PRACTICAL DRUG SAFETY

Drug Safety 1999 Dec; 21 (6): 503-512
0114-5916/99/0012-0503/$05.00/0

Prevention of the Gastrointestinal Adverse Effects of Nonsteroidal Anti-Inflammatory Drugs
The Role of Proton Pump Inhibitors

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Contents

Abstract

The associations between nonsteroidal anti-inflammatory drugs (NSAIDs) and the presence and complications of gastroduodenal erosions and ulcers are well established. Evidence that acid aggravates NSAID-induced injury provides a rationale for minimising such damage by acid suppression. Other strategies discussed include avoidance of NSAIDs or minimising their dosage, selecting NSAIDs known to cause less damage, and co-prescription of various agents.

Cytoprotection with misoprostol, a prostaglandin analogue, has been shown to be effective in reducing NSAID-related peptic ulcers and their complications. Unfortunately, adverse effects may limit compliance in some patients. Histamine H_2 antagonists have only limited efficacy in the prevention of NSAID-induced ulcers in humans, particularly in the stomach, except at higher than standard dosages. This may relate to their relatively modest effect in elevating gastric pH, especially in comparison with proton pump inhibitors.

Several studies now confirm the efficacy of proton pump inhibitors in the short and longer term prevention of NSAID-induced upper gastrointestinal injury. Pla-

cebo-controlled studies suggest reductions of over 70% in gastric and duodenal ulcer rates over 3 to 6 months. The recent ASTRONAUT (Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-Associated Ulcer Treatment) study documented the greater prophylactic efficacy of omeprazole over ranitidine at standard dosages for 6 months. The OMNIUM (Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management) study showed omeprazole to be slightly more effective overall than misoprostol in preventing the upper gastrointestinal adverse effects of NSAIDs, with both substantially more effective than placebo, although misoprostol was somewhat less well tolerated.

Although substantial reductions in NSAID ulceration are now achievable when co-therapy with a proton pump inhibitor is given, a few patients will still develop ulcers and their complications. Hence the judicious use of NSAIDs in the first instance cannot be overemphasised.

The aims of this review are to briefly define the problem of ulceration of the upper gut induced by nonsteroidal anti-inflammatory drugs (NSAIDs), then discuss the rationale for the hypothesis that markedly reducing gastric acidity should reduce this ulcer risk. The remainder of the review addresses the evidence for clinical benefit when a proton pump inhibitor and some other agents are co-prescribed with NSAIDs. The literature was searched using Medline supplemented with scanning of abstracts of recent major scientific meetings.

1. Background

1.1 Risks of Damage and Ulceration Induced by Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

The toxic effects of NSAIDs on the upper gastrointestinal tract are a frequent cause of morbidity and even mortality.[1] Awareness of peptic ulcer as a complication of anti-inflammatory dosages of NSAIDs is high and, probably because of this, NSAID usage has diminished recently in some Western countries.[2] There is also hope that the newer NSAIDs that are selective inhibitors of cyclo-oxygenase (COX)-2 (rather than of the constitutive isoenzyme COX-1) will cause less gastroduodenal ulceration in the future. On the other hand, prescribing of low dosage (75 to 300 mg/day) aspirin (acetylsalicylic acid) for the prevention of stroke and myocardial infarction is increasing, and this will produce an increasing burden of ulceration as an adverse event.

With the current generation of NSAIDs, the great majority of patients develop some erosions in the stomach after each dose,[3] and about 15 to 25% of patients who have been taking NSAIDs regularly will be found to have a discrete ulcer if they are examined with gastroscopy at any point in time.[3,4] Most ulcers found in this way are asymptomatic and quite small.[3] They presumably heal and reappear a number of times before reaching a threshold for diagnosis in normal practice.

