

ABC of the upper gastrointestinal tract

Indigestion and non-steroidal anti-inflammatory drugs

J M Seager, C J Hawkey

Non-steroidal anti-inflammatory drugs (NSAIDs) are usually thought to pose a dilemma for doctors wishing to prescribe them. Their anti-inflammatory and analgesic properties have led to their widespread use for rheumatoid and (much more commonly) other conditions often regarded as more trivial. However they are ulcerogenic to the stomach and duodenum and lead to a threefold to 10-fold increase in ulcer complications, hospitalisation, and death from ulcer disease.¹

In fact, the dilemma is more complex than whether potentially life threatening drugs should be used to manage conditions that are uncomfortable but not in themselves life threatening. There is growing evidence that NSAIDs have other incidental benefits. The only study to investigate overall life expectancy with drug use found non-significant trends towards enhanced rather than reduced life expectancy. Aspirin has benefits in preventing cardiovascular disease and probably cancer that seem to far outweigh the hazards of gastrointestinal ulceration. Limited evidence suggests that these benefits may be shared by other NSAIDs.

NSAID use

About 24 million prescriptions a year are written for NSAIDs in the United Kingdom. Half of these are given to patients over the age of 60. At any one time about 15% of elderly people are taking an NSAID. Average prescribing rates are calculated to be 426 scripts per 1000 population per year.

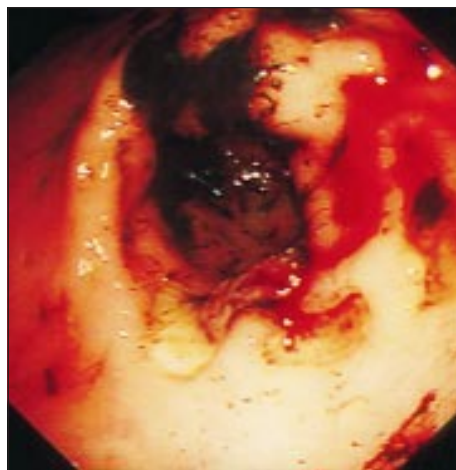
Less than 10% of NSAIDs used in the community seem to be for rheumatoid arthritis, and less than half for any form of arthritis. They are widely used for acute soft tissue injury and more chronically for undiagnosed pains in the back and elsewhere. Chronic use is more common in elderly than younger patients, and prophylactic use of aspirin, mostly in relatively low doses, for cardiovascular events is increasing, amounting to 9.5% of a relatively elderly population.

Gastrointestinal toxicity of NSAIDs

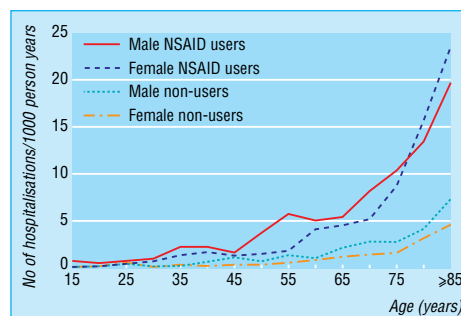
NSAIDs are important in causing both (non-ulcer) dyspepsia and ulcers (often silent and presenting with a complication). The unreliability of dyspepsia as a pointer to ulceration underlies many of the problems of managing patients taking NSAIDs.

Within 90 minutes of taking 300 mg or 600 mg of aspirin, nearly everyone develops acute injury consisting of intramucosal petechiae and erosions. Non-aspirin NSAIDs cause less florid acute injury, but endoscopic studies show that about 20% of those taking non-aspirin NSAIDs or aspirin at anti-inflammatory doses chronically have a gastric or duodenal ulcer. Many patients who start NSAIDs will not be able to continue because of drug associated dyspepsia.

