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AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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- ☆ Interactions with grapefruit juice
- ☆ Miconazole oral gel elevates INR — a reminder
- ☆ Fluoroquinolones and tendon disorders
- ☆ Online reporting of adverse reactions — coming soon

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

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

1. INTERACTIONS WITH GRAPEFRUIT JUICE

The serendipitous discovery in 1991 of the interaction of grapefruit juice with drugs occurred when grapefruit juice was used to mask the taste of ethanol in a study testing an interaction between the dihydropyridine calcium channel blocker felodipine and ethanol.[1] It is now known that grapefruit juice can interact with a number of drugs, the basis of the interaction being the local inhibition of one of the cytochrome P450 enzymes (CYP3A4) and P-glycoprotein (Pgp) in enterocytes in the intestinal wall.[2] It has been shown that grapefruit juice *does not affect* hepatic CYP3A4.

Interactions with grapefruit juice have been most frequently studied with the dihydropyridine calcium channel blockers (CCBs) including felodipine and nifedipine. Significant interactions have also been found for some of the HMG-CoA reductase inhibitors (statins), particularly simvastatin but possibly also atorvastatin; the benzodiazepines midazolam and triazolam; as well as cyclosporin, saquinavir, and cisapride. This is not an exhaustive list and there are a number of other drugs with a potential for interaction which have not been studied. A recent article in the *Australian Prescriber* contains a more comprehensive list.[3] The two most important characteristics of the "target" drugs are metabolism by gut wall CYP3A4 and/or Pgp and associated low oral bioavailability.

ADRAC has received 14 reports describing possible interactions with grapefruit juice. Most have involved either the dihydropyridine CCBs (5) or statins (5). Three of the reports with CCBs have involved amlodipine, an interaction which is usually considered clinically insignificant. Grapefruit juice can inhibit the metabolism of target drugs and increase the amount of parent drug available for absorption, which may result in an increase in its pharmacological or toxic effects. For the CCBs, the reports usually describe hypotension and related symptoms, and for the statins, most reports describe myalgia and associated effects.

Prescribers should be aware that there are several groups of drugs that may interact with grapefruit juice and patients taking these drugs should be made aware of the possibility. It should also be noted that problems can arise from whole grapefruit (as in four of the ADRAC reports), and that the extent of the interaction can vary with different brands and strengths of juice. It is believed that with the exception of bitter Seville oranges, the interaction does not occur with other citrus fruits.

Options for discussion with patients include:

- Avoid grapefruit juice all together
- Take medication with grapefruit juice every day (with dose adjustment if necessary)
- Separate grapefruit juice and medication by a minimum of 2 hours

References:

1. Bailey DG, Spence JD, Munoz C, Arnold JMO. Interaction of citrus juices with felodipine and nifedipine. *Lancet 1991; 337: 268-269.*
2. Bailey DG, Malcolm J, Arnold O, Spence JD. Grapefruit juice-drug interaction. *Br J Clin Pharmacol 1998; 46: 101-110.*
3. McNeece J. Grapefruit juice interactions. *Aust Prescr 2002; 25: 37* (comprehensive table available at www.australian prescriber.com)

2. MICONAZOLE ORAL GEL ELEVATES INR — A REMINDER

ADRAC has previously drawn attention to the possibility of an interaction between miconazole oral gel (Daktarin Oral Gel) and warfarin resulting in elevation of INR.[1] The Committee has now received 18 reports describing this interaction which is the most serious and important of the reactions described in the 32 reports to ADRAC involving oral miconazole. In most cases there was a clinically significant increase in the INR of patients who had been stabilised on warfarin. This usually occurred within a week or two of commencing miconazole. In the 17 patients in whom the INR values were documented, the INR rose to between 7.5 and more than 18. In 9 cases, there were no symptoms but in the other 8 cases, the patients presented with bruising, haematuria or mucocutaneous bleeding. Most patients required the withdrawal of one or both drugs. At least 9 patients were given vitamin K and 5 of these required fresh frozen plasma.

Miconazole oral gel is absorbed to a sufficient extent to affect warfarin metabolism and hence increase its blood concentration and activity. This may occur through inflamed oral mucosa or from the bowel after swallowing the gel. An interaction is probably less likely when miconazole is administered to the skin or vaginally but ADRAC

has received one report of an interaction involving topical miconazole cream.

