Management of nonsteroidal anti-inflammatory drug-induced gastroduodenal disease by acid suppression

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R Lad, D Armstrong. Management of nonsteroidal anti-inflammatory drug-induced gastroduodenal disease by acid suppression. Can J Gastroenterol 1999;13(2):135-142. One major cause of peptic ulceration is the use of nonsteroidal anti-inflammatory drugs (NSAIDs). The precise mechanisms through which NSAIDs cause peptic ulceration are unknown, but the discovery that they reduce the production of 'cytoprotective' prostaglandins led to the hypothesis that coadministration of exogenous prostaglandins heals and prevents NSAID-induced gastroduodenal ulcers and other mucosal lesions. Studies using high doses of misoprostol have shown that it does have a protective effect; however, gastrointestinal intolerance of this prostaglandin E2 analogue is common. Early indications that acid suppression was effective in the management of NSAID-related peptic ulcers came from studies showing that gastric ulcers could be healed by omeprazole in patients who continued to take NSAIDs. Other studies suggested that acid suppression reduces the incidence of mucosal lesions but that standard dose ranitidine protects only against duodenal lesions. Subsequent studies reported that higher dose H2 receptor antagonist therapy can protect against both gastric and duodenal ulcers during continued NSAID therapy. An ideal therapeutic strategy would protect NSAID-related ulcers and prevent the development of new NSAID-related lesions and complications in patients who are unable to discontinue NSAID therapy. A number of recent studies indicate that effective acid-suppressive treatment with the proton pump inhibitor omeprazole can achieve these aims. Overall, data from recent studies show that acid suppression with the proton pump inhibitor omeprazole at a dose of 20 mg daily is the most effective means of healing NSAID-associated gastroduodenal lesions and that it is the most effective prophylactic therapy. In the long run, the role of omeprazole will have to be evaluated with respect to its cost effectiveness compared with other strategies and with respect to the development of less damaging NSAIDs.

Key Words: Famotidine, Misoprostol, Nonsteroidal anti-inflammatory drugs, Omeprazole, Peptic ulcer, Ranitidine

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Le traitement de la maladie gastro-duodénale liée aux AINS par la suppression acide

RÉSUMÉ : L’une des principales causes de l’ulcère gastro-duodénal est l’emploi d’anti-inflammatoires non stéroïdiens (AINS). Les mécanismes précis par lesquels les AINS provoquent l’ulcère gastro-duodénal nous échappent toujours, mais la découverte du fait qu’ils réduisent la production des prostaglandines cytoprotectrices a conduit à l’hypothèse selon laquelle l’administration concomitante de prostaglandines exogènes permet de guérir et de prévenir les ulcères gastro-duodénaux provoqués par les AINS et d’autres lésions des muqueuses. Des études sur les effets de doses fortes de misoprostol ont démontré qu’il exerce un effet protecteur. Par contre, l’intolérance gastro-intestinale à l’endroit de cet analogue des prostaglandines E2 est fréquente. Les premiers signes de l’efficacité de la suppression acide en traitement des ulcères gastro-duodénaux ont été fournis par des études dans le cadre desquelles les ulcères gastro-duodénaux ont pu être guéris par l’oméprazole chez des patients qui continuaient de prendre des AINS. Selon d’autres études, la suppression acide réduit la fréquence des lésions muqueuses, mais la dose standard de ranitidine ne protège que contre les lésions duodénales. D’autres études ont montré que la suppression acide était une protection contre les ulcères gastro-duodénaux provoqués par les AINS et prévenait l’installation des nouvelles lésions et complications dues aux AINS chez les patients qui ne peuvent pas se passer d’anti-inflammatoires. Un certain nombre d’études récentes indiquent qu’un traitement de suppression acide efficace au moyen de l’inhibiteur de la pompe à protons oméprazole peut donner de tels résultats. De façon globale, les données tirées d’études récentes révèlent que la suppression acide au moyen de l’inhibiteur de la pompe à protons oméprazole à dose de 20 mg par jour est la plus efficace de faire cesser les lésions gastro-duodénales associées aux AINS et qu’il s’agit du traitement prophylactique le plus efficace. A longue échéance, le rôle de l’oméprazole devra être vérifié en ce qui a trait à sa rentabilité comparativement à d’autres stratégies et en ce qui a trait à la mise au point d’AINS moins dommageables.
Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most widely used medications, and some are now available over-the-counter. They are indicated for a variety of ailments, and their anti-inflammatory actions make them the cornerstone for management of chronic rheumatic and degenerative musculoskeletal disorders. However, these agents are associated with gastrointestinal toxicity ranging from mild dyspepsia to significant gastrointestinal bleeding or perforation, and death. Mechanisms of NSAID-induced gastrointestinal injury include direct toxicity to the mucosa and indirect inhibition of prostaglandin production via cyclo-oxygenase-1 inhibition. It is estimated that 24% of serious gastrointestinal events related to peptic ulcer disease in the general population can be attributed to the use of NSAIDs (1).