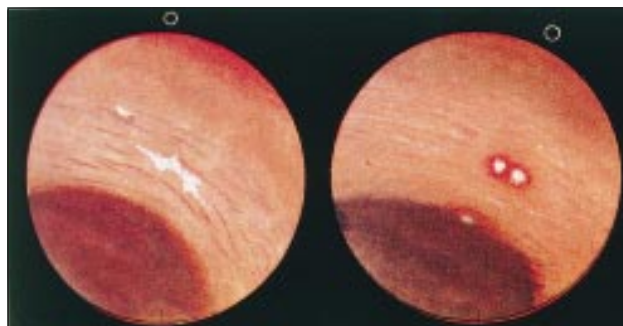
Ulcers probably form and heal spontaneously in most NSAID users and usually cause little harm. However, about once in every 50-100 patient years, ulcer bleeding or perforation develops that requires hospitalisation.² As a consequence, probably at least 1200 patients die each year in the United Kingdom.¹



Three ulcers (one bleeding) in the gastric antrum caused by NSAIDs. Such ulcer complications are estimated to cause up to 16 500 deaths each year in the United States and 2000 deaths a year in Britain



Hospitalisations due to complications associated with NSAID use are a problem in elderly patients



In 1938 Douthwaite and Lintott provided the first endoscopic evidence that aspirin caused gastric mucosal damage. Images show gastric antrum before (left) and after (right) administration of aspirin (reproduced from Douthwaite AH, Lintott JAM. *Lancet* 1938;ii:1222-5)

Who is at particular risk?

Risk factors for gastroduodenal ulcer complications are now fairly well defined. Most patients with NSAID associated ulcer complications are elderly. This is because elderly people have a higher background prevalence of ulcer problems, are more likely to receive NSAIDs, and are probably more sensitive to them. A history of ulcers (whether or not associated with NSAIDs) is a further risk factor.

A meta-analysis of recent studies shows that ibuprofen (≤ 1200 mg/day) is associated with a lower level of risk than other NSAIDs, whereas others such as azapropazone and piroxicam are associated with a higher risk.³ These differences probably relate at least in part to effective dose, since doses of ibuprofen greater than 1200 mg carry risks similar to those with other NSAIDs.³ Among NSAIDs in general, risks rise steadily with dose.³

As would be expected, the risk of ulcer bleeding is much higher if patients taking NSAIDs also receive warfarin. Interestingly, use of corticosteroids has been shown fairly consistently to magnify the risk of ulcer complications, to the extent that ulcers associated with NSAIDs and steroid may account for the probably incorrect belief that corticosteroids were themselves ulcerogenic.

Managing patients taking NSAIDs

Management of patients who need to take NSAIDs should be based more on assessment of risk than on clinical, laboratory, or endoscopic investigation. NSAID use should be avoided in patients with two or three of the risk factors for ulcer complications, or if this is not possible they should receive prophylactic treatment.

Although development of dyspepsia soon after starting an NSAID may preclude its use and can sometimes lead to discovery of a previously silent ulcer, NSAID associated dyspepsia is generally a poor guide to the presence of an ulcer. Development of anaemia or new onset dyspepsia can identify NSAID associated ulcers, but upper gastrointestinal investigation is often negative and reliance on these signs will miss most ulcers, which most commonly present with complications on a relatively silent background.

Available drugs to treat ulcers

Preclinical studies in animals and humans suggest that two components contribute to development of NSAID associated ulcers. Firstly, inhibition of prostaglandin synthesis, by impairing mucosal defences, leads to erosive breach of the epithelial barrier. Secondly, acid peptic attack deepens this into frank ulceration, and pH is also an important determinant of passive NSAID absorption and trapping in the mucosa. Preventive treatment aimed at either mucosal defence or acid attack is available.

Misoprostol is a stable analogue of prostaglandin E₁. Several studies show that it prevents acute gastric injury by a wide variety of agents including NSAIDs. In doses of 400-800 μ g daily misoprostol prevents gastric (and probably duodenal) ulcers. A large study has shown it to reduce the incidence of hospitalisation for NSAID associated gastrointestinal complications.² Unfortunately, as a prostaglandin, it causes diarrhoea, abdominal cramps, and reflux at the doses necessary to protect against NSAID associated ulcers.

