AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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- ☆ Depression with interferon
- ☆ Coumadin and Marevan are not interchangeable
- ☆ Drug-induced gingival overgrowth
- ☆ A comparison of dicloxacillin with flucloxacillin

Prepared by the ADVERSE DRUG REACTIONS ADVISORY COMMITTEE (ADRAC), a subcommittee of the Australian Drug Evaluation Committee.
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1. DEPRESSION WITH INTERFERON

Interferon alfa (2a - Roferon-A and 2b - Intron A) is used in a variety of conditions including leukaemias, some carcinomas, multiple myeloma, non-Hodgkin's lymphoma, malignant melanoma and more recently, hepatitis B and C. The most commonly reported adverse reactions in association with interferon alfa are flu-like symptoms such as fever, fatigue, myalgia, joint pain, and headache. Serious effects documented include severe hypersensitivity reactions, and haematological, hepatic, cardiovascular and neurological effects, particularly at high dose. Psychiatric effects have been described and include depression and suicidal ideation. [1]

ADRAC has received 19 reports of **depression** or **suicidal ideation** associated with interferon alfa therapy. Eleven patients had depression alone, 4 had depression and suicidal ideation or attempt and there were 4 additional reports of suicide attempts. Three of the reports of suicide attempt were fatal. The onset was as early as the first day of treatment to 10 months after the start of therapy but most of the reports described a time to onset of a few weeks. In the 19 cases, interferon was used for a variety of conditions with hepatitis C (11 cases) and malignant melanoma (3 cases) the most common.

Prescribers should be aware that the adverse effects of interferon alfa may include mood changes, depression or suicidal ideation. If interferon alfa becomes more widely used in the treatment of hepatitis B and C, the occurrence of these problems is likely to increase. Particular care should be taken with the use of the drug in patients with a history of depression.

Reference:
1. Renault PF, Hoofnagle JH, Park Y et al. Psychiatric complications of long-term interferon alfa therapy. *Arch Intern Med 1987; 147: 1577-80.*

2. COUMADIN AND MAREVAN ARE NOT INTERCHANGEABLE

Warfarin is available in two brands ? Coumadin and Marevan. Coumadin is marketed in 1 mg, 2 mg and 5 mg tablets whereas Marevan is marketed in 1 mg, 3 mg and 5 mg tablets. ADRAC recently received a report describing an increased therapeutic response in association with the Coumadin brand of warfarin. The problem arose when a patient who had been taking Marevan 2 x 1 mg was prescribed 2 mg warfarin. Only Coumadin is available in this strength and after its use the patient's INR rose from its normally stable value of around 2 to over 5. The reporter indicated that this was the third similar case in the previous 18 months.

ADRAC believes that it is important for prescribers to recognise that Coumadin and Marevan **have not been demonstrated to be bioequivalent** and are therefore not interchangeable. This information is also presented in the Schedule of Pharmaceuticals Benefits booklet and the issue has been the subject of debate in the pages of the Australian Prescriber. [1]

Reference:
1. See for example, Fry FK, PBAC, Boots. Warfarin tablets. *Aust Prescr 1997; 20: 33.*

3. DRUG-INDUCED GINGIVAL OVERGROWTH

Gingival overgrowth or enlargement has been reported in 114 of the 128,000 reports contained in the ADRAC database. Those 114 cases are dominated by the presence of five drugs which account for 68% of the reports, as shown in Table 1.

In the series of patients reported to ADRAC in association with the dihydropyridine calcium channel blockers (CCBs), phenytoin and cyclosporin, ages ranged from 3 to 77 (median: 55) years. The reaction occurred

Table 1: Reports of Gingival Overgrowth	
Drug	Number of Reports
Nifedipine	25
Amlodipine	22
Felodipine	14
Phenytoin	13
Cyclosporin	9

from a few days to more than 4 years after commencing treatment although more than half of the patients had been treated for at least 6 months. The majority of patients had not recovered when the report was submitted to ADRAC. When recovery was documented, it was slow and ranged from weeks to more than a year after ceasing the drug. These findings are in keeping with a recent report.[1]

