Review Article

NSAID Gastropathy: An Update on Prevention

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Abstract: Adverse reactions to non-steroidal anti-inflammatory drugs (NSAIDs) are common. Upper gastrointestinal complications including ulcer bleeding, perforation and obstruction are the most serious complications that can result in substantial morbidity and mortality. Many NSAID-using patients present with complications without any preceding symptoms. Risk factors for NSAID-related gastrointestinal bleeding include advanced age, past history of ulcers and bleeding and concomitant use of anticoagulants or corticosteroids. The role of Helicobacter pylori infection in NSAID-related peptic ulcer is unclear. In high-risk patients who need to continue NSAIDs, prophylactic treatment against ulcer development is required. Options include concomitant use of anti-ulcer drugs, use of selective COX-2 inhibitors and eradication of H. pylori. This review summarizes the current status of these regimens in the prevention of NSAID-related peptic ulcer complications.

Keywords: COX-2 inhibitor, duodenal ulcer, gastric ulcer, Helicobacter pylori, NSAIDs, proton-pump inhibitor

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used classes of drugs.1 In the United States, non-aspirin NSAID use is common in the elderly (≥65 years old) and 10-20% of these people have a current or recent NSAID prescription.2 In Hong Kong, data from the Hospital Authority showed that about 75,000 patients in the public sector were on long-term non-aspirin NSAIDs in the year 1999 to 2000 (unpublished data). Among the 75,000 patients, 40% were over 60 years of age. These figures had not included over-the-counter prescriptions and prescriptions in private sectors.

Although most NSAIDs are generally well tolerated, a small but important percentage of patients develop adverse gastrointestinal complications, resulting in substantial morbidity and mortality. Each year, 1-3% of NSAID users will have gastrointestinal bleeding.3 Almost all deaths from NSAID-related gastrointestinal side effects occur in elderly persons.2

Risk Factors

Overall Risk

NSAID users have a three- to four-fold increase in risk of developing ulcer bleeding, perforation and death.4 The mortality rate attributed to NSAID-related gastrointestinal toxicity was 0.22% per year, with an annual relative risk of 4.21 as compared with the risk for persons not taking NSAIDs. Although the absolute mortality rate is low, the risk is enormous because a large number of patients are exposed to NSAIDs.

Individual Risk Factor

Factors identified to predict an increased risk of ulcer complications include advanced age, history of ulcer/bleeding, higher NSAID dose, use of multiple NSAIDs, concomitant corticosteroids or anti-coagulant use and first month of NSAID therapy.5 The interaction between H. pylori...
and NSAIDs in causing ulcers or ulcer complications is rather complex and controversial. In a case control study, Aalykke et al.\(^6\) found that NSAID users infected with \textit{H. pylori} had an almost doubled risk of bleeding peptic ulcer compared with uninfected NSAID users. However, this was not supported by other epidemiological studies, which showed either no effect with \textit{H. pylori} or evidence of possible protection with \textit{H. pylori} in NSAID-related gastroduodenal bleeding.\(^7-10\) A recent meta-analysis suggests an interaction between NSAIDs and \textit{H. pylori} infection in causing gastroduodenal injury.\(^11\) However, several large and important NSAIDs trials were not included in this meta-analysis.

**Prevention**

Although GI complications can be avoided by the use of non-NSAID analgesics or decreased by use of the lowest effective dose of an NSAID, many patients with chronic arthritis still need regular NSAIDs to control their symptoms. Therefore, preventive measures are needed to reduce ulcer complications, particularly in high-risk patients. Three currently available options, each with its own merits and problems, have been studied extensively. These include concomitant therapy with anti-ulcer drugs, use of highly selective inhibitors of cyclo-oxygenase-2 enzyme (COX-2 inhibitors) and eradication of \textit{H. pylori}.

