Therapeutic options in the treatment and prevention of nonsteroidal anti-inflammatory drug-induced ulceration

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ABSTRACT: This article reviews the current status of H₂ receptor antagonists, omeprazole, sucralfate and misoprostol as therapeutic options for the prophylaxis and treatment of nonsteroidal anti-inflammatory drug (NSAID)-induced gastrointestinal ulceration. The efficacy of the H₂ receptor antagonists appears to be restricted to prophylaxis and treatment of NSAID-induced duodenal ulcer disease. Omeprazole may have a place in the future treatment of NSAID-induced gastric ulcers. However, more studies are necessary to examine this drug's efficacy in both the prophylaxis and treatment of NSAID-induced ulceration. Sucralfate improves symptoms, but does not appear to have any effect on improving gastric mucosal damage when compared to placebo. It may, however, be useful in the treatment of NSAID-induced duodenal ulcers. Misoprostol is effective in both the prophylaxis and treatment of NSAID-induced gastric ulcers; however, its exact role in the prophylaxis and treatment of NSAID-induced duodenal ulcers remains to be defined. *Can J Gastroenterol* 1990;4(3):113-119

Key Words: H₂ receptor antagonists, Misoprostol, NSAIDs, Omeprazole, Sucralfate, Ulcer

Options thérapeutiques dans le traitement et la prévention de l'ulcération provoquée par les anti-inflammatoires non stéroïdiens

RESUME: Cet article examine le statut présent des antagonistes du récepteur H₂, l'oméprazole, le sucralfate et le misoprostol, comme choix thérapeutiques indiqués dans la prévention et le traitement de l'ulcération gastro-intestinale provoquée par les anti-inflammatoires non stéroïdiens. L'efficacité des anti-H₂ semble se limiter à la prophylaxie et au traitement de l'ulcère gastro-duodénal provoqué par les AINS. L'oméprazole a peut-être sa place dans le traitement à

THIS REVIEW ARTICLE DISCUSSES therapeutic options in the prophylaxis and treatment of NSAID-induced damage and ulceration to the gastrointestinal mucosa. The following drugs are reviewed: H₂ receptor antagonists, omeprazole, sucralfate and misoprostol. The studies cited in this paper are controlled comparative studies published as full manuscripts. Open uncontrolled studies and studies reported only in abstract form will not be reviewed.

Nonsteroidal anti-inflammatory drug (NSAID)-induced ulceration occurs more commonly in the antrum and the prepyloric area of the stomach. It also occurs more commonly in women and elderly patients (1-3). McCarthy (4) estimated crude prevalence of gastric ulcers as 13% for NSAID users with arthritis compared with 0.28% in the normal population. This yielded an increased relative risk of 46 for developing gastric ulcer in patients taking NSAIDs. In addition, the crude prevalence of duodenal ulcer was estimated as 11% in NSAID users compared with 1.2% in the normal population. The relative risk of

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venir des ulcères gastriques provoqués par les AINS. Néanmoins, il est nécessaire d'effectuer d'autres études pour déterminer l'efficacité de cette substance, à la fois dans la prophylaxie et le traitement de cette affection. Le sucralfate soulage les symptômes mais ne semble entraîner aucune amélioration des lésions de la muqueuse gastrique comparé au placebo. Il peut toutefois s'avérer utile dans le traitement des ulcères duodénaux provoqués par les AINS. Le misoprostol est cependant efficace à la fois dans la prophylaxie et le traitement des ulcères gastriques provoqués par les AINS; son rôle exact dans la prophylaxie et le traitement des ulcères gastro-duodénal reste à définir.

duodenal ulceration in patients taking NSAIDs was determined as eight times that of the normal population. Thus, if NSAID use is a causal factor, the user is six times more likely to develop a gastric versus duodenal ulcer as a consequence of NSAID therapy.

The etiology of the ulcer must be considered when determining the appropriate therapy for both prophylaxis and treatment of NSAID-induced ulceration. The NSAID-induced ulcer has an etiology and pathophysiology which is different from that of the acid-mediated ulcer. In a recent review, Roth and Bennett (5) summarized this difference as an NSAID-induced ulcer being mediated by prostaglandin deficiency secondary to the cyclooxygenase inhibition of the NSAID. This deficiency results in decreased mucosal defences of the gastric and duodenal mucosa. Prostaglandins have been shown to be important in the production of bicarbonate and mucus and in maintaining mucosal bloodflow, which are significant components of gastrointestinal mucosal defence mechanisms. An acid-mediated ulcer is due to a combination of excess acid, particularly in the duodenum, and decreased resistance of mucosal defences, particularly in the stomach.

Drugs which are known to act on the stomach should also be taken into consideration when choosing therapy, since NSAIDs inflict the majority of their damage in the stomach.

H₂ RECEPTOR ANTAGONISTS

The following H₂ receptor antagonists will be discussed: cimetidine, in relation to both prevention and treatment; and ranitidine, in relation to prevention only.

Treatment: A study conducted by

Loludice and colleagues (6) demonstrated in 70 patients that cimetidine healed NSAID-induced ulcers compared to placebo. However, NSAID therapy was discontinued prior to patients being randomized to either cimetidine or placebo.