Acid suppressing drugs—Normal doses of H₂ antagonists have relatively little effect on acute aspirin and NSAID associated injury in animals and in humans. High doses of H₂ antagonists

Risk factors for gastrointestinal complications occurring with NSAIDs

Patient related factors

- Age > 60 years
- History of ulcer disease

Drug related factors

- Use of relatively toxic NSAID
- High dose of NSAID (or two NSAIDs used concurrently)
- Concurrent use of anticoagulant
- Concurrent use of corticosteroid

Uncertain or possible risk factors

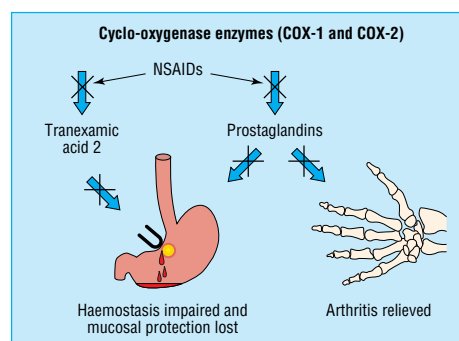
- Duration of NSAID treatment
- Female
- Underlying rheumatic disease
- Cardiovascular disease
- *Helicobacter pylori* infection
- Smoking
- Alcohol consumption

Comparative toxicity of NSAIDs for gastrointestinal complications*

Drug	No of studies	Pooled relative risk (95% CI)†	P value (heterogeneity)
Ibuprofen	NA	1.0	NA
Fenoprofen	2	1.6 (1.0 to 2.5)	0.310
Aspirin	6	1.6 (1.3 to 2.0)	0.685
Diclofenac	8	1.8 (1.4 to 2.3)	0.778
Sulindac	5	2.1 (1.6 to 2.7)	0.685
Diffunisal	2	2.2 (1.2 to 4.1)	0.351
Naproxen	10	2.2 (1.7 to 2.9)	0.131
Indometacin	11	2.4 (1.9 to 3.1)	0.488
Tolmetin	2	3.0 (1.8 to 4.9)	0.298
Piroxicam	10	3.8 (2.7 to 5.2)	0.087
Ketoprofen	7	4.2 (2.7 to 6.4)	0.258
Azapropazone	2	9.2 (4.0 to 21.0)	0.832

*Adapted from Henry et al.³

†Relative to ibuprofen.



Inhibition of cyclo-oxygenase enzymes by NSAIDs relieves inflammation and pain but also removes mucosal protection of gastric epithelium

and normal doses of proton pump inhibitors are protective, and long term studies have shown them to prevent both gastric and duodenal ulcers. There have been no randomised studies of the effect of acid suppression on NSAID associated complications, although indirect evidence from epidemiology is encouraging.

Choice of treatment

Patients with NSAID associated ulcers

If patients present with ulcers NSAIDs should be stopped if possible since they retard healing. For patients who need to continue taking NSAIDs, large comparative studies have shown that omeprazole 20 mg daily results in faster healing of gastric and duodenal ulcers than ranitidine 150 mg twice daily⁴ or misoprostol 200 µg four times daily and is better tolerated than misoprostol.

Subsequent prevention of relapse

Studies have shown that, once healing is achieved, NSAID associated ulcer relapse can be retarded by use of omeprazole, misoprostol, or high dose famotidine.⁴ These comparative studies—based on preventing the development of ulcers, multiple erosions, or moderate to severe dyspepsia—have shown overall higher efficacy for omeprazole 20 mg daily than misoprostol 200 µg twice daily or ranitidine 150 mg twice daily.⁴ In these studies omeprazole protected against ulcers, both gastric and particularly duodenal, and erosions. Misoprostol was associated with the same rate of duodenal ulcer formation as placebo but was particularly effective in preventing multiple erosions. In these studies the site of the initial lesion was a strong predictor of the site of subsequent relapse.

NSAID users without ulcers

Many studies have shown that misoprostol can inhibit ulcer development in such patients, as can famotidine 40 mg twice daily and omeprazole. These drugs have not been compared for relative effectiveness in this group of patients.