The exact degree to which NSAIDs cause gastrointestinal complications varies. A number of meta-analyses and cohort studies on this subject found that NSAID users are at approximately two to four times greater relative risk than nonusers for development of bleeding or perforation, hospitalization, or death from NSAID-induced gastrointestinal events (2-4). The risk increases for the elderly, those on corticosteroids, those with a prior history of peptic ulcer disease, and those taking multiple or high dose NSAIDs. The risk of complications appears to be highest in the first month of use but continues at a constant rate thereafter. Individual agents such as azapropazone, tolmetin, piroxicam and ketoprofen carry the highest risks, with lower risks attributable to ibuprofen and diclofenac (5). Interpretation of these data is complicated by the fact that many patients who develop gastrointestinal complications, especially the elderly, are asymptomatic before the event. In addition, there is poor correlation among endoscopic damage, upper gastrointestinal symptoms and the occurrence of major bleeding.

A number of agents have been studied for both the treatment and prevention of NSAID-induced gastroduodenal ulceration. These include the prostaglandin analogue misoprostol, histamine H2 receptor antagonists (H2 RAs) and proton pump inhibitors such as omeprazole. One of the most effective management strategies is to discontinue the NSAID in question; however, many patients require NSAIDs for ongoing control of pain and inflammation in place of or as an adjunct to more toxic or slower acting disease-modifying agents. The purpose of this review is to examine the literature to assess the role of acid-suppressing drugs in the treatment and prevention of NSAID-induced gastroduodenal ulceration.

H2 RAs
The role of H2 RAs in the healing and prevention of NSAID-induced ulcers has been extensively studied. For patients who do develop ulceration secondary to NSAIDs, discontinuation of these agents can be problematic because alternative therapies may provide inferior control of pain and inflammation. In these cases, it may be preferable to continue NSAID therapy while using acid suppression to heal the ulcer. Lancaster-Smith et al (6) examined the efficacy of ranitidine in the healing of NSAID-induced gastric and duodenal ulcers and erosions, and compared healing rates in those who continued NSAID treatment with rates in those who did not. In this study, 211 patients with NSAID-induced gastroduodenal ulceration were randomized to continue or discontinue NSAID treatment while starting ranitidine 150 mg twice daily. The healing rates of gastric ulcers, confirmed endoscopically, in those who stopped using NSAIDs were 71%, 95% and 100% at four, eight and 12 weeks, respectively, compared with 54%, 63% and 79% in those who continued NSAIDs. These differences were statistically significant at eight and 12 weeks. In those with duodenal ulcers, similar results were found, with healing rates for the group stopping NSAIDS of 74%, 100% and 100% at four, eight and 12 weeks, respectively, compared with 57%, 84% and 92% for the group continuing NSAIDs. These results were statistically significant at eight weeks due only to the high healing rates with ranitidine. Healing rates were faster for those with duodenal ulcers than for those with gastric ulcers on continued anti-inflammatory therapy. The high healing rates for those who discontinued NSAID therapy were comparable with healing rates for non-NSAID-associated peptic ulcers treated with H2 RAs, suggesting that NSAID-induced ulcers are just as responsive to H2 RAs after the NSAID has been withdrawn. Unfortunately, no placebo group of subjects, without ranitidine therapy, was included to examine the ulcer healing rates in those who simply discontinued use of NSAIDs. This study suggests that NSAID-induced gastroduodenal ulceration can be treated effectively with ranitidine 150 mg twice daily, even if NSAID use is continued. Although healing is slowed by continuation of the anti-inflammatory agent, substantial rates of healing can be achieved. Walan et al (7) reported comparable healing rates in those with NSAID-induced ulcers in a study of gastric ulcer patients who were randomized to high (40 mg daily) or low dose (20 mg daily) omeprazole, or ranitidine 150 mg twice daily while continuing NSAIDs. Gastric ulcer healing with ranitidine was 53% after eight weeks of therapy with continued NSAID use.

