REVIEW

Misoprostol in the prevention of gastroduodenal damage in rheumatology

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Abstract

Patients receiving non-steroidal anti-inflammatory drugs (NSAIDs) are at an increased risk of gastroduodenal erosions, ulcers, and the associated complications of haemorrhage, perforation, and death. Many NSAID associated ulcers that bleed or perforate have been asymptomatic until the time of presentation and conversely many patients with dyspepsia do not have ulcers. Symptoms are a poor guide to the presence of an ulcer. During continued treatment with NSAIDs misoprostol is the best choice for NSAID induced gastroduodenal damage; it achieves higher rates of healing than other drugs in these circumstances. Misoprostol is superior to other drugs in the prevention of gastric damage but misoprostol and H_2 antagonists are of similar benefit in the duodenum. Prophylactic studies have all used endoscopic damage as an endpoint, and much larger studies will be needed to show an effect of misoprostol on the incidence of ulcer complications. There are no clear guidelines as to which patients should receive prophylactic treatment with misoprostol but those particularly at risk of ulcer complications—that is, those with previous peptic ulceration, the elderly, medically unfit, patients receiving large doses of NSAIDs, and those patients receiving steroids in addition to NSAIDs—should be considered.

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Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed and are effective for treating inflammatory arthritis. Their therapeutic benefits are accompanied by clinically significant gastrointestinal side effects including dyspepsia, gastroduodenal ulcers, and the associated complications of haemorrhage and perforation. Fries *et al* [1] have shown in a large number of patients with computerised clinical records that there is a relatively unfavourable risk/benefit ratio for the long term use of NSAIDs due to gastrointestinal toxicity. There is, however, the potential to prevent some of this toxicity by co-prescribing the synthetic prostaglandin misoprostol. Overviews have given conflicting advice about the value of misoprostol for the prophylaxis of NSAID induced gastroduodenal damage. Soll *et al* [2] thought the balance of evidence was in favour of prophylaxis with misoprostol especially in some groups at high risk of gastroduodenal damage. By contrast Barrison[3] suggested there is no benefit to be gained from long term prophylaxis.

When should misoprostol be used? To resolve this issue we have reconsidered the incidence, pathogenesis, treatment, and prevention of NSAID induced gastroduodenal damage, focusing on the role of misoprostol and its advantages and drawbacks.

Incidence of NSAID induced gastroduodenal damage

Although a subject's risk from NSAIDs is not high, their widespread use makes gastroduodenal damage due to NSAIDs a major problem in the population as a whole. Extrapolation from 'record linkage' data indicates that NSAID use is associated with 30 000 serious gastrointestinal events each year in the United Kingdom[4] with an associated mortality of 10%. The prevalence of ulcers in the stomach and duodenum of long term users of NSAIDs ranges from 10 to 30%[5–7] and there is an increased occurrence of upper gastrointestinal haemorrhage and perforation. Case control studies show a clear relation between upper gastrointestinal bleeding and NSAIDs. Holvoet *et al* [8] studied 161 patients admitted to hospital with upper gastrointestinal bleeding who had oesophagitis, gastric erosions, and gastric or duodenal ulcers at endoscopy. Using age and sex matched hospital inpatients as controls they found a highly significant difference between patients and controls in the use of non-aspirin NSAIDs and aspirin. Previous NSAID use was a risk factor for bleeding from gastric and duodenal ulceration but not oesophagitis or gastric erosions. A similar study of Somerville *et al* [9] found patients with upper gastrointestinal bleeding used NSAIDs three times more often than did subjects in the community or hospital control groups. Such case control studies have potential for bias as patients who believe NSAIDs cause ulcers are more likely to report their use. In the aspirin myocardial infarction study[10] where patients and investigators were blinded, 4524 subjects received aspirin or placebo; over three years the relative risk for admission to hospital from duodenal ulcer disease was 10·7 times higher in subjects treated with aspirin than placebo treated subjects. Forty per cent of patients treated with aspirin admitted to hospital for peptic ulcer disease had gastrointestinal bleeding. Many NSAID associated ulcers that bleed or perforate are clinically silent with little or no antecedent ulcer-type

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pain before the onset of complications.[11] Conversely many patients receiving NSAIDs have dyspepsia but do not have an ulcer or erosions at endoscopy.