**Concomitant Therapy**

(a) Misoprostol

Multiple endoscopic trials have demonstrated the efficacy of misoprostol, a synthetic prostaglandin, in the prevention of NSAID-associated ulcers. In a randomized placebo-controlled trial, Graham et al. showed that both gastric and duodenal ulcers developed in fewer patients using NSAIDs and misoprostol compared to NSAIDs plus placebo.\(^12\) Besides preventing endoscopically detectable ulcers, misoprostol also prevents serious ulcer-related complications. In the 6-month prospective outcome study involving 9000 NSAID-using rheumatoid arthritis patients, 0.36% of patients receiving misoprostol 200 ug qid developed serious gastrointestinal complications as compared to 0.74% of patients receiving placebo (\(p=0.049\)).\(^13\) However, more than 10% of patients receiving misoprostol may develop other adverse events, predominantly diarrhoea and abdominal pain. Although lowering the dose of misoprostol may reduce the side effect, low-dose misoprostol 200 ug bid may not be as efficacious in preventing ulcer development, suggesting the drug needs to be taken at least three times a day or at full dose of four times daily.\(^14\)

(b) \(H_2\) Receptor Antagonists

Ordinary dose of ranitidine (150 mg bid) was effective in preventing duodenal but not gastric ulcers. A recent European study found that high dose famotidine (40 mg bid) was effective in preventing both gastric and duodenal ulcers.\(^15\) However, not only the rate of recurrence of ulcers seemed very high (e.g. 12.8% after 4 weeks) in those receiving famotidine but also this was higher than the rate expected with misoprostol. The rate of relapse for patients without \textit{H. pylori} infection receiving famotidine therapy was 21.4% and almost identical to those receiving placebo (23.8%). Moreover, an American trial of high-dose famotidine for the prevention of NSAID-related ulcers was unable to confirm the results of the European trial.\(^16\) Further studies are required before high-dose famotidine can be widely used in prophylaxis against NSAID-related peptic ulcers.

(c) Proton-pump Inhibitors (PPI)

Omeprazole 20 mg daily was found to be more effective than ranitidine 150 mg b.d\(^17\) and misoprostol 200 \(\mu g\) b.d.\(^18\) in preventing the recurrence of a combination of upper GI adverse events including ulcers, erosions and dyspepsia during continued NSAID use in carefully conducted endoscopy studies. In the Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management (OMNIUM) study, more patients remained in remission during maintenance treatment with omeprazole (61%) than with misoprostol (48%, \(p=0.001\)) and with either drug than with placebo (27%, \(p<0.001\)). Pilotto et al. found that in \textit{H. pylori} positive patients over 60 years old with symptoms and/or a history of ulcer and who had no severe gastroduodenal lesions on endoscopy, maintenance pantoprazole 40 mg daily for 1 month, concomitantly with NSAID therapy, significantly lower the incidence of severe gastroduodenal damage than 1-week anti-helicobacter therapy.\(^19\) In another 6-month placebo-controlled study, Chan et al. found that 4.4% of patients receiving 20 mg of omeprazole daily had recurrence of peptic ulcer bleeding after 6 months of NSAID therapy as compared with 18.8% for patients receiving eradication therapy. These results suggest that proton-pump inhibitors are effective in the prophylaxis of NSAID-induced gastroduodenal mucosal injury.\(^20\)
Although omeprazole was consistently superior to placebo for the prevention of ulcer recurrence in chronic NSAID users, a re-analysis of the data in the OMNIUM study with reference to the status of H. pylori infection and using ulcers as the only endpoint demonstrated that omeprazole was not significantly better than the subtherapeutic dose of misoprostol (400 µg/day); 400 µg of misoprostol was actually superior to omeprazole for the prevention of gastric ulcers among those NSAID ulcers without H. pylori infection (8.2% vs. 16.6% for misoprostol and omeprazole, respectively; p<0.05). Omeprazole was also not statistically different from misoprostol for gastric ulcer prevention in those NSAID users with an active H. pylori infection. In another prospective, double-blind, multicenter, active- and placebo-controlled study among 537 patients without H. pylori who were long-term users of NSAIDs and who had a history of endoscopically documented gastric ulcer, significantly more patients on full-dose misoprostol (93%) were free of gastric ulcers than patients on lansoprazole 30 mg daily (82%). Both these therapies were better than placebo in maintaining remission. Since a significantly higher proportion of patients in the misoprostol group reported treatment-related adverse events and withdrew from the study, the remission rate for each treatment group was similar (69% for both groups).

