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AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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Drug interactions and adverse drug reactions

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

Acamprosate (Campral)
Candesartan (Atacand)
Celecoxib (Celebrex)
Clopidogrel (Iscover, Plavix)
Entacapone (Comtan)
Eprosartan (Teveten)
Gelatin succinylated (Gelofusine)
Leflunomide (Arava)
Montelukast (Singulair)
Naltrexone (ReVia)
Orlistat (Xenical)
Quetiapine (Seroquel)
Raloxifene (Evista)
Repaglinide (NovoNorm)
Rofecoxib (Vioxx)
Sildenafil (Viagra)
Telmisartan (Micardis/Pritor)
Tramadol (Tramal)
Zafirlukast (Accolate)
Zanamavir (Relenza)

DRUG INTERACTIONS AND ADVERSE DRUG REACTIONS

One important cause of adverse drug reactions is altered drug metabolism as a result of drug interactions mediated by the cytochrome P450 (CYP) drug oxidation system. These enzymes are present in greatest amounts in the liver, but are also present in many other organs such as the lung, gut wall and kidney.[1] Most drug oxidation can be attributed to 6 main P450 cytochromes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Knowledge in this area has expanded rapidly in recent years and increasing numbers of clinically relevant interactions have been described. Clinically important effects usually arise when drugs are used which either inhibit or induce particular CYP enzymes. If such a drug inhibits the metabolism of a second drug, then this may result in the accumulation of that second drug and possible toxicity. Alternatively, if a drug induces the metabolism of a second drug, then this may result in a decrease in the concentration of that second drug with possible problems of clinical efficacy. A number of recent reports to ADRAC have demonstrated some of the possible outcomes.

Reference:

1. Shenfield G, Gross A. The cytochrome P450 system and adverse drug reactions. *Adv Drug React Bull 1999; 194: 739-42.*

1. CYCLOSPORIN AND ST JOHN'S WORT: CYP3A4

CYP3A4 is the most abundant cytochrome P450 enzyme in the liver and gut wall. It has a number of important substrates (eg. nifedipine, cyclosporin, simvastatin) as well as specific inducers (eg. carbamazepine, rifampicin) and inhibitors (eg. erythromycin, verapamil, grapefruit juice). In a report to ADRAC, a 50 year old female with a renal transplant was taking cyclosporin. Her blood concentrations of cyclosporin were stable for the weeks before she began to take a St John's wort preparation. Within a period of 22 days after starting to take this product, her blood cyclosporin concentration had fallen from around 180 µg/L to 42 µg/L and one week later it was 40 µg/L. The treating doctor could find no other cause for the change in cyclosporin concentration and asked the patient to stop taking St John's wort. About 6 days later, the concentration had risen to 89 µg/L and a further 8 days later it was 150 µg/L.

A recent study has shown a large reduction in the concentration of an HIV protease inhibitor, indinavir, by concomitant St John's wort.[1] Since CYP3A4 is the only major route of metabolism for indinavir, this study provides strong evidence that St John's wort induces CYP3A4. Two cases of heart transplant rejection due to reduction in cyclosporin blood concentrations have also bee reported.[2] Apart from the rejection, these two cases are very similar to the ADRAC report. It seems likely that St John's wort induces CYP3A4 and this results in increased metabolism of, and consequent reduction in the blood concentration of, cyclosporin.

References:

1. Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J. Indinavir concentrations and St John's wort. *Lancet 2000; 355: 547-8.*
2. Ruschitzka F, Meier PJ, Turina M, Lüscher TF, Noll G. Acute heart transplant rejection due to Saint John's wort. *Lancet 2000; 355: 548-9.*

2. SIMVASTATIN AND NEFAZODONE: CYP3A4

A 79 year old male had been taking gemfibrozil for three years for hyperlipidaemia together with nefazodone for depression. Simvastatin was added to improve lipid control. About two weeks after simvastatin was initiated, the patient presented to hospital with myositis and myopathy. He was treated in intensive care where a muscle biopsy showed "grouped atrophy consistent with a denervation process" and creatine kinase was measured at 122,480 units/L (reference range: 0-180 U/L). He then developed acute myoglobin-induced renal failure followed by respiratory failure with secondary pneumonia and septic shock with a fatal outcome.

