Prepared by the ADVERSE DRUG REACTIONS ADVISORY COMMITTEE (ADRAC). ADRAC is Dr Tim Mathew (Chair), Dr Roberta Chow, Dr Paul Desmond, Dr David Isaacs, Dr Cecilie Lander, Professor John McNeil, Professor Gillian Shenfield, Dr Dana Wainwright

AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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

Bupropion (Zyban)
Candesartan (Atacand)
Celecoxib (Celebrex)
Clopidogrel (Iscover, Plavix)
Entacapone (Comtan)
Eprosartan (Teveten)
Gelatin succinylated (Gelofusine)
Leflunomide (Arava)
Naltrexone (ReVia)
Orlistat (Xenical)
Quetiapine (Seroquel)
Raloxifene (Evista)
Repaglinide (NovoNorm)
Rivastigmine (Exelon)
Rofecoxib (Vioxx)
Rosiglitazone (Avandia)
Sildenafil (Viagra)
Telmisartan (Micardis/Pritor)
Tramadol (Tramal)
Zolpidem (Stilnox)

1. RESTRICTION OF INDICATIONS FOR CISAPRIDE

As most readers would be aware, cisapride (Prepulsid) has been associated with serious cardiac arrhythmias and has been subject to regulatory action in many countries. Its use has been suspended in the United Kingdom and its availability greatly restricted in the United States.

Earlier this year, ADRAC conducted a comprehensive review of the safety of cisapride. There had been 343 reports to ADRAC of adverse reactions involving cisapride and it was the only suspected drug in 210 of the cases. Five of the reports were associated with a fatal outcome but cisapride toxicity did not seem to play a major role in any of them. Approximately 12% of the reports concerned patients aged 12 years or less.

There were 52 reports describing cardiac reactions. Many of these described minor effects such as palpitations or tachycardia but there were 12 reports of serious arrhythmias including prolonged QT interval or torsades de pointes.

In 10 cases cisapride was suspected of interacting with another drug to result in an adverse effect. Four of these involved concomitant erythromycin and in 3 of these cases, the combination resulted in a prolonged QT interval.

ADRAC reviewed the results from several postmarketing studies and other information provided by the sponsor. The Committee concluded that the benefit risk balance of cisapride was less favourable than had previously been considered. It was also noted that other drugs such as proton pump inhibitors were now available to treat some of the indications for cisapride.

Following the review, the indications have been revised by the TGA as follows:

- Gastroparesis where the diagnosis has been made or confirmed by a specialist physician.
- Severe reflux oesophagitis in adults where other available treatment including acid suppression with proton pump inhibitor drugs has failed.
- Severe, proven gastro-oesophageal reflux in children.

The sponsor has sent a “Dear Doctor” letter to all Australian prescribers and pharmacists, advising of these changes, and a boxed warning highlighting the cardiac and interaction issues has been included in the Product Information.

2. INTERACTION BETWEEN ERGOTAMINE AND ERYTHROMYCIN

Ergotism is manifested by symptoms and signs of peripheral ischaemia due to constriction of vascular smooth muscle caused by direct action of an ergot derivative. Headache, intermittent claudication, muscle pain, numbness, coldness and pallor of the extremities may occur, and gangrene has been reported. Ergotism is usually associated with excessive dosing of ergot preparations but has also been reported with normal doses of ergotamine preparations when there was concomitant use of macrolides (particularly erythromycin). The mechanism of the interaction is not established but may involve an inhibition of ergotamine metabolism or an increased gut absorption resulting in an increase in serum ergotamine concentration.

In recent years, ADRAC has received two reports describing severe ergotism in association with the combined use of ergotamine and erythromycin. The first report described a 47 year old female who developed loss of power and sensation in her feet, an acutely tender left gastrocnemius muscle, absent peripheral pulses and evidence of early gangrene. This followed the addition of erythromycin to her long-term Migral (ergotamine tartrate, cyclizine, caffeine) therapy. On the fourth day of the course of erythromycin, the patient experienced right arm claudication and left arm paraesthesia after she had taken 3 Migral tablets over the preceding 48 hours. On the 5th day, a worsening of her symptoms of peripheral ischaemia followed within minutes of taking two Migral tablets. The

patient survived but the left leg required amputation below the knee.

