Prophylaxis against non-steroidal induced upper gastrointestinal side effects

The gastroenterologist has a fundamentally different perspective on the adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs) on the stomach from the rheumatologist. He regards the drugs (which he rarely prescribes) as responsible for at least half of the cases of upper gastrointestinal bleeding in the elderly which he encounters.1

For rheumatologists NSAIDs are an essential therapeutic tool and therefore the arrival of an apparent antidote to NSAID induced gastrointestinal disease in the form of a prostaglandin derivative given orally may be seen by them as a major advance. This review attempts to put both these viewpoints into perspective.

There are now a large number of clinical studies on the gastrointestinal effects of NSAIDs, but most are retrospective or uncontrolled and attempts to measure the risk of gastrointestinal bleeding, perforation, sudden death, or simply peptic ulceration for an individual patient are bedevilled by the huge number of NSAID prescriptions (26 million in 1989)2 and the rarity of attributable complications.

Although this review will concentrate on the effects of NSAIDs on the stomach and duodenum, NSAID induced small intestinal damage may be an important cause of diarrhoea and unexplained iron deficiency anaemia in patients with arthritis.3

When considering prophylaxis certain aspects of the disease in question need to be established. What is the incidence? What is the natural history? What are the predisposing factors? Are the symptoms characteristic? What are the complications? What are the costs of prophylaxis?

Incidence

Hawkey has recently reviewed the association between NSAID use and gastrointestinal bleeding and gastric and duodenal ulceration.4 Case-control studies, especially the large number of early studies using retrospective data collection, seem to overestimate the risks of NSAID use because a drug history is more likely to be sought in the cases than the controls, and therefore these studies should be interpreted with great caution.

The few studies using prospective data collection and an involuntary end point, such as well defined complications—for example, death, are probably least open to bias, and in these studies an overall relative risk is found of between 3 and 5 for the association of NSAIDs with gastrointestinal bleeding.

Cohort studies, particularly those of well monitored populations using group insurance schemes in North America, find that the relative risk of presentation with upper gastrointestinal bleeding or perforation after NSAID use increases by 50%.

If these figures are accurate (and further prospective surveys are in progress) then the difference between the high risks obtained in the case-control studies and the much lower risk in the cohort studies would indicate that the problem with NSAIDs is not that they are particularly dangerous but that they are so widely prescribed.

Prospective studies on gastric ulceration following the use of NSAIDs in arthritic patients with normal initial endoscopy results show an incidence varying from 6% to 22% for gastric ulceration and from 8% to 3-5% for duodenal ulceration.4 A multicentre survey from the United Kingdom of 156 patients with arthritis taking NSAIDs, in whom endoscopy was performed and who had omitted all drugs for the week before endoscopy, showed that 63 patients (40%) had either gastric or duodenal damage at endoscopy (Levi S, Hodgson H J F, unpublished data). Twenty one patients (13%) had one or more active ulcers (gastric in 13, duodenal in seven, combined in one) and 42 patients (27%) had non-ulcer damage (erosions or haemorrhagic lesions or both, gastric in 27, duodenal in eight, both sites in seven). Only 12/21 (57%) patients with ulcers and 14/42 (33%) patients with non-ulcer lesions were symptomatic.

These figures have to be contrasted with the incidence of gastric and duodenal ulceration in a healthy population. One survey carried out in 346 Finns, where endoscopy was performed on healthy, asymptomatic subjects, showed a prevalence of 0·3% for gastric ulceration and 1·4% for duodenal ulceration.7

Although these data imply a considerably increased risk of peptic ulceration in patients receiving NSAIDs, this is of course not borne out by findings in clinical practice. Clearly many of these ulcers are asymptomatic and the question is therefore raised as to whether NSAID induced ulcers have
the same pathogenic significance as 'standard' peptic ulcers or are these ulcers in some way less serious and less liable to produce complications?