Pathogenesis of ulcers associated with NSAIDs

The mucosal lining of the stomach resists injury by several mechanisms. Secretion of mucus and hydrogen carbonate allows the apical surface of cells to be relatively alkaline compared with the acidic environment of the stomach lumen. Epithelial cells migrate along the basement membrane to fill in gaps which form in the epithelial cell lining after mucosal damage. Mucosal blood flow provides continuous nutrients, O_2 and hydrogen carbonate, and disposes of diffused acid. Endogenous prostaglandins play an important part and bind directly to parietal cells to inhibit acid secretion,[12] stimulate secretion of mucus and hydrogen carbonate,[13] and maintain mucosal blood flow.

NSAIDs damage the gastric mucosa by an irritative topical effect and an indirect systemic effect owing to the inhibition of production of prostaglandins. Enteric coating of NSAIDs reduces damage following acute administration but is not effective in preventing ulceration.[14] Sulindac, a prodrug which is not active until after absorption and hepatic metabolism, is associated with peptic ulceration[15] and parenteral administration of NSAIDs produces gastric ulceration.[16] Levi *et al* [17] showed that NSAIDs inhibit proliferation of mucosal cells at the edge of ulcers, a process important for ulcer healing, and this effect was reversed by misoprostol.

It has been suggested that with continued administration of NSAIDs gastric mucosal injury lessens and may resolve, a process termed adaptation that is well documented in healthy volunteers.[18 19] The situation may be different in patients, however. Two studies[20 21] have shown that the risk of complications from NSAID induced peptic ulcers is greatest in the first month of treatment. This finding is consistent with the development of mucosal adaptation with long term administration of NSAIDs but could also result from early discontinuation of these drugs among patients who are intolerant of side effects. Other studies have shown no relation between duration of treatment and development of ulcer complications.[8] In one study[22] 78 patients with arthritis who had been receiving long term treatment with NSAIDs had non-ulcer damage at an initial screening endoscopy; after two further weeks of treatment with NSAIDs 19% had developed peptic ulcers. Serial endoscopies do not show a decrease in mucosal injury with continued administration of NSAIDs for up to one year.[23 24]

Treatment of NSAID associated ulcers

When patients develop gastrointestinal ulceration while receiving NSAIDs it is best to stop treatment wherever possible and heal the ulcer. In this situation misoprostol will heal 95% of gastric ulcers after four weeks of treatment compared with 75% healing in placebo treated patients.[25] Although there have been no comparative trials of misoprostol and H_2 blockers, in a similar study cimetidine achieved only 71% healing after four weeks of treatment.[26]

When it is clinically preferable to continue the treatment with NSAIDs, misoprostol is the treatment of choice to achieve ulcer healing. Roth *et al* showed that misoprostol coadministered with aspirin is effective in healing aspirin associated gastroduodenal damage in patients with rheumatoid arthritis[27]; 238 patients received a baseline endoscopy and were then randomised to receive either misoprostol or placebo while continuing treatment with aspirin. After eight weeks healing of gastric mucosal injury had occurred in 70% of the misoprostol treated group compared with 25% of the placebo treated subjects. Gastric ulceration was reduced in the misoprostol treated group; by eight weeks the healing rates were 62% in misoprostol treated subjects compared with 32% receiving placebo. Duodenal injury healed in 86% of the misoprostol treated group and 53% receiving placebo. Of these only 18 patients had duodenal ulcers on the baseline endoscopy; by eight weeks healing was seen in 90% receiving misoprostol and in 50% of controls.

Most studies have shown no benefit of H_2 antagonists over placebo in healing NSAID induced ulcers and damage during continued administration of NSAIDs.[28–30] In patients with classical peptic ulceration misoprostol (200 μg four times daily) is as effective as cimetidine (300 mg four times daily) in healing gastric and duodenal ulceration at four and eight weeks.[31 32] There have been no long term studies directly comparing misoprostol with H_2 antagonists or other antiulcer drugs in the healing of NSAID induced damage during continued administration of NSAIDs but the data which are available suggest that misoprostol is superior.