The use of famotidine, another H2 RA, was assessed by Hudson et al (8) in 1997. After long term NSAID therapy, rheumatic patients with NSAID-induced gastroduodenal ulcers were treated with open label famotidine 40 mg twice daily for 12 weeks; 88 patients continued NSAIDs, while 16 discontinued them. At four weeks, the cumulative intention to treat healing rate was 65.9% for those continuing NSAIDs compared with 81.3% for those discontinuing them. At 12 weeks, healing rates rose to 89% in those who remained on NSAIDs compared with 100% in those who discontinued them. Again, healing rates for duodenal ulcers were somewhat higher than those for gastric ulcers.

A number of trials have evaluated the use of prophylactic H2 RAs in the prevention of gastroduodenal injury. In healthy volunteers taking short term, high dose acetylsalicylic acid (ASA), famotidine 20 mg significantly decreased the rate of gastric microbleeding and antral hemorrhagic lesions (9). For patients receiving NSAIDs, cimetidine was
one of the first H$_2$RAs to be studied; however, no significant protective effect was found for the prevention of gastroduodenal ulceration in rheumatology patients (10,11).

A large European multicentre, double-blinded, placebo controlled trial was conducted in a cohort of 297 rheumatoid and osteoarthritis patients who continued NSAIDs while using ranitidine 150 mg twice daily for ulcer prophylaxis (12). Although no protective effect for gastric ulcers was found, there was a significant decrease in the number of duodenal ulcers at eight weeks in the ranitidine group compared with the placebo group (1.5% versus 8%). Robinson et al (13) showed a similar protective effect on duodenal ulcers but no effect on gastric ulcers in an American population.

Famotidine prophylaxis has also been assessed over a longer period of time in chronic NSAID users. Rheumatic patients who had taken NSAIDs for over one month were randomized to high dose famotidine (40 mg twice daily), low dose famotidine (20 mg twice daily) or placebo while NSAIDs were continued (14). They were reassessed endoscopically and with respect to symptoms after four, 12 and 24 weeks of therapy. After six months, there was a significant decrease in gastroduodenal ulceration in those treated with high and low dose famotidine compared with those who received placebo (10.8% and 16.8% versus 28.7%) (Figure 1). Compared with placebo, the higher dose of famotidine was associated with a lower incidence of both gastric and duodenal ulcers, whereas the lower dose was associated with a lower incidence of duodenal ulcers only. The prevalence of abdominal pain decreased from 30% at baseline to 19% after 24 weeks of famotidine but was unchanged in the placebo group. The famotidine was well tolerated; the main side effect was a small, but statistically significant decrease in platelet count.

In conjunction with the previously described trial of famotidine for ulcer healing, Hudson et al (8) investigated famotidine maintenance therapy over a period of six months in 78 patients who continued to use NSAIDs. In this double-blind study, the patients were randomized to receive famotidine 40 mg twice daily or placebo after their initial ulcers healed. There was a significant decrease in gastroduodenal ulceration at six months in those receiving famotidine compared with those receiving placebo (26% versus 53.5%), but the rate of ulcer occurrence was higher in patients who had prior confirmed ulceration than in patients who had not had prior ulceration (14) (Figure 1). When analyzed separately, the reduction in both gastric and duodenal ulceration was similar with high dose famotidine prophylaxis.

