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AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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- ☆ Fluticasone and adrenal crisis
 - ☆ The glitazones – early experience
 - ☆ Interstitial nephritis with the proton pump inhibitors
 - ☆ Interactions with grapefruit juice - amendment
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Please report **all** suspected reactions to these **Drugs of Current Interest**

Esomeprazole (Nexium)	Pioglitazone (Actos)
Fondaparinux (Arixtra)	Reboxetine (Edronax)
Galantamine (Reminyl)	Risedronate (Actonel)
Gatifloxacin (Tequin)	Rivastigmine (Exelon)
Lercanidipine (Zanidip)	Rosiglitazone (Avandia)
Meloxicam (Mobic)	Sibutramine (Reductil)
Mirtazapine (Avanza, Mirtazon, Remeron)	Tadalafil (Cialis)
Moxifloxacin (Avelox)	Tegaserod (Zelmac)
Oxcarbazepine (Trileptal)	

1. FLUTICASONE AND ADRENAL CRISIS

There have recently been several reports worldwide of adrenal insufficiency developing in children using inhaled corticosteroids. ADRAC has received 10 such reports from Australia. Eight involved the use of fluticasone, either alone (Flixotide) or in combination with salmeterol (Seretide).

In these 8 cases, the ages ranged from 3 to 10 years, and the doses of fluticasone from 250 to 1500µg daily; the daily dose was over 500µg in 6 of the reports. Six of the children had adrenal crisis, which was associated with hypoglycaemia in all cases, convulsions in 2, and coma in one. In 3 of the reports the adrenal crisis had been precipitated by an episode of gastroenteritis.

Adrenal crisis associated with inhaled corticosteroid use occurs because of the systemic absorption of the corticosteroid and consequent suppression of endogenous glucocorticoids, leaving insufficient adrenal reserve to respond to stress (for example, infection). It may also result from abrupt discontinuation or non-compliance with treatment, leading to acute steroid deficiency. It may present as hypoglycaemia, abdominal pain, tiredness or vomiting, with or without convulsions or coma.

Although adrenal insufficiency can occur with any inhaled corticosteroid, it may be more common with fluticasone because of its greater potency and hence lower equivalent dose (half the dose of budesonide or beclomethasone).^{1,2}

The Australian approved dose of inhaled fluticasone for children is 100-200µg daily. At this dose, adrenal suppression is unlikely.³ The use of higher doses, however, is common. The Thoracic

Society of Australia and New Zealand recommends a maximum dose of 250µg daily in children up to 5 years, and 500µg daily in children over 5 years, before referral to a respiratory physician.⁴ The National Asthma Council recommends a maximum dose of 500µg daily for all children, before referral to a respiratory physician. Higher doses may not confer greater efficacy; a meta-analysis of trials of fluticasone in adolescents (≥12 years) and adults indicated that in patients using regular, long-term inhaled corticosteroids, maximal efficacy was achieved at doses around 500 µg/day, but 90% of the benefit was achieved at doses of 100-250 µg/day.²

Prescribers are reminded that inhaled corticosteroids should be given at the lowest effective dose and reviewed regularly, and should not be discontinued suddenly. Screening for adrenal insufficiency in children receiving high dose inhaled corticosteroids is generally not useful. Instead, parents of these children should be warned of the potential for adrenal suppression, and advised to seek medical attention if the child experiences any of the symptoms described above, particularly in the setting of an intercurrent illness.⁵

References:

1. Todd GRG et al. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Arch Dis Child* 2002; 87: 457-461.
2. Holt S et al. Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis. *BMJ* 2001; 323: 1-8.
3. Flixotide Australian approved Product Information.
4. van Asperen PP et al. The role of corticosteroids in the management of childhood asthma. *Med J Aust* 2002;176:169-174.
5. Macdessi JS et al. Adrenal crisis in children treated with high-dose inhaled corticosteroids for asthma. *Med J Aust* 2003; 178: 214-216.

2. THE GLITAZONES – EARLY EXPERIENCE

Pioglitazone (Actos) and rosiglitazone (Avandia) are thiazolidinediones, a new class of oral antidiabetic drugs, which act on the peroxisome proliferator activated gamma (PPARγ) nuclear receptor to reduce tissue insulin resistance. These glitazones may be used alone or in combination with sulfonylureas or metformin. Pioglitazone is also approved for use with insulin.

Although neither drug has a PBS subsidy, ADRAC has received 44 reports associated with

rosiglitazone, and 28 reports with pioglitazone. Twelve reports with rosiglitazone and 4 with pioglitazone were of hepatic reactions, including elevated liver enzyme levels (13 reports; 1 with jaundice), abnormal liver function (1), hepatocellular damage (1) and hepatitis (1). However, liver enzyme levels may be elevated with diabetes or obesity.