It was considered that the patient developed rhabdomyolysis secondary to simvastatin. Although it is recognised that simvastatin and other HMG-CoA reductase inhibitors can induce myalgia, the rapid onset of rhabdomyolysis in this case is likely to be a result of the inhibition

of the metabolism of simvastatin producing abnormally high concentrations of the drug. Simvastatin is a known substrate for CYP3A4 and nefazodone is both a substrate and an inhibitor of this isoenzyme. It seems probable that in this case, nefazodone inhibited simvastatin metabolism causing an increase in simvastatin plasma concentrations. A similar case has been reported in the literature. [1]

Reference:

1. Jacobson RH, Wang P, Glueck CJ. Myositis and rhabdomyolysis associated with concurrent use of simvastatin and nefazodone. *JAMA 1997; 277: 296.*

3. PERHEXILINE AND PAROXETINE: CYP2D6

An elderly female was admitted to hospital with a history of dizziness, recurrent falls and nausea. Long-term medication included amiodarone, digoxin, captopril, thyroxine, frusemide, aspirin and perhexiline. Six weeks before admission, the patient had commenced paroxetine for treatment of depression. On admission, her trough serum perhexiline concentration was measured at 2.02 mg/L (reference range: 0.15 – 0.60 mg/L) and both paroxetine and perhexiline were stopped. Five weeks before admission, perhexiline concentration was 0.67 mg/L and 10 days after the drugs were stopped, serum concentration had decreased to 1.42 mg/L. The patient remained symptomatically toxic for 2 weeks before she died, probably from unrelated causes. Paroxetine is an inhibitor of CYP2D6 and it is this enzyme which is responsible for the metabolism of perhexiline. The addition of paroxetine caused inhibition of the metabolism of perhexiline, an increase in the serum concentration, and the development of symptoms of perhexiline toxicity. This case has been published. [1]

CYP2D6 is the most studied of the CYP450 enzymes under polymorphic genetic control. Well over 50 drugs are metabolised by this enzyme including codeine, perhexiline and nortriptyline. In general, the majority of the population can metabolise substrate drugs efficiently and have become known as extensive metabolisers (EM). In Caucasian populations, about 6-7% are poor metabolisers (PMs) and just under 1% are ultrarapid metabolisers (UMs). PMs are always at risk of adverse drug reactions as the slower rate of metabolism can result in a high concentration of a substrate drug at conventional doses. However EMs and UMs are the individuals at risk of elevation of plasma drug concentrations if they also take a CYP2D6 inhibiting drug.

The half-life of perhexiline ranges from about 2 to over 30 days depending on individual metabolism. In this patient, the perhexiline half-life was estimated to be approximately 23.5 days which accounted for the slow drop in perhexiline concentration and the continued signs of perhexiline toxicity even though the drug had been stopped.

Reference:

1. Alderman CP. Perhexiline-paroxetine drug interaction. *Aust J Hosp Pharm 1998; 28: 254-5.*

4. FLUVOXAMINE AND WARFARIN: CYP1A2

An elderly male with aortic stenosis had been taking 5 mg warfarin daily for years with a stable INR in the range 2-3. He then also took the selective serotonin reuptake inhibitor, fluvoxamine and within a month his INR was measured at 5.8.

The metabolism of warfarin is complex and many drugs can interact with it. The major metabolic pathway is CYP2C9 but CYP1A2 is also important. Fluvoxamine is a potent inhibitor of CYP1A2 and can also inhibit CYP2C19 (a minor metabolic pathway) and there is some evidence to suggest that it may inhibit CYP2C9.[1] Although the mechanism may have several components, it appears that fluvoxamine has inhibited the metabolism of warfarin resulting in an increase in the INR. A similar case has been reported in the literature.[2]

References:

1. Duncan D, Sayal , McConnnell H, Taylor D. Antidepressant interactions with warfarin. *Int Clin Psychopharmacol 1998; 13: 87-94.*
2. Yap KB, Low ST. Interaction of fluvoxamine with warfarin in an elderly woman. *Singapore Med J 1999; 40: 480-2.*

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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