These studies demonstrate a protective effect of H$_2$RAs primarily in the duodenum, supporting the theory that pathogenic and defence mechanisms in the duodenum may be different from those present in the stomach. H$_2$RAs are useful in healing gastroduodenal ulcers for patients who discontinue NSAID therapy and for those who do not. Patients who continue NSAID therapy have slower rates of healing, but these rates are still relatively high. Low doses of H$_2$RAs are effective in the prevention of duodenal ulcer, but higher doses are necessary for gastric ulcer prevention. It is possible that greater acid suppression is needed in the stomach than in the duodenum to minimize NSAID-mediated mucosal injury.

Some reports have suggested that the efficacy of H$_2$RAs decreases after prolonged periods of treatment. For example, when gastric acidity was assessed at initiation, after eight days and after one month of H$_2$RA therapy, the degree of reduction in gastric acidity was found to decrease over time, suggesting that a significant degree of tolerance results from continued H$_2$RA therapy (15,16). Thus, the prophylactic efficacy of H$_2$RA therapy may be lower in the long term than would otherwise be expected from the results of standard, six-month follow-up studies.

**PROTON PUMP INHIBITORS**

Based on the above data showing that H$_2$RAs have a dose-dependent effect in healing or preventing NSAID-related peptic ulcers, it seems plausible that increased acid suppression will result in faster and more effective healing of NSAID-induced ulcers. Natural candidate drugs for these effects are proton pump inhibitors, which block the final common pathway in acid secretion.

As was noted above, the early randomized, double-blinded trial by Walan et al (7) showed significantly increased healing rates for all gastric ulcers with continued use of NSAIDs with omeprazole therapy compared with rates with ranitidine at both four and eight weeks. Healing at eight weeks was 82% for omeprazole 20 mg, 95% for omeprazole 40 mg and 53% for ranitidine 150 mg twice daily. Similar healing rates of 82% and 96% at four and eight weeks, respectively, have been demonstrated for both gastric and duodenal ulcers in those continuing NSAIDs with omeprazole 20 mg daily, with a substantial benefit over sucralfate therapy (17).

More recently, the effect of omeprazole on ulcer healing has been compared with the effect of misoprostol. The Omeprazole versus Misoprostol for NSAID-induced Ulcer Man-
agement (OMNIUM) Study Group randomized 921 chronic NSAID users with gastroduodenal ulceration or 10 or more erosions to omeprazole 20 mg daily, omeprazole 40 mg daily or misoprostol 200 µg four times daily while at least a minimum dose of their NSAIDs was continued (18). At eight weeks, the healing rates for gastric ulcers were significantly higher in those treated with omeprazole 20 mg (87%) than in those given misoprostol (73%). The healing rate with omeprazole 40 mg was 80% but was not significantly different from that with misoprostol. The healing rates for duodenal ulcers were also significantly higher with omeprazole 20 mg (93%) and omeprazole 40 mg (89%) than with misoprostol (81%). Erosions were significantly decreased in those treated with omeprazole compared with those receiving ranitidine (Figure 2). There was no significant difference between the two doses of omeprazole for the healing of gastric or duodenal ulcers or erosions. Overall, when the results of the OMNIUM and ASTRONAUT studies are pooled, the data indicate that misoprostol produced higher healing rates for gastric ulcers than did ranitidine although the two agents produced comparable healing rates for duodenal ulcers (Figure 3); however, omeprazole 20 mg daily produced higher healing rates than either ranitidine or misoprostol for both gastric and duodenal ulcers. Dyspeptic symptoms were also better controlled by omeprazole 20 mg daily than by either misoprostol or ranitidine (Table 1).

The incidence of moderate or severe adverse events during the healing phases of the OMNIUM and ASTRONAUT studies was greater for patients receiving misoprostol than for patients receiving ranitidine or omeprazole (Figure 4); differences were noted primarily for the occurrence of abdominal pain, diarrhea and flatulence, consistent with the gastrointestinal side effects of prostaglandin analogues reported previously in the literature (20,21).

