was shown recently and supports evidence that prostacyclin synthesis is COX-2 dependent.[3]

Given available evidence and uncertainties, what provisional advice should be given regarding the selective COX-2 inhibitors in the symptomatic treatment of osteoarthritis? On the grounds of cost alone, paracetamol should remain the drug of first choice for those in whom it provides worthwhile symptomatic relief. Patients for whom NSAIDs could provide significant relief, were it not for unacceptable adverse effects or the risk of upper gastrointestinal events, stand to benefit most from COX-2 inhibitors. However, 500 low-risk patients may need to be treated with a COX-2 inhibitor instead of an NSAID to prevent one complicated ulcer.[4] It has not yet been resolved whether age itself constitutes a risk of upper gastrointestinal events which is large enough to warrant selection of a COX-2 inhibitor instead of a conventional NSAID.

However, it should be noted that low dose aspirin should be continued where it is indicated and particularly so when a selective COX-2 inhibitor is being used (see above). Since the known variability between individuals in responsiveness to particular NSAIDs seems to extend to COX-2 inhibitors, patients who are changed from an NSAID that gives relief to a COX-2 inhibitor may be disappointed. The advantage of reduced risk for a seemingly remote contingency may be associated with less complete control of symptoms.

With regard to the inflammatory arthropathies, it should be noted that management of the prototypic disorder, rheumatoid arthritis, has changed considerably.[5] In recent onset polyarthritis, there is an impetus for early intervention with multiple therapies in patients at risk for ongoing disease and a poor prognosis. While definitive therapeutic strategies are yet to be determined, combinations such as methotrexate (with a modest folate supplement), sulfasalazine and hydroxychloroquine seem to hold most promise.[6] NSAIDs, including the COX-2 inhibitors, have a marginal role in these protocols as they may reduce symptoms without improving long-term outcomes, while displacing potentially more effective longer-acting interventions. The early use of prednisolone (or other glucocorticoids) is generally unhelpful, as it confounds clinical assessment and, through its endocrine action, is associated with inevitable unwanted effects. The place of newer biological therapies such as etanercept has not yet been resolved. On the grounds of cost alone, they are likely to be restricted to patients who do not respond to conventional long-acting drugs.

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Letters

Letters, which may not necessarily be published in full, should be restricted to not more than 250 words. When relevant, comment on the letter is sought from the author. Due to production schedules, it is normally not possible to publish letters received in response to material appearing in a particular issue earlier than the second or third subsequent issue.

Rifampicin and contraception

Editor, – The article 'Common questions about the management of meningococcal disease' (Aust Prescr 1999;22:117-8) discusses the efficacy of oral contraception following chemoprophylaxis for contacts of meningococcal disease. I have discussed this issue with the Family Planning Association and believe in-depth advice on how to manage contraception while taking rifampicin should be given to the contact.

Appropriate advice is: 'In the case of short term concurrent drug treatment, a barrier method should be used both during treatment and for seven days after discontinuation. If this would continue into the next oral contraceptive tablet-free interval, the woman should skip the tablet-free interval and start the next pack as soon as she has finished the pack in use.'[1]

This is an important issue, as advising women to stop oral contraception or use another method for four weeks after completion of chemoprophylaxis, increases the risk of non-compliance and causes further stress to the contact. It is also excessive and not necessary.

Giulietta Pontivivo
Registered Nurse
South East Sydney Public Health Unit
Sydney, NSW

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Debra Rowett and Tricia Warrick, Drug and Therapeutics Information Service (DATIS), Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia, comment:

The letter from Giulietta Pontivivo highlights the importance of providing clear advice to ensure both compliance with rifampicin and ongoing effective oral contraceptive use. It was not the intent of the article to recommend that oral contraceptives be ceased whilst on concomitant rifampicin and for four weeks after cessation of rifampicin, but rather to emphasise that, if using hormonal contraception, additional non-hormonal contraception is required over this time. This recommendation is in accordance with the Australian Medicines Handbook[1] and other standard reference texts.[2,3,4] Importantly, the British National Formulary[2] specifically highlights that 'rifampicin is such a potent enzyme-inducing drug that even if a course lasts for less than 7 days the additional contraceptive precautions should be continued for at least 4 weeks after stopping it.' Given the serious consequences of unwanted pregnancy, the recommendation of using additional non-hormonal contraception for four weeks was included in accordance with other standard reference sources. As conflicting opinion and advice is potentially confusing for both health professionals and patients, inclusion of this matter in the forthcoming revised NHMRC guidelines for the control of meningococcal disease in Australia would be welcomed.

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Assessing the statins

Editor, – We refer to the article 'Assessing the statins' by E. Hurley (Aust Prescr 1999;22:114-7). Recent updates to the pravastatin product information in relation to the drug interaction potential of the statins reflect a different perspective to that conveyed by the article.

Following a review by the Therapeutic Goods Administration a new paragraph has been inserted in the 'Drug Interactions' section. This reads:

> 'Unlike simvastatin and atorvastatin, pravastatin is not significantly metabolised *in vivo* by cytochrome P450 3A4. Therefore, plasma concentrations of pravastatin are not significantly elevated when cytochrome P450 3A4 is inhibited by agents such as diltiazem and itraconazole.
>
> In interaction studies with aspirin, gemfibrozil, nicotinic acid or probucol, no statistically significant differences in bioavailability were seen ...'

Further, we are unaware of data supporting the assertion that there is significant P450 2C9 and 2D6 isoenzyme involvement in the metabolism of pravastatin.

Simvastatin, but not pravastatin, has been associated with rhabdomyolysis in a population at high risk of drug-drug interactions (cardiac transplant patients).[1]

The article represented a degree of uniformity among the statins that is not supported by the approved product information, a situation that we feel deserves clarification for your readers.

Kim Magner
Bristol Myers-Squibb Pharmaceuticals
Noble Park, Vic.

REFERENCE

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Ms Eve Hurley, the author of the article, comments:

In vivo data on pravastatin's hepatic metabolism and the likelihood of drug interactions through CYP P450 3A4 are useful, and superior to results of an *in vitro* study which found moderate affinity for P450 2C9, 2D6 and 3A4.[1] However, the section regarding interaction studies (which include gemfibrozil and nicotinic acid) if taken out of context, could give the impression that it is 'safe' to use these drugs in combination with pravastatin. The product information also includes information about gemfibrozil significantly increasing concentrations of a metabolite of pravastatin and the combination being 'not generally recommended'.

Rhabdomyolysis has been reported very rarely with statins, including pravastatin.[2] Statins are well tolerated and have few clinically important interactions. My review did not include information on the management of interactions, which are given in the Australian Medicines Handbook. In preference to listing approved indications, the major clinical studies (on which the indications are based) were summarised, enabling prescribers to assess the potential benefits of treatment for their patients.

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