The most important complications of NSAID-induced ulceration of the stomach or duodenum are haemorrhage and perforation. Case-control studies have shown that NSAIDs increase the risk of these complications by about 3 to 10 times,[4] and for some particular NSAIDs the risk is higher still. Even low dosage aspirin increases the chance of ulcer haemorrhage or perforation by 2 to 4 times.[5]

1.2 Rationale for Acid Suppression

Luminal acid appears to contribute to NSAID injury in the stomach in 2 ways. First, most NSAIDs are weak acids with pKa values in the range 3.5 to 6. This means that they are mostly non-ionised at the usual pH of the stomach and the duodenal bulb. As a consequence, they are usually lipid soluble and can diffuse into the surface cells fairly readily. This increase in gastric absorption at

high pH is well documented with aspirin.[6,7] Having gained entry to the surface cells, aspirin becomes trapped at the higher intracellular pH and causes local toxicity. There is, however, much less evidence that this local effect is important with other NSAIDs.[8]

Secondly, acid (and possibly pepsin) appears to produce a 'second wave' of injury, deepening some of the superficial erosions that are very widespread soon after administration of an NSAID. Much of the superficial injury repairs within an hour or two, but here and there the damaged surface seems not to repair in time before the acid in the lumen causes further deeper destruction of tissue.[9] These focal, deeper, areas are the macroscopic erosions seen endoscopically in most patients who are taking NSAIDs. In rats, vagotomy reduces this deeper damage without altering the initial superficial injury by NSAIDs.[10,11] More recent data from Elliott et al.[12] show that gastric mucosal injury in the rat is much reduced when the luminal pH is elevated above a threshold of about 4.0 (fig. 1). This pH is rarely achieved for long after H_2 antagonists, but can be readily achieved for at least half of each 24-hour period during administration of proton pump inhibitors at standard dosages.[13,14]

2. Non–Proton Pump Inhibitor Strategies for Risk Reduction

2.1 NSAID Selection

Against this background of ulcer risk, there are a number of clinical and pharmacological strategies that can be employed to reduce it. The first and most obvious is to avoid NSAIDs when they are not necessary. Secondly, when NSAIDs do need to be used, there is now good evidence that the risk of ulcer complications is dosage dependent,[15] so the NSAID should be used at the lowest effective dosage. A recent meta-analysis has confirmed that some NSAIDs are more damaging than others.[15] For example, the short-acting NSAIDs ibuprofen and diclofenac (at standard dosage) have usually been found to have relative risks of the order of 3 to 5 for ulcer bleeding, whereas some of the long-acting drugs recommended for once-daily administration have relative risks of 10 or higher. Thus the clinician should consider choosing an agent from the less damaging end of the spectrum unless there is a particular need for one of the more potent agents or formulations. The new highly selective COX-2 inhibitors, already marketed in some countries, offer a further choice, particularly in patients at high risk of NSAID ulceration.

2.2 Cytoprotection

Coadministering a prostaglandin analogue reduces the gastric and duodenal damage caused by NSAIDs. This approach was developed knowing that prostaglandins are defensive factors in the normal gastric mucosa and that NSAIDs exert their damage, at least in part, by inhibiting the production of these mucosal prostaglandins. In short term studies, prostaglandins markedly reduce the number of erosions in the stomach during NSAID administration.[16-18] In longer term studies (3 to 12 months), misoprostol – an analogue of prostaglandin E_1 – has been shown to reduce the incidence of gastric and duodenal ulcers by about 60 to 70%,[3,19] although higher protection rates have also been reported.[20] One large study also showed an approximate halving in the number of episodes of ulcer bleeding over a 6-month period.[21]

Thus, cytoprotection with a coadministered prostaglandin is an effective strategy for reducing

Fig. 1. Effect of gastric luminal pH on the gastric damage (% of mucosa with macroscopic haemorrhagic lesions) produced by indomethacin in rats. Injury was markedly reduced when the pH of the lumen was buffered to higher than 4 (after Elliott et al.,[12] with permission).

NSAID injury and its complications. The protection is dosage dependent, but so are the adverse effects of diarrhoea and abdominal cramps, which occur in about 10% of patients.

2.3 Histamine H_2 Antagonists

Histamine H_2 antagonists, at least at standard dosages, have only limited efficacy for preventing NSAID-induced ulcers in humans. Two well-conducted controlled trials showed that ranitidine 150mg twice daily gave substantial protection against the development of duodenal ulcers during NSAID administration.[22,23] Unfortunately, there was no significant protection against gastric ulcers in either study, and these are a greater problem than duodenal ulcer in NSAID users. Similarly, in another large survey of patients with arthritis, the use of cimetidine produced no reduction in the incidence of ulcer bleeding.[24]

More marked acid suppression with larger doses of H_2 antagonists may give better results. A recent trial by Taha et al.[25] showed a 60% reduction in gastric ulceration, and an 85% reduction in duodenal ulcers, during 6 months treatment with famotidine 40mg twice daily.

