Nonsteroidal anti-inflammatory drug gastropathy — is it preventable?

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INTRODUCTION
The non-steroidal anti-inflammatory drugs (NSAIDs) make up a group of the most commonly prescribed pharmaceuticals. It is estimated that more than 30 million people throughout the world consume an NSAID each day. The number of NSAID prescriptions written each year in the USA doubled between 1985 and 1998, while in Australia the prevalence of NSAID use in elderly subjects has been estimated to be in excess of 20%. To a large extent this is a reflection of the high prevalence of rheumatic diseases in the community but an annual growth rate of 6% in NSAID prescriptions as seen in Canada during 1989 is unlikely to be due to increased disease incidence alone. As the population ages it is at risk from painful musculoskeletal diseases such as osteoarthritis, for which NSAIDs may not be the most appropriate treatment, and yet it seems that it is for these primarily non-inflammatory forms of arthritis that the majority of NSAIDs are prescribed.

NSAIDs are associated with a wide spectrum of side effects including those involving renal, hepatic and haematological function and skin rashes. It is, however, the gastrointestinal (GI) side effects of NSAIDs which are most common and serious and make NSAIDs the most frequent cause of drug side effects reported to the Committee on Safety of Medicines in Britain each year. It is because of this that it is important to try to ascertain the true relationship between NSAID use and the clinically important gastrointestinal side effects and to develop strategies which might diminish this problem. In this review we will discuss briefly the pathophysiology of so-called ‘NSAID gastropathy’, review the epidemiology of NSAID associated GI side effects and examine the clinical trial evidence that drugs might influence the ulcer healing rate and perhaps even prevent their development.

PATHOPHYSIOLOGY OF NSAID GASTROPATHY
Mucosal damage in the gastrointestinal tract is the product of a fine balance between acid production and mucosal events. Surface epithelial cells secrete mucus and bicarbonate and have the ability to rapidly repair injury. These properties are essential for maintaining mucosal integrity in the stomach. Environmental factors such as smoking and stress, genetic predisposition, the bacterium Helicobacter pylori and NSAIDs (Figure 1) all play a role in predisposing to peptic ulceration. The epithelial cells can be damaged by acid, pepsin, refluxed bile acids, NSAIDs or the products of H. pylori. NSAIDs produce a wide spectrum of injury to the gastrointestinal tract ranging from petechial haemorrhages and erosions to ulcers. It is clear that the whole of the gastrointestinal tract at risk from NSAID associated damage with small and large bowel mucosal ulceration noted. NSAIDs probably have both a local and a systemic influence on GI mucosal physiology. Aspirin produces much of its damage topically, after it has entered the gastric surface mucus cells from the lumen. Evidence for this includes the high speed with which aspirin causes surface injury and the partial protection against injury which is provided by enteric coating of the aspirin. However, the non-aspirin NSAIDs seem to produce most of their injury systemically, after they have been...
absorbed. For example, in rats, parenteral administration of simple NSAIDs produces at least as much gastric damage as does oral administration. Furthermore, studies in humans have shown that pro-drugs such as sulindac, enterically coated NSAIDs and rectally administered NSAIDs are all still associated with gastric damage - both acute and chronic, albeit less frequently than with oral administration.

It is possible that much of the gastric injury produced by NSAIDs is a consequence of the inhibition of the production of prostaglandins by the mucosal cells. This is caused by a blockade of cyclooxygenase at the start of the prostaglandin biosynthetic pathway which is an effect common to all NSAIDs and, therefore, all NSAIDs share the capacity to produce gastric injury.

There is now mounting evidence for several protective effects of gastric prostaglandins. They stimulate mucus and bicarbonate secretion from various cells and seem to also increase the capacity of the mucosal surface to repel luminal acid - by increasing its hydrophobicity or 'non-wettability'. Conversely, bicarbonate secretion is inhibited by several NSAIDs. Moreover, severe gastric ulcers can be produced in experimental animals by inducing or administering antibodies to prostaglandins but not by antibodies to inactive prostaglandin analogues. Inhibition of prostaglandin production might enhance susceptibility to damage by bile acids, hypertonic saline and even food. Prostaglandins might also stimulate serosal-mucosal water flux so histodulating injurious agents.

