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AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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☆ Problems with colloids in fluid resuscitation
☆ Reactivation of hepatitis B virus following cytotoxic or immunosuppressant therapy
☆ Sibutramine — Four years experience

Please report all suspected reactions to these Drugs of Current Interest

- Atomoxetine (Strattera)
- Ezetimibe (Ezetrol)
- Ezetimibe/Simvastatin (Vytorin)
- Fenofibrate (Lipidil)
- Pimecrolimus (Elidel)
- Pregabalin (Lyrica)
- Teriparatide (Fortéo)
- Iron sucrose (Venofer)
1. Problems with colloids in fluid resuscitation

The Australian and New Zealand Saline versus Albumin Fluid Evaluation (SAFE) study compared outcomes at 28 days after administration of saline or 4% serum albumin for intravascular-fluid resuscitation of adult intensive care unit patients. In the overall population, the study found no clinically significant benefit of albumin over saline.\(^1\) Although the SAFE study was designed as a safety study and not powered to examine efficacy in subgroup populations, the findings suggest that the risks of available colloids, particularly the risk of anaphylaxis, should be considered carefully.

Succinylated gelatin (Gelofusine) is a colloidal plasma volume substitute used in the treatment and prevention of hypovolaemia almost exclusively in hospital settings. Since it was first registered in late 1998, ADRAC has received 83 reports for succinylated gelatin, 70 of which have been of hypotension and/or hypersensitivity reactions. Hypotension or anaphylactoid reactions were the only feature listed in 27 of these, while the remaining 43 reports mentioned signs and symptoms consistent with anaphylactoid reactions, including cutaneous (35), respiratory (18) or cardiac (10) manifestations. In some cases several other drugs had been administered shortly beforehand. Recovery was documented in 60 of the reports, but one patient died following cardiac arrest.

ADRAC has received reports of similar reactions with the other plasma expanders, polygeline (Haemaccel), albumin (Albumex) and dextran.

In all cases, the number of reports of anaphylactoid reactions, as a proportion of total reports, is similar to the proportion of reports of these reactions received for gelofusine. Many of the reports with polygeline were associated with a quality control problem in the manufacturing process occurring in 1998,\(^2\) but further reports have been received since this problem was addressed. There is some evidence of cross-reactivity between polygeline and succinylated gelatin.\(^3\)

Diagnosis of paradoxical hypotension or anaphylaxis occurring during intravascular administration of colloids may be difficult in a patient who is already hypovolaemic. If the patient’s blood pressure continues to fall despite apparently adequate volume replacement, this possibility should be considered.

Given that saline and albumin have been shown to be of equivalent efficacy\(^1\), the safety of colloids such as gelatin should be considered carefully in the initial choice of resuscitation fluid.

References:

2. Reactivation of hepatitis B virus following cytotoxic or immunosuppressant therapy

In the last two years ADRAC has received five reports of reactivation of hepatitis B infection in chronic carriers (HBsAg positive). Prior to reactivation, these patients had received chemotherapy for cancer or immunosuppressive therapy for autoimmune disease. One patient had HIV infection and lamivudine was stopped when anti-retroviral therapy was changed due to an increase in HIV viral load. Two of these cases were fatal and one required a liver transplant.

The first fatal case was a 61 year old male who received 7 cycles of cyclophosphamide, doxorubicin, vincristine and prednisolone treatment for large B cell lymphoma. Reactivation of hepatitis B occurred (HBV DNA >600 pg/mL) and the patient died from decompensated liver disease despite treatment with lamivudine.

The other fatal case was a 29 year old woman with mixed connective tissue disease who was treated with low dose prednisolone and hydroxychloroquine. She developed aseptic meningitis and was given high dose prednisolone (60 mg) for two months. Hydroxychloroquine was replaced by chloroquine due to ongoing headache and the prednisolone dose was reduced.
About a month later she developed progressive liver failure due to biopsy-proven fibrosing cholestatic hepatitis. Despite lamivudine therapy she died from multi-organ failure.

Hepatitis B reactivation resulting in severe hepatitis has also been reported following hematopoietic stem cell transplantation, chemotherapy for breast cancer and other solid tumours, and in organ transplant recipients. Systemic chemotherapy, and particularly high dose corticosteroid therapy, is thought to promote high levels of HBV replication. Subsequent recovery of immune function after cessation of chemotherapy or withdrawal of corticosteroids triggers cytopathic virus elimination, resulting in massive liver damage.

The possibility of reactivation of hepatitis B infection should be considered in HBsAg positive individuals requiring chemotherapy for haematologic malignancy or cancer, solid organ transplantation or high dose corticosteroid therapy. Such patients should be screened for HBsAg and prophylaxis with an oral antiviral agent active against hepatitis B virus should be considered for carriers.

References:

### 3. Sibutramine — Four years experience

Sibutramine is a noradrenaline and serotonin reuptake inhibitor indicated for weight loss. It has been available in Australia since January 2002 but is not funded by the PBS. To date, ADRAC has received 138 reports (404 adverse reactions) associated with the use of sibutramine. The common adverse reactions reported are consistent with the product information and are listed in the Table:

<table>
<thead>
<tr>
<th>SOC</th>
<th>Number of reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system</td>
<td>62 (headache 20, dizziness 14, serotonin syndrome 5)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>50 (depression 12, anxiety 11, insomnia 10, aggression 6, agitation 6)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>33 (nausea 9, constipation 6, dry mouth 6)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>31 (rhythm disorders 11, palpitations 9, chest pain 4)</td>
</tr>
<tr>
<td>Vascular</td>
<td>26 (hypertension 8)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>15 (dyspnoea 11)</td>
</tr>
</tbody>
</table>

Psychiatric reactions have been reported at both extremes of the spectrum, specifically depression and mania. Sibutramine was the sole suspected medicine in 11 of the 12 cases of depression. The time to onset was relatively short, ranging from 1 to 13 days. Most patients (11) recovered after stopping sibutramine. The 12 reports included 2 of suicidal ideation and 2 of suicide attempt.

Sibutramine was the sole suspected medicine in 2 of the 3 reports of mania. Both of these patients recovered after ceasing sibutramine. The other manic event occurred in a patient with a history of previously well controlled bipolar disorder.

Reported cardiovascular adverse reactions have included cardiac rhythm disorders, palpitations and chest pain. Sibutramine was the sole suspected medicine in 27 cases. The two most serious adverse reactions were ventricular fibrillation with cardiac arrest and myocardial infarction. There have also been 8 reports of hypertension.

Serotonin syndrome was reported in 5 cases, with time to onset ranging from 1 to 22 days. Sibutramine was used with tramadol in 2 cases, with sertraline in 1 case and was the sole medication in the other 2 cases.

Sibutramine should not be used in combination with other CNS-active drugs, such as MAOIs and SSRIs, due to a possible interaction and the risk of serotonin syndrome. Sibutramine is not recommended for use in patients with a history of heart disease as it tends to increase heart rate and blood pressure.
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