Practical prescribing

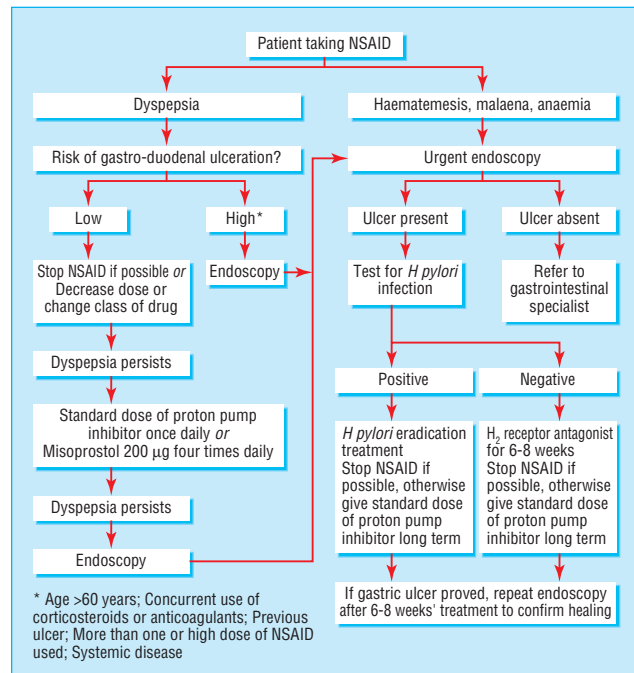
Patients presenting with gastric or duodenal ulcers who need to continue taking NSAIDs should be treated with omeprazole 20 mg daily or another proton pump inhibitor until the ulcer heals. Although omeprazole is the only proton pump inhibitor to have been studied in large scale trials, its benefits are probably a class effect. Patients with multiple erosions instead may be better served by misoprostol.

Overall, subsequent maintenance treatment is likely to be more effective and better tolerated with a proton pump inhibitor than misoprostol. Recognition that the site and nature of the original lesion is a strong predictor of the site and nature of relapse can aid management.

For patients who present with duodenal ulcers a proton pump inhibitor is an appropriate maintenance treatment. For patients with multiple erosions misoprostol is appropriate if tolerated. On current data there is little to choose between proton pump inhibitors and misoprostol with regard to efficacy in preventing gastric ulcers, but proton pump inhibitors are better tolerated.

Role of *Helicobacter pylori* eradication

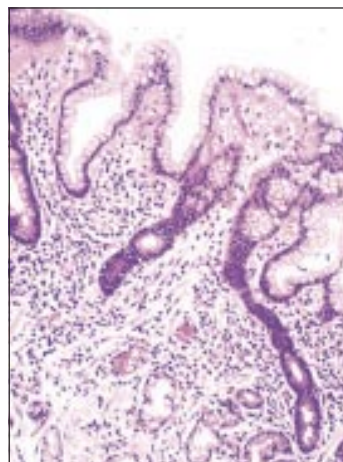
This is an extremely controversial topic. One study, of patients starting NSAIDs (naproxen) for the first time without a history of dyspepsia or ulceration, showed that eradication of *H pylori* substantially reduced the rate of gastric ulcer formation at two



Algorithm for managing gastrointestinal side effects of NSAIDs

Side effects of NSAIDs

- Dyspepsia
- Oesophagitis
- Oesophageal strictures
- Gastric and duodenal petechiae, erosions, ulceration, bleeding, and perforation
- Type C gastritis
- Small and large bowel ulceration, bleeding, and perforation
- Exacerbation of colitis



Chemical (type C) gastritis showing oedema and mild chronic inflammation of lamina propria and vertical smooth muscle fibres and slight foveolar hyperplasia. Contrast with *H pylori* induced gastritis, which has a marked neutrophil infiltrate in the lamina propria and deeper gastric glands

months. In another study, of patients who had previously had ulcers or moderate to severe dyspepsia, *H pylori* eradication did not influence outcome at six months. Finally, although omeprazole is effective prophylaxis in patients without *H pylori* infection, it is more effective in those who remain infected.⁴

Most doctors, feeling uncomfortable about persistent *H pylori* infection, eradicate it in NSAID users. In our view this is irrational if these patients are at sufficiently high risk to be candidates for co-treatment with acid suppressing drugs.

