minimise drug exposure.

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

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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