Annals of the
RHEUMATIC DISEASES

Leaders

Arthrotec for all?

The incidence of peptic ulceration and its complications has been falling considerably since the Second World War, especially in the young and middle aged, and it seems likely that this reflects the falling prevalence of *Helicobacter pylori*.[1 2] However, since the late 1960s a marked contrast to this trend has been observed in elderly women where the prevalence of peptic ulcer and its complications has risen steeply.[3 4] Since this has occurred during the period when non-steroidal anti-inflammatory drugs (NSAIDs) have been widely available and ulcer complication rates have closely paralleled prescribing rates in this group, it was natural to ask whether the two are related.

The most reliable data come from epidemiological studies of patients presenting involuntarily with gastrointestinal complications. Case control studies have estimated that in the elderly, non-steroidal anti-inflammatory drug usage enhances the risk of peptic ulceration complications 3 to 6 fold, whilst cohort studies have shown lower estimates of risk.[5] Other studies suggest that about a quarter of all ulcer complications are caused by NSAIDs.[3 4] In 1991 the Office of Population Census and Surveys (OPCS) recorded 4334 deaths from peptic ulcer, 4223 of them were over the age of 60.[6] If 25% are attributable to NSAID use, this implies a death rate from peptic ulcer attributable to NSAIDs of 1100 per annum.

This death rate, combined with the costs of associated morbidity, make NSAID ulcer disease a significant health problem. One approach to this problem is to try to prevent NSAID injury to the gastric mucosa either by prostaglandin 'replacement' with misoprostol or acid inhibition with H2 antagonists. In short term studies (up to three months) misoprostol is highly effective in preventing gastric and duodenal ulcers and H2 blockers are highly effective in preventing duodenal but not gastric ulcers.[7–9] There are no controlled long term studies using H2 blockers for prophylaxis of NSAID ulcers. Those that have been conducted with misoprostol show continuing benefit though the advantage over placebo appears numerically somewhat less.[10 11] Omeprazole is very effective in the healing of NSAID induced peptic ulceration even if NSAIDs are continued,[12] and publications relating specifically to prophylaxis with proton pump inhibitors can be expected over the next few years.

Against this background the results of the first comparative NSAID study by Melo Gomes *et al* (this issue, page 000) were perhaps predictable. Of 643 patients with osteoarthritis randomised to receive a fixed combination of diclofenac 50 mg with misoprostol 200 mcg, piroxicam 10 mg or naproxen 375 mg, all given twice per day, only three of those (1·5%) on diclofenac/misoprostol developed ulcers compared with 21 (10·3%) of those given piroxicam and 17 (8·6%) of those receiving naproxen. Perhaps less predictable, was the finding that improvement in the mean osteoarthritis severity index (but not physician or patient global assessments of osteoarthritis) was also greater in the diclofenac/misoprostol group than in the piroxicam group. This is probably indicative of the differing efficacies of these NSAIDs, rather than some cryptic benefit of misoprostol, as a previous study by Bolten and Melo Gomes *et al* showed almost identical efficacy for the treatment of osteoarthritis between diclofenac/misoprostol and diclofenac/placebo.[13]

These data represent a strong case for using diclofenac/misoprostol, but there are caveats to consider. Firstly, many patients receive NSAIDs inappropriately and the first approach in osteoarthritis must be to try to avoid NSAID use where possible. The data concerning this area is also conflicting. One study found that most (85%) geriatric patients on long term non-steroidal anti-inflammatory drugs were able to stop these drugs if alternative physical treatments were provided.[14] Conversely, our own study of patients surviving an NSAID associated ulcer bleed found that most of them reported further joint symptoms and one quarter received further NSAID treatment during the mean follow up period of 34 months.[15] Secondly, growing epidemiological data identify ibuprofen as being associated with a lower risk of gastrointestinal complications than other NSAIDs including, piroxicam, naproxen and indomethacin, though it is far from clear whether this reflects anything other than the potency of ibuprofen.[16 17] Nevertheless, for patients in whom physical treatment and paracetamol are inadequate, ibuprofen in doses up to 1600 mg per day seems fairly safe and worthy of trial.

For the remaining patients, the study by Melo Gomes *et al* establishes a case for diclofenac/misoprostol. In deciding whether to use this preparation, prescribers need to consider another unanswered question. The prevention of ulcers that are visible endoscopically is one thing, but given that many of these ulcers are asymptomatic the purpose of prophylaxis is the prevention of ulcer complications. The trial by Melo Gomes *et al* contains tantalising observations, since one patient on piroxicam, 4 on naproxen and none on the combination, developed

haematemesis and melaena. Firm evidence that this combination treatment prevents ulcer complications would greatly strengthen the case for using it.

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