It has been estimated that gingival overgrowth occurs in about 50% of patients taking phenytoin, 25-80% of patients taking cyclosporin, and 15-20% of patients receiving nifedipine, but severe cases with nifedipine occur in less than 1%.[2,3] ADRAC has received only 2 reports each with diltiazem and verapamil so it is possible that gingival overgrowth is mainly associated with the dihydropyridine CCBs. It may be that these drugs all affect gingival tissue in the same way as the clinical features and histological characteristics of gingival overgrowth caused by all 3 classes of drug are similar. The pathogenesis of drug-induced gingival overgrowth is unknown with a number of mechanisms proposed.

Although it is an unusual adverse effect, prescribers should be aware of the possibility of gingival overgrowth associated with use of phenytoin, cyclosporin or the dihydropyridine CCBs. It is usually reversible with withdrawal of the offending drug. It is believed the condition can be minimised or even prevented with meticulous plaque control or dosage reduction.

References:
1. Brunet L, Miranda J, Farré M, Berini L, Mendieta C. Gingival enlargement induced by drugs. *Drug Safety 1996; 15: 219-31*.
2. Lawrence DB, Weart W, Laro JJ, Neville BW. Calcium channel blocker-induced gingival hyperplasia: case report and review of this iatrogenic disease. *J Fam Practice 1994; 39: 483-8*.
3. Johnson RB. Nifedipine-induced gingival over-growth. *Ann Pharmacother 1997; 31: 935*.

4. A COMPARISON OF DICLOXACILLIN WITH FLUCLOXACILLIN

Early in 1997 dicloxacillin was introduced onto the Australian market to provide an alternative to flucloxacillin in the treatment of staphylococcal infections. It was hoped that the incidence and severity of hepatic reactions would be less than with flucloxacillin. Table 2 shows the results after the first two calendar years of marketing.

Table 2: Dicloxacillin versus Flucloxacillin in 1997-98		
	Dicloxacillin	Flucloxacillin
Community prescriptions	493,000	1,182,000
Reports to ADRAC	151	175
Hepatic reactions	24	62
Cholestasis	3	17
Renal reactions	12	4
Interstitial nephritis	5	-

The table shows total reports, reports of hepatic reactions including those of cholestasis, reports of renal reactions and an estimate of community usage.[1] It shows a similar level of reporting despite a higher use of flucloxacillin in the community (hospital usage is unknown). However, this might be expected given that dicloxacillin is a new drug and a "Drug of Current Interest". There are fewer reports of hepatic reactions with dicloxacillin but more importantly, there are considerably fewer reports of cholestasis, and at this stage, no reports of a severe prolonged nature as were observed with flucloxacillin,. Also of interest is the fact that there have been 5 reports of interstitial nephritis with dicloxacillin whereas none have been reported for flucloxacillin in this period.

Reference:
1. McManus PR. Drug Utilisation Subcommittee, personal communication.

WHAT TO REPORT?

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 Section

☎ 02-62328386, 02-62328387, 02-62328388, or from the website: http://www.health.gov.au/tga/adr.pdf

Tear-out blue cards can also be found at the front of all recent editions of the "Schedule of Pharmaceutical Benefits", and at Appendix F of the “Australian Medicines Handbook”.

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

Secretary: ☎ 02-62328381 Executive Secretary: ☎ 02-62328382

Fax: 02-62328392

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

The Bulletin can also be found on the Internet at the TGA website: http://www.health.gov.au/tga

Drugs of Current Interest

Candesartan (Atacand)
Carvedilol (Dilatrend, Kredex)
Clopidogrel (Iscover, Plavix)
Donepezil (Aricept)
Gelatin succinylated (Gelofusine)
Montelukast (Singulair)
Naltrexone (ReVia)
Naratriptan (Naramig)
Nefazodone (Serzone)
Raloxifene (Evista)
Sildenafil (Viagra)
Tiludronate (Skelid)
Tramadol (Tramal)
Trovafloxacin (Trovan)
Zafirlukast (Accolate)
Zanamavir (Relenza)
Zolmitriptan (Zomig)

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