O'Laughlin and colleagues (7) compared cimetidine 300 mg qid to placebo in 18 patients with NSAID-induced gastric ulcers. In both groups antacids were allowed as needed. NSAID therapy was continued during this study. The number of patients with a healed gastric ulcer after eight weeks was not significantly different in the two groups: cimetidine 56% (five of nine) versus placebo 44% (four of nine). The smaller gastric ulcers (less than 5 mm in diameter) showed significantly better healing than the larger ulcers. In addition, there was no significant difference in the relief of epigastric pain when cimetidine was compared to placebo.

In a study conducted by Davies and colleagues (8), 27 patients with NSAID-induced ulcers were randomized to either cimetidine 400 mg qid or placebo for six weeks. NSAID was continued and there was no significant difference in the healing of ulcers or in antacid or analgesic consumption in either group over the six week period. No significant difference was found in the healing of either gastric ulcers or duodenal ulcers in this study, ie, cimetidine healed two of three duodenal ulcers and seven of 10 gastric ulcers; placebo healed two of three duodenal ulcers, and four of seven gastric ulcers.

In a double-blind, long term evaluation of cimetidine therapy in NSAID gastropathy, Roth and colleagues (9) compared cimetidine to placebo in both short term healing and long term maintenance therapy. One hundred and four patients with NSAID-induced mucosal lesions, ie, gastritis and erosions, but no ulcers, were randomized to either cimetidine 300 mg qid or placebo. Of patients randomized to cimetidine and placebo, 56% (22 of 43) and 52%, respectively, showed progression of endoscopic lesions during the eight week short term phase (Figure 1). Thirty-nine patients whose endoscopic scores improved were then randomized to a 10 month main-

Figure 1) Progression of NSAID-induced gastrointestinal damage with cimetidine. NS Not significant; n Number of patients. (Reproduced with permission from Roth SH, Bennett RE, Mitchell CS, Hartman RJ. *Arch Intern Med* 1987;147:1798-801). ©1987, AMA

Figure 2 a NSAID-induced gastric ulceration. b NSAID-induced duodenal ulceration. Duration of treatment was eight weeks. NS Not significant; n Number of patients. (Adapted with permission from Ehsanullah RSB, Page MC, Tildesley G, Wood JR. *Br Med J* 1988;297:1017-21)

tenance regimen of either cimetidine 400 mg at bedtime or placebo. Fifty per cent (seven of 14) of placebo-treated and 42% (five of 12) of cimetidine-treated patients showed progression of lesions during the maintenance phase. There were no data in terms of symptoms in this study.

Prevention: In a recently published study, Robinson and colleagues (10) examined the efficacy of ranitidine versus placebo in the prophylaxis of NSAID-induced gastrointestinal mucosal damage. After a normal endoscopy, NSAIDs were given and 144 patients randomized to receive either ranitidine 150 mg bid or placebo. No significant difference was found in the degree of gastric mucosal damage when ranitidine was compared to placebo. The degree of maximal mucosal injury in the duodenum, however, was significantly less with ranitidine compared with placebo ($P=0.01$). After four weeks of NSAID therapy, four of 57 patients (70%) on placebo developed duodenal ulcers compared with none of the 62 patients taking ranitidine. In

addition, no statistically significant differences were found between ranitidine and placebo groups with respect to symptoms of peptic distress or incidence of gastrointestinal pain. Furthermore, there was no association between symptoms and degree of mucosal damage documented by endoscopy.

In the second study, by Ehsanullah and colleagues (11), ranitidine 150 mg bid was compared with placebo in patients on NSAIDs for arthritis. After a normal endoscopy, 297 patients were randomized to either the ranitidine or placebo groups. NSAID therapy was continued and endoscopy repeated after eight weeks. No significant difference was found between the two groups with respect to incidence of gastric ulcers, which was 6%. Duodenal ulceration developed in 1.5% (two of 135) of patients taking ranitidine compared to 8% (10 of 126) taking placebo (Figure 2). However, ranitidine was not more effective than placebo in preventing development of grade 2 to grade 4 lesions (multiple erosions with or without an ulcer) in the duodenum:

ranitidine 12% (17 of 137); placebo 13% (17 of 126). Patients with a previous history of ulceration appeared to be more prone to develop ulcers in this study. There was no significant difference in upper gastrointestinal symptoms when ranitidine was compared to placebo.

In a large, double-blind, endoscopically controlled study, Stalnikowicz and colleagues (12) compared cimetidine to placebo in 191 patients with acute musculoskeletal disorders for a period of one week. The effect of two doses of cimetidine, 400 mg at bedtime and 400 mg bid, was compared to placebo in the prevention of indomethacin-induced mucosal damage (50 mg tid). Endoscopy was performed before and after five to seven days of treatment. The mean total damage score of all gastric and duodenal lesions in the placebo-treated patients and in those taking cimetidine 400 mg at bedtime were significantly higher than that of the cimetidine 400 mg bid group ($P=0.0122$). Analysis of the regional total lesion scores demonstrated that damage to antral mucosa was slightly reduced by cimetidine, although not significantly. Significant ($P=0.0004$) protection, however, was afforded to the duodenal mucosa in the cimetidine 400 mg bid group. No significant difference was found in the gastric mucosal lesion scores. Cimetidine did not ameliorate gastrointestinal symptoms induced by indomethacin when compared with placebo during this one week study.