Even at these larger dosages, H_2 antagonists have a fairly modest effect in elevating intragastric pH. For instance, in patients taking a standard dosage of ranitidine, median pH in the stomach over a 24-hour period is rarely greater than 3.[14] In contrast, median intragastric pH in patients taking standard dosages of proton pump inhibitors is usually at least 1 unit higher, of the order of 4 to 5.[13] These are the pH values that we had previously shown need to be reached if the acid component of NSAID gastric injury is to be reduced.[12] The next section reviews the data now available about the use of proton pump inhibitors for preventing NSAID injury.

3. Clinical Studies of Proton Pump Inhibitors for Prophylaxis of NSAID Injury

Given the limitations of standard preventive measures, it is not surprising that attention has been focused on proton pump inhibitors as an effective yet tolerable means of protecting the stomach from the important adverse effect of NSAIDs – peptic ulceration.

3.1 Short Term Studies (Up To 1 Month)

Whether or not proton pump inhibitors protect against acute NSAID damage in humans has been examined in a number of short term trials. In most instances, the proton pump inhibitor used has been omeprazole.

Table I summarises the findings from 8 controlled, randomised, double-blind trials since 1988. The study by Bianchi Porro et al.[26] recruited patients with arthritis, who were treated with omeprazole or placebo concurrently with an NSAID for 3 weeks. This was the largest of the short term studies. All the others used healthy volunteers given an NSAID (mostly aspirin) as a single dose or for up to 2 weeks. In those studies where the NSAID was given for 5 days or less, the proton pump inhibitor or comparator drug was started a few days before the NSAID. It takes several days from the start of treatment before steady state plasma concentrations and acid suppression are reached with proton pump inhibitors,[13] so this design ensured that acid suppression was well established when the NSAID was given.

All studies demonstrated protection against NSAID gastric damage when co-therapy was given with either omeprazole or lansoprazole.

Daneshmend et al.[27] assessed gastric damage by using a gastric lavage technique to measure gastric micro-bleeding after aspirin. Blood loss was reduced about 80% when omeprazole 20 or 80 mg/day was given for a week, then aspirin 900mg administered daily on the last 2 days. The gain in protection by increasing the omeprazole dosage was small, although the study was not powered to examine the effect of dosage. However, they found a significant negative correlation between the volume of micro-bleeding and the intragastric pH achieved.

All the other studies measured gastric damage endoscopically. Usually only erosions are found

during such short term studies, and these were quantified on an ordinal scale in each report. Table I shows the percentage reduction in the proportion of patients with numerous erosions in the active treatment arms compared with placebo. The cut-off categories are arbitrary and vary somewhat between studies, but 'protected' patients generally had less than 10 erosions in gastric mucosa. Protection against erosions, defined in this way, was seen in 79 to 100% of patients treated with omeprazole 20 to 40 mg/day. A similar protection was seen in the study by Bigard[28] using omeprazole 60 mg/day, and in the small study with lansoprazole 30 mg/day.[29] Protection may be somewhat less when lansoprazole 15 mg/day is used.[30] Two studies included arms treated with ranitidine 300 mg/day, which did not confer significant protection.[30,31]

It is uncommon for ulcers to develop during such short term administration of NSAIDs. However, a few acute ulcers were seen in the studies by Scheiman et al.[32] and Bianchi Porro et al.[26] Omeprazole 40 or 20 mg/day reduced this incidence by 80 to 100% (table I), although the numbers were small and significance was reached only in the larger study.[26]

Duodenal ulcers also appeared in a few patients. In the Scheiman et al.[32] study, none occurred in the omeprazole group but 15% developed them while taking placebo plus aspirin ($p < 0.01$). Only 2 duodenal ulcers developed in the Bianchi Porro et al.[26] study, 1 in each group.

Table I. Blinded controlled studies of effects of co-treatment with proton pump inhibitors on gastric damage during short term treatment with nonsteroidal anti-inflammatory drugs (NSAIDs)