The protective effects of omeprazole on gastric microbleeding and endoscopic damage scores have been demonstrated in a number of studies of healthy controls taking short term ASA (22,23). However, the prevention of mucosal injury in healthy volunteers does not provide incontrovertible evidence that the same treatment would prevent peptic ulceration or other sequelae in patients receiving NSAID therapy. The first large, randomized, double-blinded,
controlled trial to evaluate omeprazole prophylaxis in patients on long term NSAID therapy was the Nordic multicentre study (SCUR), published in 1996 (24). In this study, 177 patients with rheumatic disease requiring chronic NSAID therapy for at least three months were randomized to omeprazole 20 mg daily or placebo for three months while at least a minimum dose of NSAID therapy was continued. Endoscopy and clinical assessment were performed after one and three months. Gastroduodenal ulceration occurred in 4.7% of omeprazole-treated patients compared with 16.7% of placebo-treated patients; 15.3% of those treated with omeprazole developed dyspeptic symptoms requiring active treatment compared with 35.6% of those on placebo.

It is interesting that there was no significant difference between the two treatment groups regarding the number of patients with more than 10 erosions in the stomach or duodenum but without ulcer. This brings into question the use of erosions as a surrogate marker for gastroduodenal damage. The high frequency of erosions in other studies may reflect damage done early in the course of NSAID treatment, whereas mucosal adaptation occurs with longer term exposure. When the data were assessed for all indices of recurrence including gastroduodenal ulcers, more than 10 erosions or worse than mild dyspeptic symptoms, there was a statistically significant difference, with recurrences occurring in 24.7% of the omeprazole group compared with 50% of the placebo group (Figure 5). However, the overall number of recurrent ulcers in this study was small, and this may explain the lack of statistical significance.

The Omeprazole versus Placebo as Prophylaxis against Ulcers or Erosions from NSAID Treatment (OPPULENT) study was conducted in 19 centres throughout Europe and the United states for long term NSAID users who had dyspeptic symptoms that were no worse than mild (25). Subjects who had no ulcers and no more than 10 gastric or duodenal erosions were randomized to omeprazole 20 mg daily or placebo for six months with a follow-up endoscopy at one, three and six months or if symptoms recurred. End-points consistent with treatment failure were gastric or duodenal ulcers (more than 3 mm in diameter), more than 10 erosions in the stomach or duodenum, and dyspeptic symptoms sufficiently severe to require active treatment. The proportions of patients remaining in remission at six months were 64.7% for placebo and 81.9% for omeprazole. There was a significant increase in ulcers in the placebo arm (16.5%) compared with the omeprazole treatment arm (3.6%). The number of instances of multiple erosions and severe dyspeptic symptoms requiring treatment was similar. A number of variables were associated with a lower probability of treatment failure.

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*P=0.04 versus ranitidine; †P=0.004 versus misoprostol. Data adapted from references 18 and 19.
omeprazole therapy, having rheumatoid arthritis compared with osteoarthritis, and younger age. This study confirms that low dose omeprazole therapy is effective prophylaxis against NSAID-induced ulcers (Figure 5) although there were insufficient patients to determine whether omeprazole therapy would lead to a decrease in the number of clinically significant events.

The OMNIUM study group comparing omeprazole with misoprostol for ulcer healing was followed by a maintenance phase in which those with successful ulcer healing were randomized to omeprazole 20 mg daily or ranitidine 150 mg bid (Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-associated Ulcer Treatment study [ASTRONAUT] top) and omeprazole 20 mg daily, misoprostol 200 µg bid or placebo (Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management study [OMNIUM] bottom). The legends indicate the number of patients in each treatment group and the number who developed gastric or duodenal ulcers. Data adapted from references 18 and 19.

Figure 7) Pooled data from the Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-associated Ulcer Treatment (ASTRONAUT), Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management (OMNIUM), Omeprazole versus Placebo as Prophylaxis against Ulcers or Erosions from NSAID Treatment (OPPULENT), and Nordic multicentre (SCUR) studies showing the overall rates of gastric or duodenal ulcer development during prophylactic therapy with omeprazole 20 mg daily, misoprostol 200 µg bid, ranitidine 150 mg bid or placebo. The legends indicate the number of patients in each treatment group. Data adapted from references 18,19,24 and 25.

