Prepared by the Adverse Drug Reactions Advisory Committee (ADRAC). Members of ADRAC are Associate Professor Duncan Topliss (Chair), Dr David Isaacs, Dr Cecilie Lander, Professor John McNeil, Dr Peter Pillans, Dr Simone Strasser, Dr Dana Wainwright

AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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- ☆ Cardiac valvulopathy with pergolide
- ☆ Clopidogrel – haemorrhage and haematological disorders
- ☆ Pulmonary toxicity with long-term nitrofurantoin
- ☆ Tramadol-warfarin interaction

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

Aripiprazole (Abilify)
Atomoxetine (Strattera)
Ezetimibe (Ezetrol)
Fondaparinux (Arixtra)
Levetiracetam (Keppra)
Pimecrolimus (Elidel)
Pioglitazone (Actos)
Reboxetine (Edronax)
Rosiglitazone (Avandia)
Sibutramine (Reductil)
Tegaserod (Zelmac)

1. CARDIAC VALVULOPATHY WITH PERGOLIDE

Pergolide (Permax) is a dopamine agonist and ergot derivative indicated for the adjunctive treatment of Parkinson's disease. An association has recently been identified between pergolide and valvular heart disease.[1] This evidence has been subsequently supported by a study which found cardiac valvulopathy in 26 of 78 patients (33%) with Parkinson's disease who were treated with pergolide, but in none of 18 patients who had never been treated with ergot-derived dopamine agonists.[2] Mean cumulative dose in the pergolide group was 3000g and mean duration of use was 18 months. There was a trend to more severe disease with greater exposure to pergolide (tenting areas of mitral valves correlated with cumulative dose). The mitral valve was affected in most (20) of the patients and smaller numbers had restriction of the aortic and tricuspid valves. Mean systolic pulmonary artery pressures were significantly higher in the pergolide recipients versus the control group ($p = 0.02$). Pergolide was discontinued in only six of the patients with restrictive valvular heart disease and improvement had occurred in two of them six months after discontinuation of pergolide.

Pergolide-related valvulopathy involves fibro-restrictive lesions of the cardiac valves and is typically associated with valve regurgitation. Other ergot derivatives, such as methysergide and ergotamine, and the appetite-suppressants fenfluramine and dexfenfluramine (withdrawn worldwide in 1997), are known to cause a similar cardiac valvulopathy.[3,4] Valvulopathy associated with the carcinoid syndrome and with ergot derivatives including pergolide is attributed to high serotonin levels. Fenfluramine and dexfenfluramine also cause pulmonary hypertension and along with pergolide interact with the serotonin 5-HT_{2B} receptor.[2]

ADRAC has as yet received no reports of valvular heart disease with pergolide, possibly reflecting lack of recognition of the association. Although cabergoline (Cabaser, Dostinex) is also an ergot derivative, there are, at present, no associated reports of valvulopathy to ADRAC or in the published literature. ADRAC requests reports of any cases of valvular heart disease possibly associated with use of pergolide or cabergoline.

Before pergolide is prescribed, patients should be advised of the risk of valvulopathy. Prescribers should conduct a thorough baseline clinical cardiovascular examination including a check of patient history, and perform regular follow-up checks of patients taking pergolide. Echocardiography should be considered if a murmur is detected. Consideration should be given to discontinuation of pergolide if new-onset valvular disease is confirmed.

References:
1. Van Camp G et al. *Neurology* 2003;61:859-61
2. Van Camp G et al. *Lancet* 2004;363:1179-83
3. *Aust Adv Drug Reactions Bull* 2000;19:15
4. *Aust Adv Drug Reactions Bull* 1998;17:3

2. CLOPIDOGREL – HAEMORRHAGE AND HAEMATOLOGICAL DISORDERS

Clopidogrel (Plavix, Isocover) is indicated for the prevention of myocardial infarction and stroke in patients with atherosclerosis and, in combination with aspirin, for the treatment of acute coronary syndrome. It inhibits platelet aggregation, with activity persisting for as long as seven days. In 2003, 1.3 million PBS prescriptions were dispensed.