Twelve possible cardiac reactions were reported with rosiglitazone and 6 with pioglitazone. The

events were myocardial infarction (4 reports), cardiac failure (4), prolonged QT-interval (2), ventricular fibrillation with cardiac arrest (1) and dependent oedema (7; all with rosiglitazone). In 3 of the 4 cases of myocardial infarction or cardiac failure with rosiglitazone the patient had a history of ischaemic heart disease.

The cardiac events in these patients may be related to co-morbidities, including age, diabetes, hypertension and ischaemic heart disease. However, the glitazones have been associated with cardiac failure.¹

The first glitazone, troglitazone (Rezulin) was briefly marketed, but was withdrawn due to hepatotoxicity. The glitazones should not be used in patients with liver disease (including increased transaminase levels > 2.5 times the upper limit of

normal), or in patients whose cardiac failure limits their physical activity. Careful monitoring of hepatic and cardiac function is required, including liver function tests every two months for at least one year, even in patients with normal baseline liver enzyme levels.

The glitazones can increase subcutaneous fat, and cause fluid retention, with oedema and haemodilution. Clinical studies suggest that weight gain may be associated with improved glycaemic control, but treatment should be re-evaluated in patients with excessive weight gain. The effect of glitazones on mortality and their role in long term treatment of type 2 diabetes are not yet established.

Reference:

1. Wooltorton E. Rosiglitazone (Avandia) and pioglitazone (Actos) and heart failure. *Can Med Ass J* 2002;166:219.

3. INTERSTITIAL NEPHRITIS WITH THE PROTON PUMP INHIBITORS

Interstitial nephritis is a well-recognised but rare hypersensitivity reaction to omeprazole (Acimax, Losec, Maxor, Probitor; Klacid HP 7, Losec HP 7).¹ Patients present with non-specific symptoms of illness. The classic triad for interstitial nephritis of fever, rash and eosinophilia is uncommon.² Laboratory investigation confirms the presence of renal dysfunction and urine examination, including microscopy, may show haematuria and proteinuria but may be unremarkable.³ The diagnosis can only be confirmed by renal biopsy. Management involves withdrawal of omeprazole and supportive treatment. Cases are commonly treated with glucocorticoids, but the efficacy of this therapy has not been demonstrated in controlled trials.²

ADRAC has received 18 biopsy-confirmed reports of interstitial nephritis with omeprazole. The median age was 68 (range 47-86) years, with 5 males and 13 females affected. The median time to onset was 3 months (range 12 days to 12 months). In 7 cases the association was not made immediately, and withdrawal of omeprazole occurred 3 weeks to 6 months after the first symptoms of interstitial nephritis. Nine of the 18 patients had recovered at the time of the reporting, including two who showed rapid recovery over 2 or 3 weeks.

Presenting symptoms included weight loss, malaise, fever and nausea. Polyuria and polydipsia were present in one case. Elevation of plasma urea

and/or creatinine was documented in most cases. Urine microscopy, in 3 cases, showed red cells, white cells and casts. In the 8 cases for which details of the results of renal biopsy were provided, mononuclear infiltrates of lymphocytes, plasma cells and eosinophils were usually present and some also had histiocytes.

ADRAC has also received two reports of biopsy-proven interstitial nephritis with rabeprazole (Pariet). No reports have been received in Australia for the other proton pump inhibitors, but interstitial nephritis is listed as an adverse effect in the product information for esomeprazole (Nexium), lansoprazole (Zoton) and pantoprazole (Somac).

Interstitial nephritis has also been associated with the β -lactam and sulphonamide antibiotics, diuretics, NSAIDs, cimetidine, allopurinol and rifampicin. Patients taking a proton pump inhibitor, or any of the medicines listed above who become unwell without identified cause should have renal function assessed.

References:

1. ADRAC. Omeprazole and interstitial nephritis. *Aust Adv Drug React Bull* 1995;14:15
2. Myers RP, McLaughlin K, Hollomby DJ. Acute interstitial nephritis due to omeprazole. *Am J Gastroenterology* 2001;96:3428-31
3. Savage R. Omeprazole-induced interstitial nephritis. *Prescriber Update* No.20, p.11-13, 2001

4. INTERACTIONS WITH GRAPEFRUIT JUICE - AMENDMENT

Following comments received after publication of its recent article 'Interactions with Grapefruit Juice,'¹ ADRAC has re-evaluated the literature, and wishes to revise its advice. Although there are no case reports of significant clinical problems occurring when grapefruit juice and medication ingestion have been separated by more than a few hours, studies suggest there is a potential for grapefruit juice to have an interacting effect for up

to 3 days after ingestion, particularly with daily consumption. ADRAC now considers that the safest course is to avoid grapefruit and its juice altogether when taking medicines that interact.

Reference:

1. ADRAC. Interactions with grapefruit juice. *Aust Adv Drug React Bull* 2002;21:14

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.health.gov.au/tga/adr/index.htm>

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 clicking on "Online Services" at the TGA website (<http://www.health.gov.au/tga>) and following the links.**

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

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

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The Bulletin is also available on the Internet at: <http://www.health.gov.au/tga/adr/aadrb.htm>

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