Figure 6) Estimated proportions of subjects in remission (fewer than 10 erosions, absent gastric [GU] or duodenal ulcer [DU], mild or absent dyspeptic symptoms, or absence of adverse events) on nonsteroidal anti-inflammatory drug (NSAID) therapy and on maintenance therapy with omeprazole 20 mg daily or ranitidine 150 mg bid (Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-associated Ulcer Treatment study [ASTRONAUT] top) and omeprazole 20 mg daily, misoprostol 200 µg bid or placebo (Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management study [OMNIUM] bottom). The legends indicate the number of patients in each treatment group and the number who developed gastric or duodenal ulcers. Data adapted from references 18 and 19.

omeprazole therapy, having rheumatoid arthritis compared with osteoarthritis, and younger age. This study confirms that low dose omeprazole therapy is effective prophylaxis against NSAID-induced ulcers (Figure 5) although there were insufficient patients to determine whether omeprazole therapy would lead to a decrease in the number of clinically significant events.

The OMNIUM study group comparing omeprazole with misoprostol for ulcer healing was followed by a maintenance phase in which those with successful ulcer healing were randomized to omeprazole 20 mg daily, misoprostol 200 µg twice daily or placebo for six months (14). The primary end-points were the development of an ulcer, 10 or more gastric or duodenal erosions, moderate symptoms of dyspepsia or adverse events requiring discontinuation of treatment. At six months, the proportion of patients in remission was 61% of those on omeprazole, 48% of those on misoprostol and 27% of those on placebo (Figure 6). The incidences of gastric ulcers were 13%, 10% and 32% for those on omeprazole, misoprostol and placebo, respectively. The respective rates for duodenal ulcers were 3%, 10% and 12% at six months. Prognostic factors that were associated with a higher probability of remission were treatment with omeprazole rather than misoprostol, the presence of erosions alone at baseline, non-smoking status and a positive test for Helicobacter pylori.

Although misoprostol and omeprazole had similar prophylactic effects in preventing gastric ulceration, misoprostol was associated with a slightly higher incidence of adverse effects—primarily diarrhea—than omeprazole (59% versus 48%). Misoprostol was also associated with a higher incidence of medication discontinuation because of these adverse effects.

The ASTRONAUT study, comparing omeprazole with ranitidine for the healing of ulcers, also proceeded to a maintenance phase in which the 425 patients with healed ulcers who continued their NSAIDs were randomized to omeprazole 20 mg daily, misoprostol 200 µg bid or placebo (Omeprazole versus Placebo as Prophylaxis against Ulcers or Erosions from NSAID Treatment [OPPULENT]). At six months, 72% of the patients receiving omeprazole 20 mg daily were in remission compared with 59% of the patients receiving ranitidine 150 mg bid (Figure 6). The cumulative incidence of gastric ulcers was 5.2% in the omeprazole group compared with 16.3% in the ranitidine group; the corresponding rates for duodenal ulcers were 0.5% and 4.2%.

When data from the four maintenance trials with omeprazole are pooled, the overall rate of ulcer occurrence at three (22) to six (18,19,25) months ranges from 9.1% for patients receiving omeprazole 20 mg daily to 28.8% for patients who did not receive any prophylactic therapy, and misoprostol 200 µg bid and ranitidine 150 mg bid are associated with comparable ulcer rates of about 20% (Figure 7).

Clearly, omeprazole therapy has a significant effect on NSAID-induced ulcer healing and prevention. In both high and low doses, it is superior to ranitidine in ulcer healing, with quicker healing. Low doses are superior to misoprostol and sucralfate (17). Omeprazole also substantially decreases...
the incidence of new gastric and duodenal ulceration in those who continue to take NSAIDs in the long term. It is, therefore, the agent of choice in high risk patients who must continue NSAID therapy, but its use is limited by cost.