Reference	NSAID (daily dosage)	Duration of NSAID use	No. of patients	Co-treatment (daily dosage)	Reduction in gastric damage[a]	p-Value
Scheiman et al.[32]	Aspirin (acetylsalicylic acid) [2.6g]	14 days	20	Placebo		
				Omeprazole (40mg)	79% (erosions)	<0.01
					80% (ulcers)	NS
Bigard[28]	Aspirin (600mg)	1 day[b]	20	Placebo		
				Omeprazole (60mg)	85% (erosions)	<0.001
Bianchi Porro et al.[26]	Several	21 days	114	Placebo		
				Omeprazole (20mg)	100% (ulcers)	<0.01
Oddsson et al.[31]	Naproxen (1g)	5 days[b]	15	Placebo		
				Ranitidine (300mg)	60%	NS
				Omeprazole (40mg)	100%	<0.05
Daneshmend et al.[27]	Aspirin (900mg)	2 days[b]	16	Placebo		
				Omeprazole (20mg)	79% (blood loss)	<0.01
				Omeprazole (80mg)	85% (blood loss)	<0.01
Simon et al.[33]	Aspirin (300mg)	14 days	36	Placebo		
				Omeprazole (20mg)	77% (erosions)	<0.001
				Omeprazole (40mg)	85% (erosions)	<0.001
Müller et al.[30]	Aspirin (300mg)	14 days	30	Placebo		
				Ranitidine (300mg)	43% (erosions)	NS
				Lansoprazole (15mg)	64% (erosions)	<0.05
Bergmann et al.[29]	Aspirin (1g)	1 day[b]	12	Placebo		
				Lansoprazole (30mg)	70% (mean erosion score)	<0.005
					100% (erosion score >2)	<0.05

a Erosions were usually quantified on scales of 0 to 4; percentage reductions generally calculated here as reduction in patients with grade 3 or 4 damage.

b Co-treatment started 2 to 6 days prior to NSAID treatment.

NS = not significant.

Table II. Development of nonsteroidal anti-inflammatory drug (NSAID)–related peptic ulcer during proton pump inhibitor prophylaxis in placebo-controlled trials

Authors	No. of patients	Agent	Duration	Patients developing peptic ulcer (%)		p-Value
				active	placebo	
Cullen et al.[35]	169	Omeprazole 20 mg/day	6 months	4	18	<0.01
Ekström et al.[36]	175	Omeprazole 20 mg/day	3 months	5	17	<0.05
Bianchi Porro et al.[37]	104	Pantoprazole 40 mg/day	3 months	28	41	0.29[a]

a The power of this χ^2 test was only 0.2.

Another measure of gastric mucosal injury is the fall in transmucosal potential difference which reproducibly follows a dose of an NSAID.[34] This fall occurs within minutes of giving aspirin, and reflects the widespread denudation of the cells lining the mucosal surface.[34] Bergmann et al.[29] measured this for 3 hours after administration of aspirin before performing endoscopy to quantify erosions. It is interesting that lansoprazole did not protect against this fall in potential difference, although it did protect against the development of endoscopic erosions. This is consistent with the idea presented in section 1.2 that acid is more important for the 'second wave' of injury that leads to the deeper lesions than for the initial superficial injury produced by NSAIDs.

3.2 Longer Term Studies (More Than 1 Month)

3.2.1 Proton Pump Inhibitors Versus Placebo

To date, 3 placebo-controlled studies that compared proton pump inhibitor therapy with placebo for 3 months or longer have been published (see table II). All have been well conducted, with protocols that allow their findings to be generalised to the NSAID-taking population at large. Despite varying somewhat in design, the 2 larger studies both reported reductions of more than 70% in overall ulcer rates (gastric plus duodenal) when omeprazole 20 mg/day was co-prescribed with the NSAID.[35,36] A placebo arm was also included in the large misoprostol versus omeprazole trial described in section 3.2.3. In the smaller study by Bianchi Porro et al.[37] (available only as an abstract at the time of writing), the protection by pantoprazole was less marked (32%), although the results are not readily comparable with other studies because of the very high ulcer occurrence rates in both active treatment and placebo groups.

Dyspeptic symptoms also benefited from proton pump inhibitor treatment in these studies, although it is interesting that the correlation between symptoms and endoscopic end-points was poor.

The data on site of ulcer occurrence in these papers raise the possibility that proton pump inhibitors may protect the duodenum a little better than the stomach, although the differences do not approach statistical significance. However, this would be consistent with the previous observations about the differential efficacy of H_2 antagonists in this setting.

3.2.2 Proton Pump Inhibitor Versus H_2 Antagonist

The recently published Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-Associated Ulcer Treatment (ASTRONAUT) study[38] recruited patients continuing treatment with NSAIDs who had peptic ulcer or more than 10 gastric or duodenal erosions. It consisted of 2 phases – an initial healing phase and a subsequent maintenance phase.