**COX-2 Inhibitors**

The GI side effects of conventional NSAIDs are thought to be mediated through the inhibition of cyclo-oxygenase-1 (COX-1) enzyme while the anti-inflammatory effects are mediated through the inhibition of cyclo-oxygenase-2 (COX-2) enzyme. Highly selective COX-2 inhibitors that can spare the inhibition of COX-1 enzyme have been developed with a view to reduce the GI complications associated with the use of NSAIDs. Two compounds are currently available, celecoxib and rofecoxib, and they appear to have no effect on COX-1 enzyme at doses substantially higher than those required to reduce inflammation. Several studies showed that their incidence of endoscopically detectable ulcers were comparable to placebo and was much lower than non-selective NSAIDs (ibuprofen or naproxen).

The improvement in GI safety as compared with non-selective NSAIDs was shown in two large double-blind, randomized, outcomes trials. The CLASS study (Celecoxib Long-term Arthritis Safety Study) compared celecoxib with ibuprofen and diclofenac, and the VIGOR study (VIOXX Gastrointestinal Outcomes Research) compared rofecoxib with naproxen. The VIGOR study showed a relative risk reduction for clinical upper GI events of 50% with rofecoxib, and a 60% reduction in complicated events. In the CLASS study, there was a 34% reduction in combined complicated ulcers and symptomatic ulcers for celecoxib (p=0.04). However, when only complicated ulcers were considered, a 23% reduction in risk was found and this did not reach statistical significance (p=0.45).

Replacing non-selective NSAIDs with COX-2 inhibitors is more cost effective in high-risk patients than in low-risk patients. Although the relative reduction in events with the selective COX-2 inhibitor is similar in high-risk and low-risk patients, the number-needed-to-treat with rofecoxib instead of naproxen to avert an event is smallest (approximately 10) in the highest risk patients because absolute risk reductions were higher in patients with risk factors and event rates with naproxen were higher in these patients.

Very few studies directly compare between rofecoxib and celecoxib. In an observational cohort study in Canada, Mamdani et al. compared rates of upper gastrointestinal bleeding resulting in admission to hospital in patients aged over 66 years who started treatment with non-selective NSAIDs (n=5,391), diclofenac plus misoprostol (n=5,087), rofecoxib (n=14,583), or celecoxib (n=18,908) and a randomly selected control cohort not exposed to NSAIDs (n=100,000). Over a follow-up period of less than six months, relative to controls, there was an increased short-term risk of upper gastrointestinal bleeding for users of non-selective NSAIDs (adjusted rate ratio 4.0), diclofenac plus misoprostol (3.0), and rofecoxib (1.9) but not celecoxib (1.0). Relative to celecoxib, significantly higher risks of upper gastrointestinal bleeding were observed for rofecoxib (1.9). Relative to rofecoxib, non-selective NSAID users were at significantly higher risk of upper gastrointestinal bleeding (1.9). It seems that the risk of upper gastrointestinal bleeding for the selective COX-2 inhibitors is significantly lower than for the traditional non-selective NSAIDs, and that celecoxib seems to be associated with a lower risk of bleeding than rofecoxib.