Sucralfate is not useful in the healing of gastric erosions and ulcers during continued treatment with NSAIDs. Over four weeks 1 g four times daily is no better than placebo or cimetidine.[33 34] Sucralfate and omeprazole have been compared in the healing of NSAID induced gastric and duodenal ulcers. Omeprazole (20 mg/day) produced better healing than sucralfate (1 g four times daily) and healed 100% of peptic ulcers at four weeks.[35] In a comparative trial omeprazole was significantly better than ranitidine; healing of ulcers with 40 mg omeprazole was 81% at four weeks compared with 32% with ranitidine.[36]

In conclusion, for patients with a peptic ulcer seen at endoscopy misoprostol is the current treatment of choice to achieve ulcer healing during continued treatment with NSAIDs. Dyspepsia is a poor guide to the presence of ulceration and starting treatment cannot be recommended on the basis of symptoms alone.

Prevention of NSAID associated gastroduodenal damage

Misoprostol is superior to placebo in preventing

gastroduodenal damage induced by NSAIDs in healthy volunteers and patients. Table 1 summarises recent studies. Gastroduodenal damage often occurs early (in two weeks) during treatment with NSAIDs and this is prevented by coadministration with misoprostol.[22] Longer term studies have shown that the efficacy of misoprostol is maintained. Graham *et al*[5] recruited patients with osteoarthritis receiving NSAIDs who at an initial endoscopy were free of gastric ulceration. Patients were randomly assigned to misoprostol (100–200 μg four times daily) or placebo during continued treatment with NSAIDs; repeat endoscopy was performed at one, two, and three months. The cumulative three month prevalence of gastric ulceration was 22% in the placebo group, 6% in the 100 μg misoprostol group, and only 1% in patients receiving 200 μg misoprostol. The two doses of misoprostol were significantly better than placebo. In a 12 month study the cumulative prevalence of gastric ulceration was 12·5% in the group of patients receiving misoprostol (600–800 μg/day), compared with 30% in the group receiving placebo ($p<0·05$).[23]

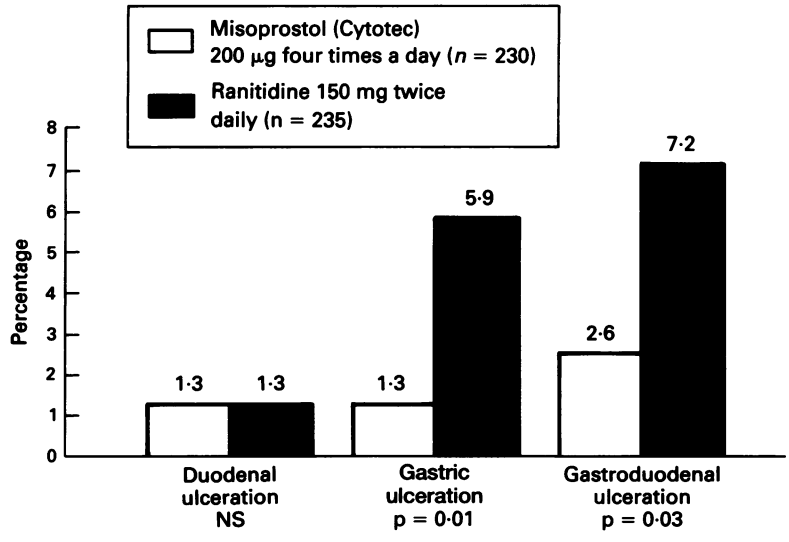
Studies with H_2 antagonists have produced variable results in placebo controlled trials. In normal volunteers cimetidine prevented acute gastric mucosal injury induced by a single dose of aspirin[43] but was not effective in reducing gastroduodenal erosions or ulcers in a one week trial during coadministration with naproxen.[44] In patients H_2 blockers have been ineffective in preventing gastric injury but are significantly better than placebo in preventing duodenal damage.[45] In comparative trials misoprostol is superior to ranitidine in the prevention of gastric ulceration but both H_2 blockers and misoprostol have produced similar results in the prevention of duodenal injury[46] (figure). Fewer trials have been conducted with either sucralfate or omeprazole; sucralfate is inferior to misoprostol[42] and is no better than placebo in preventing gastroduodenal erosions or ulceration.[44] In volunteer studies omeprazole does not prevent gastric damage but prevents duodenal damage and in this respect provides similar protection to ranitidine.[48]