Haemorrhagic events have been described in 28% of the reports ADRAC has received in association with clopidogrel (130 of a total of 460 reports). Clopidogrel was the only suspected drug in 27 cases and another 27 cases were attributed to clopidogrel plus aspirin alone (see Table 1). In 63 (48%) of the cases, the patient was taking clopidogrel plus two or more other drugs which are known to cause bleeding (anticoagulants, thrombolytics, platelet inhibitors, NSAIDs). Of the 130 reports, 18 had a fatal outcome.

Table 1: ADRAC reports of haemorrhage with clopidogrel

Suspected drug(s)	No. of cases (No. of fatal cases)
Clopidogrel alone	27 (1)
Clopidogrel + aspirin alone	27 (1)
Clopidogrel + one other drug*	25 (4)
Clopidogrel + ≥ 2 other drugs*	63 (12)
Total reports of haemorrhage	130 (18)

* Anticoagulants, thrombolytics, platelet inhibitors, NSAIDs

In the CAPRIE study, the rate of any bleeding disorder with clopidogrel was 9.3% (15% severe).[1] The risk of bleeding events had been reduced in this study by discontinuing anticoagulants and antiplatelet drugs before randomisation. Further, the MATCH study of high-risk stroke patients

found that adding aspirin to clopidogrel doubled the risk of life-threatening bleeds from 1.3% to 2.6% ($p<0.001$).[2] In addition to increasing the risk of haemorrhage, the ADRAC data suggest that concurrent use of more than two drugs with the potential to cause bleeding increases the likelihood of fatality (19% of reports with ≥ 3 suspected drugs had a fatal outcome, see Table 1).

Table 2: Reports of haematological disorders with clopidogrel and ticlopidine

	Clopidogrel	Ticlopidine
Neutropenia	14	26
Agranulocytosis	4	22
Other leukopenia	4	6
Thrombocytopenia	42	19
Thrombocytopenic purpura	4	5
Pancytopenia	1	2
Anaemia	19	4
Total reports	460	181
Total PBS prescriptions (million)	4.0	0.16

Blood dyscrasias, with a total of 80 reports to ADRAC, are another common reaction type with clopidogrel. Table 2 compares the number of these reports for clopidogrel and ticlopidine (Ticlid, Tilodene). Considering usage, ticlopidine is associated with a much higher rate of reporting of agranulocytosis, neutropenia and thrombocytopenia than clopidogrel.[3] ADRAC has received one report of the life-threatening thrombotic thrombocytopenic purpura (TTP), involving disseminated platelet aggregation, with each drug.[4,5] Clopidogrel has largely replaced ticlopidine, because of its greater safety in relation to bone marrow suppression and TTP.

Allergic cutaneous reactions, particularly urticaria, rash and puritus, are also a common adverse effect of clopidogrel (141 reports).

Prescribers should be aware of the risk of haemorrhagic complications with clopidogrel, especially when it is used in combination with other anti-thrombotic agents.

References:
1. CAPRIE Steering Committee. *Lancet* 1996;348:1329-39
2. Denier H-C et al. *Lancet* 2004;364:331-7
3. *Aust Adv Drug Reactions Bull* 1998;17:6
4. *Aust Adv Drug Reactions Bull* 1999;18:15
5. Bennett CL et al. *New Engl J Med* 2000;352:1773-6

3. PULMONARY TOXICITY WITH LONG-TERM NITROFURANTOIN

Nitrofurantoin (Macrodantin, Furadantin, Ralodantin) is indicated for the treatment of urinary tract infections. The Therapeutic Guidelines: Antibiotic also recommend nitrofurantoin for the prophylaxis of urinary tract infections.[1,2] In the 12 months to May 2004, there were 122,000 PBS prescriptions for nitrofurantoin.