CONCLUSIONS

There is a large body of evidence pertinent to the role of acid suppression therapy in the treatment and prevention of NSAID-induced gastroduodenal ulceration. Ideally, therapy should be based on discontinuation of the offending NSAID; however, this is often not possible. Although most studies are controlled, randomized trials, they are limited by variability in a number of factors such as NSAID dose, duration and type of agent. Control for these variables is difficult and may be considered unethical. Another limitation is the use of different definitions of an ulcer based on size and the use of erosions as a surrogate marker. The lack of data on clinically significant end-points such as significant gastrointestinal bleeding or perforation, or death means that whether the prevention of gastroduodenal lesions and symptoms reduces the incidence of severe NSAID-related complications cannot be asserted unequivocally. Pooled data from the four maintenance trials indicate that significant complications were noted in one of 654 patients who received omeprazole 20 mg daily and two of the 331 patients who received placebo (18,19,24,25), and, despite the relatively large numbers of patients enrolled in these four trials, this difference was not statistically significant. However, in the absence of very large multicentre trials with longer follow-up periods of one to two years or more, it is reasonable to assume that a reduced incidence of NSAID-related peptic ulcers would lead to a reduced complication rate.

Overall, the data suggest that there is an important role for acid suppression in the treatment and prevention of NSAID-induced ulceration. H2RAs heal NSAID-related ulcers, even when NSAID use is continued; ranitidine and famotidine are comparable in efficacy, but healing, particularly of gastric ulcers, may take eight to 12 weeks. Famotidine is more effective at higher doses, suggesting that acid suppression is important in the healing of NSAID-related lesions; this is borne out by the finding that omeprazole heals NSAID-induced gastroduodenal ulcers more quickly than H2RAs. Both omeprazole and H2RAs are useful in the prevention of ulcers in those who continue NSAID therapy; ranitidine appears to be beneficial in the prevention of duodenal ulcers, but its role in prevention of gastric ulcers is less well established. However, famotidine, at higher doses, is useful for the prevention of both gastric and duodenal ulcers, suggesting that acid suppression is important also for the prevention of NSAID-related gastroduodenal lesions. This is supported by the finding that omeprazole is superior to H2RAs for the prevention of NSAID-induced gastroduodenal ulcers. In this regard, the treatment of NSAID-related ulcers appears to be similar to that of all peptic ulcers; meta-analyses have shown that healing rates for both duodenal (26) and gastric (27) ulcers are proportional to the degree of acid suppression produced by the healing agent, and, for presumed NSAID-unrelated ulcers, this held true for enprostil, the only prostaglandin analogue for which acid suppression data were available. The only discrepant data regarding the importance of acid suppression for the treatment of NSAID-related ulcers, therefore, is misoprostol appears to have healing and prophylactic effects in excess of those that would have been expected solely on the basis of its ability to inhibit gastric acid secretion.

There are, clearly, a number of unresolved issues that must be addressed with respect to the routine use of acid-suppressing drugs for people taking NSAIDs. Data available are derived from studies in which patients have taken standard NSAIDs and ASA; however, with the imminent availability of more specific cyclo-oxygenase-2 inhibitors (28,29) and the development of nitric oxide-releasing NSAIDs, which produce local release of vasoactive nitric oxide (30,31), it is possible that newer NSAIDs will be associated with a much lower incidence of gastroduodenal mucosal damage and subsequent complications. However, these newer NSAIDs are likely to be more expensive than current NSAIDs, and, although proton pump inhibitors are relatively costly, the cost effectiveness of omeprazole therapy in Canada compared with other management strategies has yet to be evaluated.

The role of H pylori eradication in the management of NSAID-related ulcers remains exceedingly controversial (32). H pylori does not appear to confer any additional risk of ulceration in patients taking NSAIDs, but, because H pylori and NSAIDs appear to cause peptic ulceration by independent mechanisms, it seems reasonable to avoid the risk posed by H pylori by curing the infection in patients who must continue NSAID therapy (33,34). However, data from the ASTRONAUT and OMNIUM studies suggest that patients who are H pylori-infected are less likely to relapse. Surprising as this observation may seem, it is consistent with reports that eradication of H pylori may decrease the effect of omeprazole in suppressing gastric acidity. The recent studies (17-19,24,25,35-37) show clearly that acid suppression is effective for the management of NSAID-related gastroduodenal disease; thus, any intervention – such as cure of H pylori – that reduces the efficacy of acid-suppressing medication may be expected to produce a corresponding reduction in the prophylactic efficacy of acid suppression.

REFERENCES


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