The second report described severe peripheral ischaemia affecting both arms of a 55 year old male as a result of clinical ergotism. He was taking long-term ergotamine (two 2 mg per week) for migraine and the reaction occurred after also taking erythromycin for 2 weeks to treat an upper respiratory tract infection.

ADRAC has also received reports of ergotism arising from the combination of ergotamine with ritonavir, and with verapamil, and has noted published reports of similar interactions with protease inhibitors, particularly ritonavir.[1,2]

These reports suggest that the basis of the interaction is inhibition of either cytochrome P4503A4 in the liver or gut P-glycoprotein with subsequent increase in ergotamine concentrations. As most inhibitors of CYP3A4 also inhibit P-glycoprotein, the concomitant use of erythromycin and other known inhibitors of CYP3A4 with ergotamine preparations should be avoided.

References:

1. Phan TG, Agaliotis D, White G, Britton WJ. Ischaemic peripheral neuritis secondary to ergotism associated with ritonavir therapy. *MJA 1999; 171: 502-3*.
2. Blanche P, Rigolet A, Gombert B et al. Ergotism related to a single dose of ergotamine tartrate in an AIDS patient treated with ritonavir. *Postgrad Med J 1999; 75: 546-7.*

3. METHYSERGIDE AND CARDIAC VALVULOPATHY

Methysergide (Deseril) is an ergot alkaloid used in the prophylaxis of migraine. Its most well known serious adverse effect is retroperitoneal fibrosis. It has also been reported to be associated with fibrotic changes to other organs including heart valves.[1] ADRAC has received two recent reports describing cardiac valvulopathy.

A 74 year old female had been taking methysergide for cluster headaches since 1990. In 1995 she developed symptoms of cardiac failure and in July 1999 she had a triple valve replacement because of cardiac failure due to severe valvular regurgitation. Histological analysis showed pathological features in the aortic, anterior mitral and tricuspid valve that resembled changes described by the pathologist as methysergide dystrophy. A second report described a 43 year old male who developed extensive bilateral pleural fibrosis, atrial fibrillation and mitral incompetence after taking methysergide.

The prescribing information for methysergide states that continuous administration of the drug should not exceed 6 months and then methysergide should be withdrawn for 3-4 weeks before recommencement. Of particular interest in the two ADRAC reports was that the cardiac abnormalities occurred despite interrupted treatment according to directions.

The valve damage reported in association with methysergide appears to be similar to that reported with carcinoid syndrome, with ergotamine and more recently with fenfluramine/dexfenfluramine. Many of these reports describe the presence of a white surface plaque on the valves. These observed similarities suggest that a common factor may be causing the damage and may be related to the action of excess serotonin.

Prescribers should be aware that although methysergide drug holidays are generally recommended to prevent fibrotic changes, these changes can still occur and may affect cardiac valves.

Reference:

1. Redfield MM, Nicholson WJ, Edwards WD, Tajik AJ. Valve disease associated with ergot alkaloid use: echocardiographic and pathologic correlations. *Ann Intern Med 1992; 117: 50-2.*

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, 87, 88, or from the website: www.health.gov.au/tga/docs/html/adr.htm

Tear-out blue cards can also be found at the front of the "Schedule of Pharmaceutical Benefits", and at page 19 of the 2nd edition of the “Australian Medicines Handbook”.

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

Medical Officer: ☎ 02-62328381 Executive Secretary: ☎ 02-62328382
Fax: 02-62328392

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

The Bulletin is also on the Internet: www.health.gov.au/tga/docs/html/aadrbltn/aadrbidx.htm

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