To date, ADRAC has received 576 reports of suspected adverse reactions to nitrofurantoin, with pulmonary reactions described in 142 reports (25%), including 46 reports received since the last ADRAC publication on the subject in 1995.[3] Forty of the reports of pulmonary reactions related to long-term use and were consistent with pulmonary fibrosis or interstitial pneumonitis, on the basis of chest x-ray, CT scan, biopsy or post-mortem examination. The most common presenting symptoms were dyspnoea or cough, but some had hypersensitivity features (fever, rigors, pruritus, rash, or eosinophilia).

The reports usually involved elderly females (female 7:1 male; median age 70 years; range 47-90 years), probably reflecting usage. The nitrofurantoin doses were 50-300 mg/day (recommended daily dose for prophylaxis 50-100mg). Some reports described severe pulmonary reactions with exposure as low as 50 mg/day for 8 months. The longest time to onset was 16 years. Recovery by the time of reporting was documented in 12 cases, but some patients showed indications of persistent lung damage. Two patients died as a result of pulmonary toxicity.

The pulmonary toxicity of nitrofurantoin should be considered when treatment is extended for ≥ 6 months, especially if the patient is elderly. Patients should be made aware of the possibility of pulmonary toxicity, and advised to report dyspnoea or persistent cough. If pulmonary reactions occur, nitrofurantoin should be immediately stopped. Although cessation may be followed by regression of symptoms, the resolution of pulmonary injury arising from long-term use may be incomplete.

References:
1. Therapeutic Guidelines: Antibiotic Version 12, 2003. Therapeutic Guidelines Limited, Melbourne, Australia pp 245-9
2. *Australian Prescriber* 2004;27:83
3. *Aust Adv Drug Reactions Bull* 1995;14:14

4. TRAMADOL-WARFARIN INTERACTION

Some individuals are susceptible to an interaction between tramadol (Tramal, Zydol) and warfarin (Coumadin, Marevan). ADRAC has received 11 reports of this interaction leading to an increase in INR or a haemorrhagic event. The median onset time after addition of tramadol to stabilised warfarin therapy was 4 (range 3-7) days, with the exception of one outlier at 6 weeks. Five reports describe rapid recovery within 1-4 days of withdrawal of tramadol with or without reduction in the dose of warfarin. Two patients, aged 76 and 88 years, died of haemorrhagic stroke. In one of these patients, both tramadol and warfarin were continued for six days after an INR of 5.0 was measured.

Four cases of interaction between tramadol and warfarin have been reported in the English language literature,[1-3] and the interaction is included in the Australian product information for products containing tramadol. It is unclear whether the interaction occurs with injectable tramadol.

Boeijinga et al have conducted a pharmaco-dynamic study of the effect on INR of giving tramadol to 19 individuals stabilised on phenprocoumon (a coumarin anticoagulant with properties similar to warfarin).[4] Two of the individuals had clinically significant increases in INR to 6.0 and 7.3, respectively, while they were taking tramadol, but the mean difference in INR for all participants did not reach statistical significance. The mechanism of the interaction is unclear, but these results suggest that the interaction may be associated with a variation in metabolism present in a small proportion of the population. With a total of 4.2 million PBS prescriptions for oral tramadol and 11 reports of tramadol-warfarin interaction (c.f. 827 total reports for tramadol), this would appear to be an uncommon event in those taking both medications.

Prescribers are advised to monitor INR in the first few days for up to a week after adding tramadol to warfarin therapy.

References:
1. Madsen H et al. *Lancet* 1997;350:637
2. Sabbe JR et al. *Pharmacotherapy* 1998;18:871-3
3. Scher ML et al. *Ann Pharmacotherapy* 1997;31:646-7
4. Boeijinga JK et al. *J Clin Pharmacol* 1998;38:966-70

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

Reports of suspected adverse drug reactions are best made by using a prepaid reporting form ("blue card") which is available from at the front of the "Schedule of Pharmaceutical Benefits" and the "Australian Medicines Handbook", or from the Adverse Drug Reactions Unit ☎ 02-62328386, 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 "adverse drug reaction reporting" on the right.
Further information can be obtained from the ADRAC Secretariat:

☎ 1800 044 114 Fax: 02-62328392 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
All correspondence to be addressed to: The Secretary, ADRAC, PO Box 100, Woden, ACT, 2606