Some of the injurious effects of NSAIDs might be independent of blockade of prostaglandins. For instance, there is evidence that NSAIDs might be involved in the production of oxygen-free radicals. They may also impair angiogenesis at the base and margins of the ulcer, leading to ulcers which are more fibrous and less contractile than usual.

The interaction between H. pylori and NSAIDs may also be important. However, evidence that these are independent risk factors for ulcers is mounting. One study in patients presenting with gastric ulcer found H. pylori colonisation in nine out of ten of the patients who were not taking NSAIDs but in only five of 12 of those taking the drugs. In a much larger study, Graham, et al. found that the frequency of H. pylori infection was independent of NSAID use and that NSAID induced erosions were no more frequent in those with H. pylori infection than those without. It is, therefore, possible that there are two types of NSAID-induced ulcers - ulcers that occur de novo in histologically normal gastric mucosa and ulcers that occur as a result of NSAID administration.

The sequence of gastric mucosal events following ingestion of soluble aspirin has been reasonably well documented. Changes in the epithelial cells have been noted within minutes of aspirin ingestion, and by two hours nearly all subjects given a single dose will have red mucosal lesions and/or erosions. The subepithelial haemorrhages come and go during therapy with
NSAIDs. However, erosions occasionally fail to heal and progress to form ulcers. These, in turn, will often heal spontaneously. It is not clear, however, in what proportion of patients this sequence of events is followed. For example, not all patients taking NSAIDs chronically will have erosions or ulcers when endoscoped. Silvoso, et al., have demonstrated that patients taking eight aspirin tablets a day for at least three months show gastric erosions in 40% and gastric ulcers in 16%. This suggests that a large proportion of patients have adapted to NSAID challenge as suggested by Graham, et al. In these studies Graham showed that decreasing damage was apparent with continued exposure to aspirin and that lesions healed more rapidly if given a longer period of adaptive exposure to aspirin. Adaptation was more rapid at lower aspirin doses (1.3 gm per day) than higher doses (2.4 gm per day). This adaptation took several weeks to develop, during which time there was a gradual return to an almost normal mucosal appearance. Similar adaptation, although with a more rapid onset, has been seen in experimental animals. These experimental data are paralleled by epidemiological evidence. Carson, et al., showed that the risk of gastrointestinal bleeding increased to a maximum after four NSAID prescriptions and decreased to no measurable risk after ten prescriptions. Griffin, et al., have shown that the maximal risk of gastrointestinal bleeding occurs in the first months after an NSAID prescription. On the other hand, other groups have found no evidence of adaptation in humans using endoscopic assessment or measurement of gastrointestinal blood loss.

The majority of these studies have been done in patients who do not have chronic rheumatoid arthritis or osteoarthritis. There are, however, no clear data from the literature to suggest that there are differences between rheumatoid and non-rheumatoid gastric mucosa.

**Epidemiology**

The first point to remember is that diseases of the gastric mucosa are extremely prevalent, with approximately 10% of healthy asymptomatic people having mucosal lesions at any one time and as many as 1% showing extension into the submucosa, i.e., ulcer. Approximately 10% of us will experience frank peptic ulcer disease during our lifetime and this will increase with age. These data need to be considered when addressing the epidemiology of NSAID gastropathy. Despite this, there is incontrovertible evidence that use of NSAIDs is associated with the development of gastric ulcers, with ulcer complications (haemorrhage and perforation) and with ulcer death (Table 1).

<table>
<thead>
<tr>
<th>Ulcer occurrence</th>
<th>Ref</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>46</td>
<td>5</td>
<td>1.06-9</td>
</tr>
<tr>
<td>Duodenal</td>
<td>46</td>
<td>11</td>
<td>0.4-3.7</td>
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<tr>
<td>Ulcer complication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric</td>
<td>47</td>
<td>2.8</td>
<td>1.0-5.4</td>
</tr>
<tr>
<td>Duodenal</td>
<td>47</td>
<td>2.7</td>
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<tr>
<td>Perforation</td>
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<tr>
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<td>49</td>
<td>7.3</td>
<td>4.4-11.8</td>
</tr>
<tr>
<td>Duodenal</td>
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<td>2.9</td>
<td>1.1-7.4</td>
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<tr>
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<td>51</td>
<td>1.6</td>
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<td>53</td>
<td>2.9</td>
<td>1.4-6.3</td>
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NSAID induced reaction per 10,000 person months of prescriptions. Using the technique of automated record linkage which relates diagnostic category to drug use incorporating information contained in large data bases, relative risks for perforated ulcer or haemorrhage as a result of NSAID therapy have been calculated to be around 1.5. Prospective case control studies, which probably give a more reliable estimate, indicate a substantially higher relative risk of serious upper GI side effects of between three and seven. Fries et al., using multivariate analysis in 2,400 patients with rheumatoid arthritis (RA) followed prospectively for an average period of 3.5 years, have demonstrated a hazard ratio (approximating to relative risk) for hospitalisation due to GI adverse effects of seven times that for patients not on NSAIDs.