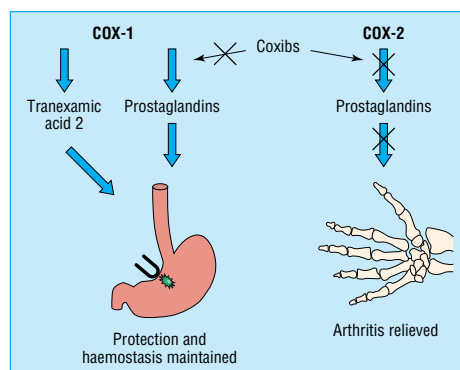
The future

A new generation of less toxic NSAIDs is probably imminent. Specific inhibitors of the inducible cyclo-oxygenase-2 enzyme (COX-2), which probably leave protective gastric prostaglandins uninhibited, are now available. Meloxicam, another recent NSAID, is well tolerated. Whether this is because it is a partially selective COX-2 inhibitor or because tested doses are low is uncertain. Other developments include NSAIDs that donate cytoprotective nitric oxide to the gastric mucosa.⁵

Conclusions

Currently, there is a wide range of views about what is an appropriate level of NSAID prescribing and no simple, all embracing resolution. In patients with risk factors for gastrointestinal complications the side effects of NSAIDs may outweigh all benefits. For such patients, omeprazole and misoprostol can provide effective protection, and the choice is between patients' generally poor tolerance of misoprostol and the higher costs of omeprazole. Finally, a growing concern is the correct management of low dose aspirin used for cardiovascular protection, and no patient studies have specifically investigated this.

- 1 Hawkey CJ. Non steroidal anti-inflammatory drugs and peptic ulcers: facts and figures multiply, but do they add up? *BMJ* 1990;300:278-84.
- 2 Silverstein FE, Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. *Ann Intern Med* 1995;123:241-9.
- 3 Henry D, Lim LL-Y, Garcia Rodriguez LA, Perez Gutthann S, Carson JL, Griffin M, et al. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *BMJ* 1996;312:1563-6.
- 4 Yeomans ND, Tulassay Z, Juhasz L, Racz I, Howard JM, van Rensburg CJ, et al, for the ASTRONAUT Study Group. A comparison of omeprazole and ranitidine for treating and preventing ulcers associated with non steroidal anti inflammatory drugs. *N Engl J Med* 1998;338:719-26.
- 5 Hawkey CJ. Future treatments for arthritis—new NSAIDs, NO-NSAIDs or no NSAIDs? *Gastroenterology* 1995;109:614-6.



Rofecoxib and celecoxib, selective COX-2 inhibitors, can relieve pain and inflammation without risking gastric ulceration

NSAID protection strategies

- Use lowest possible doses of NSAIDs
- Use safer NSAIDs
 - Low toxicity NSAIDs
 - COX-2 inhibitors
- Use NSAID prophylaxis
 - Proton pump inhibitors
 - Misoprostil

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The diagnostic sign was in the other room

A friend of one of my patients recently requested a house call. The patient was in her early 80s, and from her records I could see that she was generally healthy, although she had mild dementia, for which she was prescribed 75 mg of aspirin daily. The friend was worried that my patient generally looked ill and might have had a small nosebleed, as there was a little dry blood below one nostril. The patient herself had no complaints.

I saw my patient in her bedroom. She was possibly a little more confused than normal, but she was adamant that she had no complaints. She was perhaps a little pale with a few specks of brown blood below her left nostril, and examination was completely normal. While I was considering the cause of a slight

increase in my patient's confusion, possibly a urinary tract infection or a small stroke, I asked if I could see what tablets she was taking. I was directed to the kitchen. To get there I passed through the lounge and, out of the corner of my eye, I saw what on closer inspection was an approximately 60 cm diameter pool of coffee ground vomit on the light green sofa. The hospital later confirmed that it had come from my patient's stomach.

I was grateful that I had passed through the lounge that day, and that the sofa wasn't brown.

Philip White *general practitioner, London*