In conclusion misoprostol is significantly better than placebo and standard antiulcer treatment in the prevention of NSAID induced gastric injury. Misoprostol and H_2 blockers provide similar protection against duodenal damage. When considering prophylactic treatment, however, the drug chosen must be able to provide gastric and duodenal protection and therefore misoprostol is the current treatment of choice. In clinical studies of the coadministration of misoprostol with NSAIDs there is no evidence that the efficacy of the NSAID is decreased. Synovial fluid concentrations of prostaglandins are unchanged by misoprostol and the concentration of thromboxane B_2 is actually decreased,[49] suggesting that misoprostol exerts an anti-inflammatory effect rather than pro-inflammatory which may be expected by exogenous administration of prostaglandins.

Table 1 Controlled studies showing prevention of non-steroidal anti-inflammatory drug damage by misoprostol.

Author	*Year*	*Number of cases*	*Duration (weeks)*	*Site of damage**	*Significance†*
Bardhan *et al*[37]	1991	277	2	D/G	0·005
De Rossi *et al*[38]	1990	95	4	D/G	<0·05
Schimke *et al*[39]	1990	82	2–4	D/G	0·002
Saggioro *et al*[40]	1988	153	4	D/G	<0·01
Graham *et al*[41]	1991	374	12	D/G	<0·01
Geis *et al*[24]	1990	244	12–48	D/G	0·005
Graham *et al*[5]	1988	420	12	G	<0·001
Agrawal *et al*[42]	1990	259	12	G	<0·001
Elliott *et al*[23]	1990	83	12–48	G	<0·05

*D/G=duodenal or gastric.
†Compared with placebo or other drug used.



Intent to treat analysis of ulcer rates in patients receiving non-steroidal anti-inflammatory drugs across eight week study period[47]. p Values were obtained using Fisher's exact test.

Which patients should receive antiulcer prophylaxis?

Fries *et al* have examined a large cohort of patients with arthritis and defined patients within that group who are particularly at risk for ulcer complications.[1] High risk patients were older, had previously stopped NSAIDs because of upper abdominal pain and were often receiving corticosteroids. Their findings concur with other studies[9 50] which have also identified high doses of NSAIDs[20] and degree of functional disability as risk factors in patients with arthritis. Table 2 shows potential indications for coadministration of misoprostol with NSAIDs.

Unanswered questions

The most important question is whether coprescribing misoprostol with NSAIDs reduces the occurrence of serious life threatening complications of gastroduodenal damage. The logical extrapolation from the endoscopic studies is that it is likely to be so, but there is no direct evidence that this is true. The principal

Table 2 Recognised indications for coadministration of misoprostol with non-steroidal anti-inflammatory drugs (NSAIDs)

Elderly patients
Medically unfit who may not withstand an ulcer complication
Previous peptic ulceration
High doses of NSAIDs
Patients receiving steroids

reason is that serious complications are uncommon and that prospective studies would have to be large to have sufficient power to show a reduction in life threatening problems resulting from NSAID induced gastroduodenal ulcers. Does misoprostol reduce the incidence of all NSAID related ulcers, including those likely to bleed or perforate, or does it decrease the frequency only of the more benign ulcers? The reasonable approach is to consider the first proposition most likely, but to continue seeking confirmatory evidence.

A second question is whether misoprostol also has beneficial effects lower down the gastrointestinal tract which are clinically significant. There is some evidence[51 52] that this may be so and this would swing the pendulum in favour of coprescribing misoprostol more often.

A final point is where to draw the line in coprescribing misoprostol. Subjects in whom there is a high risk of complications from gastroduodenal ulcers are a minority. Many serious adverse events due to NSAIDs in the upper gastrointestinal tract will affect patients without other risk factors. At what point is it reasonable not to use misoprostol? This issue should be resolved from the viewpoint that the less drugs taken the less the risk of problems, but it is as yet unanswerable and must remain within the remit of the judgment of doctors.

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