These data have led Fries et al. to suggest that in the United States the syndrome of NSAID induced gastropathy can be considered to account for at least 2,600 deaths per annum and 20,000 hospitalisations each year in patients with RA alone. The studies of Fries et al. suggest that those patients particularly at risk for development of NSAID related gastropathy are the elderly, those with a previous history of peptic ulceration, those with severe rheumatoid disease and patients taking corticosteroids. The role of corticosteroids as a risk factor was recently confirmed by Piper et al. Until recently there has been little evidence that differentiates one NSAID from another with respect to inducing serious upper GI side effects. Studies which purport to show that certain NSAIDs are more or less gastrotoxic need to be interpreted carefully because equivalent anti-inflammatory
doses are not always employed. Two recent studies, however, have demonstrated significant differences between NSAIDs in their association with hospitalization\(^6\) or overall toxicity.\(^7\) In summary, although the absolute risk of a significant gastrointestinal adverse reaction with NSAIDs is not high for the individual patient, the multiple effect of exposure and relative risk translate into NSAIDs being the likely direct cause between 20% and 30% of all cases of peptic ulcer complications in countries with high usage such as Australia.\(^8\)

**ULCER TREATMENT**

There is no doubt that gastric and duodenal ulcers in patients with rheumatoid and osteoarthritis heal despite continuing NSAID therapy. However, they do seem to take longer to do so.

For NSAID associated gastric ulcer, the pooled healing rate from several studies with histamine \(H_2\) receptor antagonists averaged 67% at eight weeks.\(^1\) Many of these studies were flawed by small patient numbers and lack of controls or blinding. By comparison, eight week healing rates of close to 90% have been achieved in most studies with \(H_2\) blockers for idiopathic ulcers.\(^9\)

More direct evidence that NSAIDs delay the healing of both gastric and duodenal ulcers comes from a recent open study in which 170 patients were randomised to continue or to stop the NSAIDs, while undergoing treatment with ranitidine. After four weeks, about 20% more patients with either ulcer type had healed if the NSAIDs were stopped rather than continued.\(^10\)

The substituted aluminium-sucrose compound (sucralfate) is often prescribed for NSAID ulceration. There is little evidence for its efficacy — a modest reduction in gastric lesion scores in one study with unbalanced groups at entry\(^11\) — despite some promising short term results showing protection against NSAID induced bleeding.\(^12\) Synthetic prostaglandins accelerate NSAID ulcer healing, compared with placebo, despite continuation of NSAIDs. However, the mean eight week extrapolated healing from four studies was still only 70% to 72% much the same as the pooled mean from the studies with \(H_2\) blockers referred to above. These prostaglandin studies were all placebo controlled and blinded. The proportion of patients who healed by eight weeks in the placebo arm was only 23% (extrapolated), compared with expected values of about 50% for idiopathic gastric ulcer\(^13\) — again highlighting the slow healing of NSAID ulcers when the NSAIDs are not ceased.

Only one study has been performed so far, using the acid pump inhibitor omeprazole, in patients with gastric ulcer who continue to take NSAIDs.\(^14\) In the group given omeprazole, 40 mg daily, 95% of patients had healed ulcers after eight weeks, significantly higher than those given ranitidine, 300 mg daily, in a comparator arm of the same study. However, the NSAID treated patients were a fairly small subgroup imbedded in a larger trial of idiopathic ulcers. Further studies are needed, with larger patients numbers, to compare omeprazole directly with histamine \(H_2\) blockers (perhaps at increased dosage) and prostaglandins to answer the question of how NSAID induced ulcers should best be healed in patients who cannot easily have their NSAIDs ceased.