Prescribers should be aware that the possibility of an interaction with warfarin is the most important adverse effect of oral miconazole. It is mentioned in the product information and the consumer medicine information for both oral and vaginal miconazole products. It should also be noted that miconazole products are available without prescription and pharmacists as well as doctors need to be alert to the possible interaction.

Reference:

1. ADRAC. Interaction between miconazole oral gel and warfarin. *Aust Adv Drug React Bull 1998; 17: 7.*

3. FLUOROQUINOLONES AND TENDON DISORDERS

The association between fluoroquinolone antibiotics and tendon disorders (especially involving the Achilles tendon) has been reported by ADRAC and has recently been confirmed by an epidemiological study.[1,2,3] A group of Dutch workers reviewed data from a large UK general practice database. They studied a cohort of 46,776 patients who had used fluoroquinolones over a 6 year period and identified 704 cases of Achilles tendinitis and 38 cases of Achilles tendon rupture. Current use of fluoroquinolones was associated with 46 of these cases. The adjusted relative risk of Achilles tendon disorders with current use of fluoroquinolones was 1.9 (95% confidence interval 1.3 to 2.6). This risk was increased to 3.2 (2.1 to 4.9) among patients aged 60 and over and was not significant in patients under 60 at 0.9 (0.5 to 1.6). In patients aged 60 or over, concurrent use of corticosteroids and fluoroquinolones increased the relative risk to 6.2 (3.0 to 12.8).

There have been 112 Australian cases of tendon disorders with the fluoroquinolones reported to ADRAC, including 30 cases of tendon rupture. Almost all have involved the Achilles tendon. Most occurred with ciprofloxacin (100) but there have also been cases with norfloxacin (9), gatifloxacin, enoxacin and moxifloxacin (all 1 each). It is not known why there have been so many more reports with ciprofloxacin as it and norfloxacin have had a similar number of prescriptions (over 600,000) dispensed on the PBS over the past 5 years. The other three fluoroquinolones are not subsidised by the PBS. In the Dutch study, ciprofloxacin and norfloxacin had a similar risk but there was an increased risk with ofloxacin, which is not available in Australia. Of the 106 reports where the age was specified, 73 patients were aged 60 or over, and 20 other patients were in their fifties. Although concomitant medication was not always documented, 47 patients were taking oral corticosteroids.

With the marketing of two new fluoroquinolones (gatifloxacin, moxifloxacin), ADRAC wishes to remind prescribers that tendon disorders are a class effect of fluoroquinolones and that increasing age and concomitant corticosteroids are established risk factors. Patients should be advised to be alert for pain or discomfort in the Achilles tendon or calf and inform their doctors if this occurs.

References:

1. ADRAC. The Achilles heel of fluoroquinolones. *Aust Adv Drug React Bull 1997; 16: 6.*
2. ADRAC. Tendinitis and tendon rupture with fluoroquinolones. *Aust Adv Drug React Bull 1999; 18: 10.*
3. van der Linden PD, Sturkenboom MCJM, Herings RMC, Leufkens HGM, Stricker BHCh. Fluoroquinolones and risk of Achilles tendon disorders: case-control study. *BMJ 2002; 324: 1306-7.*

4. ONLINE REPORTING OF ADVERSE REACTIONS — COMING SOON

ADRAC is preparing to commission a new database and as part of that redevelopment, online reporting of suspected adverse reactions will be available. Potential reporters of ADRs will be able to become "registered reporters" which will allow access to past notifications as well as to request information from the database. It will also be possible to lodge ADRs as an "unregistered reporter" which is designed for people who use the service infrequently. Online reporting will be available from 1 January 2003. To access this facility, click on "Online Services" at the TGA website (www.health.gov.au/tga) and follow the links. There will also be a link from the adverse drug reactions section of the website (www.health.gov.au/tga/adr).

In addition, ADRAC is working with the Collaborating Centre for eHealth at the University of Ballarat and 3 providers of prescriber desktop software (Locum, Medical Director, MedTech 32)

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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".

Further information can be found 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

ONLINE REPORTING OF ADVERSE REACTIONS (Continued)

to provide online reporting from prescriber software. The information available from the software will be automatically used to complete the fields on the online "blue card" and the prescriber will need only to complete the details of the ADR and a few other fields before the software sends the online form to ADRAC. It is anticipated that this facility will be available from early 2003. Once this work is complete, online reporting will be extended to the pharmaceutical industry using the ICH specifications. It also hoped to extend online reporting to hospitals and pharmacies.

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