Healing of peptic ulcers in patients continuing treatment with NSAIDs was significantly better with omeprazole than with ranitidine over 2 months (87 *vs* 70.5%) but was independent of the omeprazole dosage, 20 and 40 mg/day being equally efficacious.

In the subsequent maintenance phase, those patients whose lesions healed were randomised to ei-

ther omeprazole 20 mg/day or ranitidine 150mg twice daily and assessed after 6 months. Omeprazole was again more effective, with 94% remaining ulcer-free overall compared with 79.5% on ranitidine (see fig. 2).

Again there was a trend to higher protection against duodenal ulcer: only 1 duodenal ulcer (0.5%) was noted during omeprazole maintenance treatment compared with 11 gastric ulcers (5.2%), whereas with ranitidine there were 9 duodenal and 35 gastric ulcers (4.2% and 16.3% respectively).

As expected, both these acid-suppressant drugs were well tolerated.

3.2.3 Proton Pump Inhibitor Versus Misoprostol

The Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management (OMNIUM) study[39] was of similar design to ASTRONAUT,[38] comparing omeprazole with misoprostol in the healing phase and adding a placebo arm to the maintenance phase.

Omeprazole (either 20 or 40 mg/day) was slightly more effective than misoprostol (200μg 4 times daily) for overall ulcer healing at 8 weeks (86 *vs* 74%). However, misoprostol had greater efficacy for healing erosive disease alone. As a result, there was no significant difference in efficacy between the 2 agents for the primary end-point of the study, which was a composite requiring healing of ulcers and erosions and symptom relief.

In the maintenance phase, those healed were randomised to omeprazole 20 mg/day, misoprostol 200μg twice daily or placebo for 6 months. Overall ulcer recurrence rates were 15% in patients receiving omeprazole, 21% in patients receiving misoprostol and 44.5% in patients receiving placebo (see fig. 2).

Again, examination of ulcer-site data as shown in figure 2 is of interest. Omeprazole and misoprostol have similar efficacy in the stomach (13 and 10% recurrence respectively), but omeprazole appears superior for prophylaxis of duodenal ulcer (3% recurrence *vs* 10% for misoprostol).

In terms of adverse effects, misoprostol was discontinued more often than either omeprazole or placebo (16.8 *vs* 12.1 *vs* 10.3% respectively, $p < 0.1$ by χ^2 analysis), particularly as a result of an adverse event (7.7 *vs* 3.9 *vs* 1.9%, $p < 0.02$). Rates of individual adverse effects were not dramatically different between any of the agents (e.g. misoprostol was associated with diarrhoea in 8.4% of patients compared with 7.6% of patients taking omeprazole), although this may be a function of sample size.

It is interesting to note the apparent difference in efficacy of omeprazole prophylaxis between the 2 studies despite the tandem design. It can be seen from fig. 2 that there were 3 times more ulcers on omeprazole in the OMNIUM study as compared with the ASTRONAUT study. Presumably this reflects differences in the patient populations re-

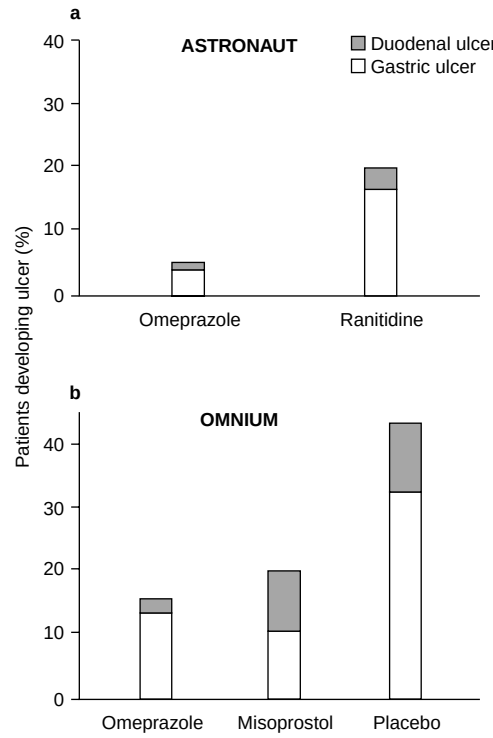

Fig. 2. Proportion of patients developing nonsteroidal anti-inflammatory drug (NSAID)–associated ulcers during 6 months of co-treatment with omeprazole 20 mg/day, ranitidine 150mg twice daily, misoprostol 200μg twice daily or placebo. (**a**) Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-Associated Ulcer Treatment (ASTRONAUT) study;[38] (**b**) Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management (OMNIUM) study.[39]

cruited in the 2 studies (including the spectrum of NSAIDs taken).