Although these agents offer considerable promise in the treatment of inflammatory arthritis, they are not free of problems and careful surveillance is still needed to determine ultimately their safety and benefit. The underlying mechanisms for the improved GI outcome are also not clearly understood. Animal work showed that COX-2 inhibitors might delay the healing of gastrointestinal ulcer.
of both COX-1 and COX-2 is required for NSAIDs-induced gastric injury in the rat and inhibition of either COX-1 or COX-2 enzyme will not produce any gastric injury.\textsuperscript{31}

Similar to nonselective NSAIDs, COX-2 inhibitors can cause salt and water retention and decrease in glomerular filtration rate.\textsuperscript{32} The reported incidence of dyspepsia in patients receiving COX-2 inhibitors did not show much advantage over NSAIDs, in that a relatively high incidence of dyspepsia was seen in patients treated with COX-2 inhibitors. However, celecoxib, at two to four times the recommended dose, still demonstrated a superior dyspepsia-related tolerability and satisfaction compared with standard dosages of diclofenac.\textsuperscript{33}

Results of pre-marketing and post-marketing trials have raised concerns about the cardiovascular safety of rofecoxib, especially at doses greater than 25 mg. In the VIGOR study, the incidence of myocardial infarction was lower among patients in the naproxen group than among those in the rofecoxib group (0.1\% vs. 0.4\%; relative risk, 0.2) In a retrospective cohort study on the occurrence of serious coronary heart disease (CHD) in non-users (n=202 916) and users of rofecoxib and other NSAIDs (rofecoxib n=24,132, other n=151,728), users of high-dose rofecoxib were 1.70 (p=0.058) times more likely than non-users to have CHD.\textsuperscript{34} However, no evidence of raised risk of CHD was seen among users of rofecoxib at doses of 25 mg or less or among users of other NSAIDs. These results indicate that high-dose rofecoxib could be associated with a raised risk of serious CHD, whereas rofecoxib 25 mg or less, naproxen, and ibuprofen are not.

For celecoxib, data submitted to the FDA showed that the 12-month data were not as satisfactory as the 6-month data and the difference in the occurrence of clinic events between celecoxib and non-selective NSAIDs became much smaller at the end of 12 months. Moreover, as noted in the CLASS study, the advantage of celecoxib was abolished in patients who received low-dose aspirin concomitantly, a situation which is not uncommon in elderly patients.

Finally, it should be noted most of the patients recruited in these studies did not have high risk factors for developing gastrointestinal complications. The use in high-risk patients needs to be examined more extensively. The efficacy of COX-2 inhibitors in direct comparison with proton pump inhibitors as co-therapy to reduce gastrointestinal complications also needs further study.

### Eradication of H. pylori

**\textit{(a) Before NSAIDs Are Started}**

Chan et al in a population of arthritic patients who had never been exposed to NSAIDs therapy showed that eradication of \textit{H. pylori} significantly reduced the risk of ulcer occurrence after 2 months of therapy with naproxen (from 26\% to 7\%).\textsuperscript{35} This is confirmed by yet another longer study from the same investigators on patients with a past history of ulcers or dyspepsia, in which 12\% of patients in the eradication group had relapse of gastric or duodenal ulcers as compared with 34\% in the group without eradication treatment.\textsuperscript{36} The benefit of \textit{H. pylori} eradication was also supported by another randomized, double blind, placebo controlled, multicenter study, which compared \textit{H. pylori} eradication, PPI co-therapy and placebo in the development of endoscopic ulcers in 660 patients who required NSAID therapy but with no past or current history of peptic ulcers.\textsuperscript{37} This study showed that both \textit{H. pylori} eradication (1.2\%) and PPI co-therapy (0\%) significantly reduced ulcer occurrence as compared to placebo (5.8\%). However, the author did not recommend universal \textit{H. pylori} testing and eradication before NSAID therapy because of the very low rate of ulcer development and the absence of ulcer complications.