Although it is reasonable to presume that NSAID prescriptions to a dyspeptic patient may be restricted by his general practitioner, only a difference in the natural history of an NSAID induced ulcer in favour of a benign progression could explain the vast difference between the epidemiological data on the prevalence of peptic ulceration in the general population and the high incidence of NSAID induced ulcers found on sequential endoscopy in asymptomatic subjects. Non-steroidal anti-inflammatory drug induced ulcers are more likely to be silent—that is, the first presentation may be haemorrhage, perforation, or sudden death or a combination of these factors. Is there any evidence that the problems of these patients might be predicted in some way?

Natural history
There are few studies in which any group of asymptomatic patients with endoscopically diagnosed gastritis or gastric erosions have been followed up with periodic endoscopy. In those that have been performed there is no evidence that these lesions either bleed or progress to gastric ulceration. Thus gastritis or gastric erosions induced by NSAIDs may not be particularly dangerous, and it is only by long term follow up in such patients that the true natural history can be established.

In support of the hypothesis that NSAID induced gastric erosions or gastritis or even gastric ulcers may not be of serious significance there is good evidence that gastric adaptation to continued ingestion of NSAIDs occurs. In one study acute lesions, either gastric erosions or petechiae, in patients taking aspirin or indomethacin continuously over an eight week period became fewer after two to eight weeks of taking the drug than during the first week. Another survey showed that the relative risk of presentation with haematemesis and melaena rose to a maximum in patients who had received four prescriptions for an NSAID and then fell to zero—that is, there was no increased risk in those who had received 10 prescriptions.

In a prospective study of the effects of misoprostol on ulcer prophylaxis the incidence of gastric ulcer diminished as the trial progressed (25% at entry and 12%, 5%, and 6% at months 1, 7, and 12 respectively) though NSAIDs were prescribed throughout. These data indicate that adaptation might take place, questioning the value of long term 'blind' prophylaxis.

Predisposing factors
Patients receiving NSAIDs are at increased risk for admission to hospital and death because of gastrointestinal disorders and at most risk are those with a previous history of gastric or duodenal ulceration, elderly women patients with previous upper abdominal pain or who had stopped taking NSAIDs because of gastrointestinal side effects, those who had previously used antacids or H2 receptor antagonists to treat gastrointestinal side effects, and those who were also frequently taking corticosteroids.

Symptoms
Which symptoms are most helpful in predicting the presence of gastro/duodenal ulceration? The use of computer generated questionnaires and multiple regression analyses has led to the identification of some specific symptoms highly suggestive of active disease. These include epigastric pain which is nocturnal and radiates through to the back, rapid relief of pain with antacids or H2 receptor antagonists, vomiting, and weight loss.

Unfortunately, it seems that symptoms cannot be used to identify those patients with serious NSAID induced effects. The analgesic effect of NSAIDs may to some degree mask the symptoms of peptic ulceration, and this is borne out by an analysis of unexpected sudden deaths at home (after necropsy). In a 10 year study of 9653 necropsies in Plymouth 154 patients were identified who died from undiagnosed peptic ulcer complications. One hundred and eighteen of these patients died suddenly at home and non-steroidal anti-inflammatory drugs had been used by 81 of them, an incidence of 60% where full drug histories were available. There is, however, no evidence as yet that prophylaxis might prevent such deaths, as few of the patients would have been identified by the criteria described above.

Costs
As stated previously, in the prospective study of misoprostol and ulcer prophylaxis there was a diminishing incidence of gastric ulceration as the trial progressed. Over the first three months of the study about 22% of patients had gastric ulcers. If an evenly spread incidence is assumed 7% of patients developed ulcers each month. If the use of prophylactic prostaglandin analogues prevented all ulceration then each month 100 patients would have to receive the drug to prevent seven ulcers (presumably for as long as the NSAID was used). All symptomatic and asymptomatic patients would have to be included, and even if treatment was limited to patients over 70 then more than 10 million NSAID prescription recipients would require prophylaxis each year in this group in the United Kingdom. Currently, the best estimate of complications in this group is of the order of 1:6000. If no prophylaxis is given what are the costs of treatment of such patients with NSAID induced gastrointestinal side effects?

