Meningococcal C vaccine: early experience is reassuring

Harmful interactions

Post-partum NSAIDs may cause hypertension

Please report all suspected reactions to these Drugs of Current Interest:

- Apomorphine (Uprima)
- Aripiprazole (Abilify)
- Esomeprazole (Nexium)
- Fondaparinux (Arixtra)
- Galantamine (Reminyl)
- Lercanidipine (Zanidip)
- Levetiracetam (Keppra)
- Meloxicam (Mobic)
- Pioglitazone (Actos)
- Pramipexol (Sifrol)
- Reboxetine (Edronax)
- Rosiglitazone (Avandia)
- Sibutramine (Reductil)
- Tadalafil (Cialis)
- Tegaserod (Zelmac)
1. MENINGOCOCCAL C VACCINE: EARLY EXPERIENCE IS REASSURING

Meningococcal serogroup C conjugate vaccines (NeisVac-C, Meningitec, Menjugate) have been included in a mass vaccination program in Australia, from early 2003. These vaccines are highly effective and have a low rate of adverse events. A single dose is recommended to confer long-term immunity in adults and children ≥ 12 months of age. Initial appraisals of efficacy against invasive meningococcal group C disease indicate the vaccine is 92% effective in toddlers and 97% effective in teenagers. It is estimated that meningococcal C conjugate vaccines have the potential to prevent over 100 cases of meningococcal infection and 5 to 10 deaths each year in Australia. No vaccine is available against group B meningococcus which causes almost 70% of all meningococcal infections. Individuals who are given meningococcal C vaccine continue to be susceptible to group B meningococcus.

Since March 2002, ADRAC has received 270 reports associated with the use of serogroup C conjugate vaccines. Commonly reported adverse events include injection site reaction (86), fever (48), rash (39), vomiting (32), urticaria (28) and headache (28). Serious events include anaphylaxis (2), angioedema (2) and convulsions (17). Seven of the cases of convulsions were associated with syncope and four with fever. Although it is not possible to develop group C meningitis from the vaccine, two reports have been received of meningitis-like symptoms. Such reactions may include headache, neck stiffness and soreness and photophobia. No deaths have been reported associated with the vaccine.

Up to 30 June 2003, around 2.5 million doses of meningococcal vaccine were distributed in Australia. Using this figure, the reported rate in Australia for convulsions is 7 per million doses. This is broadly consistent with the reported rate for convulsions in the United Kingdom, which is 16 per million doses.

References:

2. HARMFUL INTERACTIONS

A recent article has highlighted the risks of prescribing drugs that can interact with effective, well-tolerated, long-term drug therapy in the elderly. The article focussed on three interactions involving addition of a new drug to long-term therapy:

- **hypoglycaemia with trimethoprim/sulphamethoxazole added to glibenclamide**
- **digoxin toxicity with clarithromycin added to digoxin**
- **hyperkalaemia with potassium-sparing diuretic added to ACE inhibitor**

The authors found use of each of the combinations to be associated with an increased risk of hospitalisation. Patients taking an ACE inhibitor who then took a potassium-sparing diuretic had a 20-fold increased risk of admission. Some patients were hospitalised for as long as 8 days, and several patients with each of the interactions died. No increased risk of toxicity was found in patients who received an alternative drug with a similar indication but no known interaction (amoxycillin, cefuroxime, indapamide, respectively).

Australian reports received by ADRAC illustrate these interactions.

**Trimethoprim/sulphamethoxazole + glibenclamide**

Two patients stabilised on glibenclamide for their diabetes became hypoglycaemic when they commenced trimethoprim/sulphamethoxazole for a bacterial infection. One patient had previously taken trimethoprim with glibenclamide without adverse effect. This interaction occurs because sulphonamides inhibit the hepatic metabolism of
sulphonylureas by CYP2C9. In addition, high dose sulphonamides alone may, rarely, have a hypoglycaemic effect.