**PROPHYLAXIS**

Preventive treatment to reduce the risk of developing NSAID associated ulceration is possible but the choice of agent is a little complex. The data at present suggest that \(H_2\) blockers are effective for preventing duodenal ulceration in patients taking NSAIDs.\(^15\)\(^-\)\(^17\) However, they have been found wanting so far for gastric ulceration despite some promising evidence for reduction in the acute intra-mural haemorrhages caused by NSAIDs.\(^18\) Since most studies have found an increased relative risk for gastric ulcer but not duodenal ulcer in NSAID takers, it is possible that \(H_2\) blockers are mainly protective against development or relapse of incidental \(H. pylori\) induced duodenal ulcers and that the role of NSAIDs is of secondary importance in such patients.

Prostaglandins also have been shown to protect against duodenal ulcer in patients taking diclofenac, although this has been reported so far only in interim or abstract form.\(^19\) Several studies have demonstrated efficacy of the PGE\(_1\) analogue misoprostol for preventing NSAID associated gastric ulcers. These have ranged in duration from three to 12 months and have demonstrated reductions in ulcer incidence ranging between 60% and 90% compared with placebo\(^20\)\(^-\)\(^22\) or with sucralfate.\(^23\) Acid pump blockers have not yet been studied for prophylaxis of NSAID ulcers, although two large studies are about to commence.

None of the prophylaxis studies have been able to demonstrate a reduction in the frequency of ulcer complications in patients receiving NSAID but to do so would be an enormous task for a controlled trial in view of the low frequency (2% of ulcers) of such complications. However, it is likely, although admittedly unproven, that any intervention that lowers the incidence of ulcers will also lower the rate of ulcer complications.

Who should receive prophylactic therapy for peptic ulceration is currently a hotly debated question. Cost benefit issues need to be addressed as well as the question of which subgroups of patients are most at risk.

**PRACTICAL ISSUES**

As mentioned previously, NSAIDs are very commonly prescribed and are often given for degenerative
musculoskeletal complaints rather than for inflammatory joint disease. In these conditions, however, pain relief does seem to be associated with improved quality of life. The frequency of dyspepsia in these patients is high but is not predictive of the type nor indeed the presence of any gastrointestinal pathology. Although it has been suggested that patients with RA might be at particular risk, the data are not persuasive. Any increase could represent confounding by general disease severity due to poor overall health or coincident vasculitis and not any inherent liability to damage. As Fries et al. have suggested, there are some 2,600 deaths each year in the USA and 20,000 hospitalisations with NSAID associated adverse GI events in patients with RA. These figures are comparable with those suggested for the United Kingdom. The first thing for the doctor to ask is, does the patient require an NSAID? If the problem is non-inflammatory (osteoarthritis), then use of pure analgesic agents such as paracetamol, physical treatments and possibly the use of percutaneous NSAIDs should be considered. Most NSAIDs are now given as enteric coated or slow release preparations although, as mentioned previously, this does not totally prevent adverse gastric events. Other factors which might promote ulceration, such as smoking and alcohol consumption, should be reduced to a minimum although studies suggesting that these strategies will influence NSAID induced peptic ulceration are lacking.

At present there are no convincing data to support primary prophylaxis. There have been some suggestions that routine prophylaxis might be cost effective but these have used values from the optimistic end of the current efficacy data and others have not been confirmed.

If prophylactic treatment is not to be recommended at present for all, which high risk subgroups might be considered? Information is not particularly good to answer this, but a reasonable approach might be as follows:

Patients who have a past history of gastric ulceration or who are elderly (> 60 years), have severe RA or are receiving concomitant corticosteroid therapy should be considered for prophylaxis with a prostaglandin (at present misoprostol). Those having a previous history of duodenal ulcer should be placed on maintenance therapy with an H2-receptor antagonist. Just how long these drugs should be continued is not known but is the subject of considerable debate in the literature. Patients should be followed carefully to monitor for anaemia or ulcer symptoms that might suggest the need for more intensive treatment or withdrawal of NSAIDs.

The newer antiulcer preparations such as prostaglandin analogues have great potential in the management of complicated rheumatic disease but do not require proper economic evaluation before definitive guidelines for use can be made.

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