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AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

Volume 24, Number 6, December 2005

- ☆ Medicines and QT prolongation
- ☆ Skin reactions with glucosamine
- ☆ Warfarin-induced skin necrosis

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

Aripiprazole (Abilify)
Atomoxetine (Strattera)
Ezetimibe (Ezetrol)
Fenofibrate (Lipidil)
Iron sucrose (Venofer)
Levetiracetam (Keppra)
Pimecrolimus (Elidel)
Pregabalin (Lyrica)
Reboxetine (Edronax)
Teriparatide (Fortéo)

1. Medicines and QT prolongation

In the past decade, a number of medicines have been either withdrawn from the market or had their use restricted because of QT interval prolongation.[1] The QT interval is considered to be prolonged if it is more than 450 msec after adjusting for heart rate ('corrected QT interval').

Drug-induced QT prolongation may be caused by blockade of cardiac potassium channels, and can lead to a life-threatening polymorphic ventricular tachycardia known as torsade de pointes. As of June 2005, ADRAC had received 140 reports of prolonged QT interval and/or torsade de pointes, 7 with a fatal outcome. The medicines most frequently implicated in these reports are sotalol (25), cisapride (17), clozapine (14), amiodarone (12) and erythromycin (12).

Table: Some medicines with a QT prolonging effect[2†]

antibiotics	**anti-arrhythmics**	**antipsychotics**
clarithromycin*	quinidine*	risperidone
azithromycin	sotalol	fluphenazine
erythromycin*	amiodarone	droperidol
roxithromycin	disopyramide	haloperidol*
metronidazole	procainamide	thioridazine*
moxifloxacin		pimozide*
		clozapine*
		olanzapine
antifungals	**antimalarials**	**antidepressants**
fluconazole	mefloquine	amitriptyline*
ketoconazole	chloroquine	imipramine*
		clomipramine
		dothiepin
		doxepin

†More comprehensive list at www.torsades.org
*These are metabolised by major CYP-450 enzymes[3]

Other, non-drug factors which may be associated with QT prolongation include female sex, advanced age, bradycardia, cardiac failure, cardiac ischaemia and electrolyte disturbances.

Drug interactions are an important cause of QT prolongation and torsade de pointes, even in healthy people with no risk factors. These interactions are of two types. The first involves the combined use of two or more drugs, each with a QT prolonging effect, i.e. the simultaneous use of two drugs from the Table. This most commonly is a problem when a drug used short-term, such as an antibiotic, is added to a long-term anti-arrhythmic, antipsychotic, or antidepressant.

The second type of interaction involves the concomitant use of a QT prolonging agent with another drug that inhibits the cytochrome P450 isoenzyme responsible for the hepatic metabolism of the first drug, thereby increasing that drug's concentration. Commonly used cytochrome P450 enzyme inhibitors include certain anti-arrhythmics, SSRIs, antiretrovirals, azole antifungals, macrolide and quinolone antibiotics, and calcium channel antagonists.[3]

Prescribers should be aware of these possible interactions, and should use a non-interacting alternative whenever possible.

References:
1. Roden DM. Drug-Induced Prolongation of the QT Interval. *N Engl J Med* 2004;350:1013-22.
2. Jayasinghe R, Kovoor P. Drugs and the QTc interval. *Aust Prescr* 2002;25:63-5.
3. Liu BA, Juurlink DN. Drugs and the QT Interval - Caveat Doctor. *N Engl J Med* 2004;351:1053-6.

2. Skin reactions with glucosamine

ADRAC has received 51 reports of allergic skin reactions including erythematous rash, angioedema, urticaria, rash and pruritus with glucosamine. Some glucosamine is obtained from seafood, and products sold in Australia containing glucosamine from this source have a statement specifying this on the label. People with a shellfish allergy may be more susceptible to allergic skin reactions when taking glucosamine sourced from seafood. In several cases reported to ADRAC, the patient had tolerated another glucosamine-containing product without adverse effect.

3. Warfarin-induced skin necrosis

Skin necrosis associated with warfarin is rare (0.01-0.1%) but well-documented.[1] Published reports suggest it is more likely to occur in women than men (ratio 9:1) typically with a time to onset of 1 to 10 days after commencing warfarin, when loading doses are used to increase INR rapidly after venous thromboembolism.[1,2] However, onset times of up to 15 years have been documented.[1] Buttocks, thighs and breasts, where there are heavy layers of subcutaneous fat, are the most commonly affected areas,[3] but other sites have been described including feet, calves, trunk and penis.[1,2]

ADRAC has received nine reports of skin necrosis with warfarin, of which three resulted in a fatal outcome (two cases published [4,5]). The time to onset was within seven days of commencing warfarin in four cases, but in three cases the first symptoms occurred 3-8 weeks after starting warfarin.

The necrosis occurs following haemorrhagic infarction or thrombosis in the skin tissue.[1-3] The first symptoms may be paraesthesia, or a sensation of pressure, with erythema. Painful lesions occur suddenly, and over 24 hours, petechiae and haemorrhagic bullae may develop leading to full-thickness skin necrosis. Warfarin should be withdrawn and substituted by heparin. The condition may be severe and may require local wound care, debridement of necrotic tissue and skin grafting.

It has been suggested that introducing warfarin gradually starting at 1-2mg daily, to achieve the desired therapeutic level after 10 days, will reduce the risk of skin necrosis.[2] Using this approach, concomitant use of heparin can provide adequate anti-coagulation initially. Particular care should be exercised in patients with risk factors which include hereditary or acquired deficiency in proteins C or S.[2] When starting warfarin, patients should be advised to report any soreness or apparent bruising of skin tissue.

References:
1. Chan YC, Valenti D, Mansfield AO, Stansby G. Warfarin induced skin necrosis. *Brit J Surgery* 2000;87:266-72.
2. Stewart AJ, Penman ID, Cook MK, Ludlam CA. Warfarin-induced skin necrosis. *Postgrad Med J* 1999;75:233-5.
3. Ad-El DD, Meirovitz A, Weinberg A, Kogan L, Arieli D, Neuman A, Linton D. Warfarin skin necrosis: local and systemic factors. *Brit J Plastic Surgery* 2000;53:624-6.
4. Scarff CE, Baker C, Hill P, Foley P. Late-onset warfarin necrosis. *Australasian J Dermatol* 2002;43:202-6.
5. Parsi K, Younger I, Gallo J. Warfarin-induced skin necrosis associated with acquired protein C deficiency. *Australasian J Dermatol* 2003; 44:57-61.

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

ISSN 0812-3837

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