**Clarithromycin + digoxin**

A 75 year old female who had been taking digoxin 250 µg daily for almost four years was admitted with digoxin toxicity (4.2 nmol/L) on the third day after commencement of clarithromycin 250mg twice daily. The dose of digoxin was halved and clarithromycin stopped. She was discharged eight days later. Digoxin bioavailability is around 70% because p-glycoprotein in the gut wall pumps it back into the gut lumen, reducing absorption. Clarithromycin, and other macrolide antibiotics, inhibit the p-glycoprotein pump, increasing the amount of digoxin absorbed.

**Spironolactone + ACE inhibitor**

Three patients developed hyperkalaemia (two with renal failure) after the addition of spironolactone to long-term ACE inhibitor therapy. In one case serum potassium rose to 8.4 mmol/L. All three patients recovered fully following withdrawal of both medications and treatment to reduce potassium levels. Hyperkalaemia commonly occurs with ACE inhibitors alone, and adding a potassium-sparing diuretic, such as spironolactone or amiloride, exacerbates this effect by further impairing renal potassium excretion.

Prescribers are advised to be cautious about the risk of interactions when prescribing additional medication to patients on long-term drug therapy for chronic conditions. Besides potentially serious direct consequences from the interaction, the interaction may not be correctly identified and the long-term medication may be unnecessarily ceased. In the context of long-term therapy, increased surveillance is recommended in the weeks after starting or stopping other medication.

Reference:

3. **POST-PARTUM NSAIDS MAY CAUSE HYPERTENSION**

Recently ADRAC received a cluster of six reports of hypertension or hypertensive crisis in women given an NSAID (indomethacin, ibuprofen or diclofenac) post-partum. One woman, with a history of severe pre-eclampsia, died of hypertensive crisis and intracranial haemorrhage after Caesarean section. Three of the other women had a history of pre-eclampsia, but two, including one with an eclamptic seizure, had no prior hypertension. Four of the women were receiving no antihypertensive therapy at the time of the adverse event.

The efficacy and tolerability of NSAIDs for the treatment of post-partum pain following uncomplicated spontaneous delivery have been demonstrated in controlled prospective studies. However, there is a lack of data on the use of NSAIDs in the post-partum period in women with pre-eclampsia or premature delivery. Studies unrelated to pregnancy and delivery indicate that, although NSAIDs have a minimal effect on the blood pressure of normotensive individuals, they can cause major increases in hypertensive patients whose blood pressure was previously controlled by medication. Beta-blockers and ACE inhibitors are particularly susceptible to reduced efficacy in the presence of an NSAID. Limited data suggest that NSAIDs may also increase blood pressure in patients with uncontrolled hypertension. Different NSAIDs may have different degrees of effect on blood pressure.

The severe hypertension in the present cases may have been caused solely by the patients’ underlying condition. It is plausible, however, that the NSAID administered in each case made a significant contribution.

ADRC advises careful monitoring of blood pressure in women with a history of pre-eclampsia or essential hypertension given an NSAID in the post-partum period. ADRAC would be interested to hear from health professionals who observe similar rises in blood pressure following the use of an NSAID in this setting.

References:

(References continued over page)


### 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 ☏ 02-62328386, or from the website: [http://www.tga.gov.au/adr/bluecard.pdf](http://www.tga.gov.au/adr/bluecard.pdf). Tear-out blue cards can also be found at the front of the "Schedule of Pharmaceutical Benefits" and the "Australian Medicines Handbook". Reports can also be submitted electronically, by going to the TGA web site ([http://www.tga.gov.au](http://www.tga.gov.au)) and clicking on “adverse drug reaction reporting” on the right.

Further information can be obtained from the medical and scientific staff in the ADRAC Secretariat:

- ☏ 1800 044 114
- Fax: 02-62328392
- Email: adrac@health.gov.au

**ISSN 0812-3837**


All correspondence to be addressed to: The Secretary, Adverse Drug Reactions Advisory Committee, PO Box 100, Woden, ACT, 2606