**\textit{(b) After NSAIDs Are Started}**

The picture in this group is quite different. Lai et al. found that eradication of \textit{H. pylori} in a group of patients already on long term NSAIDs did not reduce the risk of ulcer development over a period of 3 months.\textsuperscript{38} Another study from Italy in patients over 60 years old with symptoms and/or a history of ulcer also showed similar finding.\textsuperscript{39} A significantly higher incidence of severe gastroduodenal damage was found in patients treated with one-week of anti-helicobacter therapy as compared with maintenance pantoprazole therapy (29\% vs. 9\%, p<0.05). In a larger scale study, Hawkey et al. found that curing \textit{H. pylori} infection did not reduce the rate of ulcer relapse in long-term NSAID users.\textsuperscript{40}

**\textit{(c) Summary}**

So what actually makes the difference? Different patient groups in different studies may explain these conflicting results. It seems that eradication of \textit{H. pylori} in patients who have not been exposed to NSAIDs may be protective for ulcer development while eradication therapy in long-term NSAIDs users may not be beneficial. Mucosal defence may be more important in determining relapse of ulcer after ulcer has developed.
As noted above, despite testing and treating *H. pylori* is likely to reduce the development of peptic ulcers in patients who is going to start NSAIDs, a proportion of patients (12%) still develops peptic ulcers even after *H. pylori* has been eradicated. Together with the fact many peptic ulcers still developed in NSAID-using patients without *H. pylori* infection, alternative preventive measures may still be considered in high-risk patients.

**Conclusion**

The morbidity and costs associated with GI complications of NSAIDs are significant. However, the costs of providing prophylactic co-therapy to all patients to prevent NSAIDs-induced ulcer complications are equally high and prohibitive. For all patients, the lowest possible dose of NSAIDs that will accomplish the goal should be prescribed and for the shortest time. Patients identified to have risk factors for a GI complication, for example older age, past history of ulcers, concomitant administration of anticoagulants or corticosteroids, can be offered co-therapy with proton pump inhibitors and misoprostol, or the alternate use of highly selective COX-2 inhibitors to prevent development of ulcer complications. *H. pylori* testing and eradication can be considered in NSAID-naive patients who are about to be started NSAIDs. Whether concomitant anti-ulcer therapy is required after *H. pylori* eradication needs further studies.

Table 1 summarized the key points in the prevention of NSAID-related gastropathy.

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<th>Table 1. Key points on the prevention strategies of NSAID-gastropathy</th>
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<td>• Avoid simultaneous use of multiple NSAIDs</td>
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<td>• Use the lowest possible dose of NSAIDs</td>
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<td>• Identify high-risk patients so that prophylactic measures can be instituted</td>
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**Concomitant therapy**

- High dose misoprostol (200 ug qid) is effective in reducing NSAID-related ulcers and ulcer complications but is associated with significant gastrointestinal side effects, predominantly diarrhea and abdominal pain, in more than 10% of the patients
- It is controversial whether high dose H₂-antagonist is as effective as misoprostol in preventing NSAID-related ulcer complications
- PPI co-therapy is at least as effective as misoprostol in prophylaxis against NSAID-related ulcer complications, but with much less side effects

**Selective COX-2 inhibitors**

- Selective COX-2 inhibitors showed a much improved GI safety profile both in terms of endoscopic ulcers and ulcer complications as compared with conventional non-selective NSAIDs
- The improved GI safety of celecoxib may be abolished in patients who take aspirin concomitantly
- Use of rofecoxib has been associated with a higher incidence of cardiovascular events, but mostly restricted to patients who use rofecoxib at doses greater than 25 mg daily

**Eradication of *H. pylori***

- Testing and eradication of *H. pylori* may be useful in patients who are about to start NSAIDs, but this will not reduce ulcer complications in patients who have developed ulcers already
- *H. pylori* eradication is not the universal prophylactic treatment since NSAID-related ulcers develop even in the absence of *H. pylori* infection
- In high-risk patients, either give concomitant therapy with misoprostol or PPI or consider changing to selective COX-2 inhibitors, whether or not *H. pylori* infection is present

**References**