3.3 Future Research Needs

Both the ASTRONAUT[38] and OMNIUM[39] studies were high quality trials with large numbers of patients. Taken together with the Omeprazole versus Placebo as Prophylaxis of Ulcers and Erosions from NSAID Treatment (OPPULENT) study,[35] they included a spectrum of patients similar to the NSAID-taking population at large, i.e. patients who ranged from low risk (young and without prior ulceration) to those at the high risk end (older and with recent ulceration). However, there are a number of questions still unanswered about the role of proton pump inhibitors in protecting against NSAID-associated ulcers. One is whether all proton pump inhibitors are equally effective at equivalent dosages. It is likely that this will be the case, although the studies so far with lansoprazole and pantoprazole have been small and have given less impressive results than the large studies with omeprazole. To settle this question, comparative studies with at least several hundred patients in each arm would be needed.

The optimally effective dosage of a proton pump inhibitor for preventing ulcers has not been examined. In the healing arms of the ASTRONAUT and OMNIUM studies,[38,39] omeprazole 20 mg/day was as effective as 40 mg/day, but only the 20 mg/day dosage was examined in the maintenance phases of the studies. Whether a higher dosage would give even better protection is therefore not known.

Protection by proton pump inhibitors against NSAID ulcer complications has now been demonstrated in a recent study.[40] To date this has been published only as an abstract. This result may be worth confirming, although it is very much to be expected that the now well documented reduction in the incidence of ulcers will be reflected in a reduction in ulcer complications as well – after all, an ulcer that is not present cannot bleed or perforate.

With these benefits come costs, mostly for the prophylactic medication. There are of course savings as well, measured in reduced medical costs and greater workplace productivity. The relationship between these deserves formal analysis. One recent cost-effectiveness study calculated that the cost of NSAID complications (in Sweden) is around US$450 (1999 values) per patient per annum.[41] The cost of prophylactic co-therapy needs to be set against this.

Another question that needs answering is whether *Helicobacter pylori* infection constitutes an additional risk factor in patients taking NSAIDs. If it did, it would be rational to routinely treat *H. pylori* in such patients. However, studies have been conflicting. In both the ASTRONAUT[38] and OMNIUM[39] studies described in section 3.2, patients who were *H. pylori* positive were more likely than patients who were *H. pylori* negative to have their NSAID-associated ulcer healed and less likely to have one develop during healing or maintenance therapy with omeprazole or ranitidine. However, 1 study has shown a marked reduction in the incidence of ulcers during 2 months' treatment with naproxen when *H. pylori* was successfully treated.[42] Another study, over a longer period in patients who had been taking NSAIDs prior to the *H. pylori* treatment, found no such benefit.[43] Differences in study populations may account in part for these opposing findings, but more research is needed to guide clinical management of this issue.

4. Conclusions

Proton pump inhibitors have demonstrated efficacy in the prevention of the adverse gastrointestinal effects of NSAIDs.

They reduce ulcer rates by up to 80% compared with no treatment, and have clear benefits over H_2 antagonists (particularly in the stomach) and to a lesser extent over misoprostol (particularly in the duodenum, and in patient tolerability).

Nevertheless there are still some 'breakthrough' ulcers on the dosages of proton pump inhibitor tested to date, especially in the stomach. Hence, the importance of reviewing the need for

NSAIDs at the outset, as well as selecting the lowest dosage of the least toxic agent, cannot be overstressed.

The new generation of highly selective COX-2 inhibitors is beginning to provide a further option for reducing ulcer risk in patients who need anti-inflammatory drugs, although they are likely to be expensive and it is a little early to assess their longer term adverse effect profile. These drugs will not, of course, be a substitute for aspirin used for its anti-platelet (COX-1) effect.

When aspirin or other nonselective COX inhibitors are used, the proton pump inhibitors appear to provide a significant advance in improving the tolerability of NSAID therapy.

Acknowledgements

This work was supported in part by the National Health and Medical Research Council of Australia. The authors thank Ms Julie Holland and Ms Lyn Kalms for administrative assistance.

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