A retrospective analysis in Pennsylvania of patients with NSAID induced gastrointestinal disease showed average treatment costs of $27 over a three month period, increasing to $393 for a gastrointestinal haemorrhage and $7209 for an inpatient operation.

The cost of prophylactic misoprostol for all NSAID users over a three month period suggests that this may be cost reducing where there is a patient compliance rate of 60%, a silent ulcer rate of 40% (a probable overestimate), and the price of misoprostol per patient is $300. Any variation in the compliance rate or in the silent ulceration rate, however, increases the inaccuracy of these figures.

In Britain it is estimated that the cost of prophylaxis for all NSAID users for one month's prescription of misoprostol would be about six hundred million pounds a year and that the cost of each life saved, calculated from epidemiological data, would be about three million pounds.

All these figures are crude estimates, but there is no doubt that huge expenditure would be incurred if prophylaxis was given to all patients taking non-steroidal anti-inflammatory drugs and in the absence of accurate data on the incidence and natural history of the problem prophylaxis should be concentrated on the most vulnerable groups.

Prophylaxis
Retrospective studies show that all the currently available peptic ulcer healing drugs can reduce short term damage caused by NSAIDs. The assumption that this short term improvement may prevent long term serious complications is not yet confirmed by available evidence.

The issue is complicated by the results of the only two
prospective placebo controlled trials that consider prophylaxis specifically). In the United States misoprostol caused a reduction in the development of gastric ulcers in one month from 21.7% to 5.6% in a dose of 400 μg/day and to 1.4% at 800 μg/day. In this study only a small proportion of patients had duodenal ulcers and it is not possible to make any specific comments on the effects of misoprostol on duodenal ulceration. In the European study ranitidine 150 mg twice daily (a low dose) reduced the higher baseline incidence of duodenal ulceration at two months from 8% to 1.5% but had very little effect on the incidence of gastric ulceration, which was 6% with or without ranitidine.

With the high incidence of NSAID induced side effects and with the knowledge that combination treatment may prevent thousands of ulcers, but possibly few complications, which specific groups should be offered prophylaxis? These would certainly include asymptomatic patients with a recently diagnosed peptic ulcer, particularly if they were older than 70. In patients with gastric ulcers misoprostol should be used in the maximum dose tolerated, building up from a low dose initially. Severe diarrhoea, however, may occur in up to 10% of patients. In patients with a previous history of duodenal ulceration H2 receptor antagonists should still be used as prophylaxis until further evidence of the effect of misoprostol on duodenal ulceration in patients taking NSAIDs is provided. In elderly women of more than 70 years, where there is a high incidence of NSAID induced side effects, prophylaxis should be considered, but the data indicating that this group is especially vulnerable are still not satisfactory. Patients who were previously asymptomatic who develop symptoms while taking NSAIDs and who do not respond to simple antacid treatment (which is usually unsuccessful) should be offered endoscopy, and treatment then adjusted according to the findings of that investigation.

In view of the good evidence that gastric adaptation to NSAIDs occurs coprescription of prophylactic treatment to asymptomatic patients with none of the specific indications described above cannot at present be justified beyond the first month of use of the NSAID, unless symptoms are present, in which case endoscopy should be performed.

**Conclusion**

The risk of a life threatening gastric or duodenal complication after receiving an NSAID is not known. Combination treatment may prevent thousands of ulcers but few complications and for the patient prophylaxis with a prostaglandin analogue may have some disadvantages, particularly those of diarrhoea.

There is no doubt that prophylaxis for all NSAID users at present cannot be recommended. It is necessary to identify groups at particularly high risk. Prospective studies of omeprazole, the most powerful acid suppressant yet developed, in combination with NSAIDs are awaited, but it may be that this drug will supplant all previous peptic ulcer healing agents for short term use.

In current circumstances there is no benefit to be gained from long term prophylaxis and this can probably only be justified for the first month that an NSAID is taken, unless symptoms appear, in which case endoscopy should be performed, or where patients are in a particularly high risk group.

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_Ann Rheum Dis_ 1991 50: 207-209
doi: 10.1136/ard.50.4.207

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