Side effects: The H_2 receptor antagonists have a low incidence of side effects. Cimetidine interferes with the metabolism of drugs which are processed by the cytochrome P450 system in the liver and has been demonstrated to increase significantly the half-life of Valium (diazepam; Roche), Coumadin (warfarin; Du Pont) and phenytoin. Other side effects related to cimetidine are diarrhea and constipation (13). Ranitidine has a very low incidence of side effects, the main complaint being headache (14). It has not been shown to interfere significantly with the cytochrome P450 mechanism in the liver.

Summary: The H₂ receptor antagonists cimetidine and ranitidine have not been shown to improve NSAID-induced gastrointestinal symptoms compared to placebo, nor have they demonstrated any efficacy in the prophylaxis and treatment of NSAID-induced gastric ulcers. Cimetidine and ranitidine have, however, been shown to be effective in the prophylaxis of NSAID-induced duodenal ulcer disease. Efficacy in the treatment of NSAID-induced duodenal ulcer disease requires further examination (15).

OMEPRAZOLE

Omeprazole works by blocking the enzyme H⁺,K⁺-ATPase in the parietal cell and thus inhibiting gastric acid production. This results in a more potent acid suppression than that conferred by the H₂ receptor antagonists. Omeprazole has recently been approved in Canada for the treatment of duodenal ulcers, gastric ulcers, reflux esophagitis and Zollinger-Ellison syndrome.

To date there has only been one study published in which NSAID-induced ulceration, as a subset of a larger study, has been examined (16). In this study of 602 patients, two doses of omeprazole were compared to ranitidine in the healing of benign gastric ulcers. In the 68 patients (11.3%) with NSAID-induced ulcers the NSAID was continued during the study.

Twenty-two patients were randomized to omeprazole 20 mg once a day, 23 to omeprazole 40 mg once a day, and 23 to ranitidine 150 mg bid. At week 8, 95% of ulcers healed with omeprazole 40 mg once a day, 82% with omeprazole 20 mg once a day, and 53% with ranitidine 150 mg bid (Table 1). Omeprazole 40 mg a day was superior to ranitidine in healing gastric ulcers ($P=0.02$). There were no data regarding symptom improvement in the subsection of patients taking NSAIDs.

Side effects: Omeprazole has a low incidence of side effects with the main complaints being nausea, diarrhea and abdominal discomfort (17). There is, however, concern about the long term safety of omeprazole. This is because raised serum gastrin levels have been

found in both animal and human studies. Animal toxicologic studies with omeprazole have reported localized enterochromaffin-like cell proliferation and in some cases carcinoid tumours in the stomachs of rats after two years of treatment with very large doses (18). These changes in serum gastrin and enterochromaffin-like cells are thought to be species-dependent and are not likely to be important clinically in short term use in humans. Considerably more clinical experience with omeprazole is required before it can be contemplated for long term therapy or for prophylaxis against NSAID-induced ulceration.

Summary: Omeprazole 40 mg once a day was shown to be superior to ranitidine 150 mg bid in healing NSAID-induced gastric ulcers in a small number of patients when the NSAID was continued. There are no data on the treatment of NSAID-induced duodenal ulcers or the use of omeprazole in preventing mucosal damage due to NSAIDs. It appears that omeprazole 40 mg once a day may have a role in the treatment of NSAID-induced gastric ulcers. Because of concerns about the long term safety of omeprazole and the fact that no studies regarding prevention have been conducted to date, omeprazole is not recommended in the prophylaxis of NSAID-induced ulceration.

SUCRALFATE

Sucralfate is a sulphated polysaccharide that has demonstrated efficacy in the treatment of both acid-mediated duodenal ulcer disease and gastric ulcer disease (19,20). In the presence of acid, sucralfate forms a chemical complex that binds to the ulcer site to establish a protective barrier, thereby blocking the back diffusion of acid. In addition, sucralfate appears to have a direct inhibitory effect on the action of pepsin and bile on the gastric mucosa. The synthesis and release of prostaglandin E₂ from the mucosa (21) has been shown to increase with sucralfate, possibly due to the aluminum component of sucralfate. (Aluminum-containing antacids have been shown to have a similar action.) Sucralfate has been

TABLE 1

Proportion of patients with healed ulcers among patients receiving concurrent treatment with NSAIDs (per protocol approach)

Drug	4 weeks	8 weeks
Omeprazole 20 mg	11/18 (61)	14/17 (82)
Omeprazole 40 mg	17/21 (81)	21/22 (95)
Ranitidine	6/19 (32)	9/17 (53)

Values are number healed/total (%). (Reproduced with permission from Walan A, Bader J-P, Classen M, et al. *N Engl J Med* 1989;320:69-75)

shown to protect the gastric mucosa in the short term administration of acetylsalicylic acid (ASA) (22). In two studies of longer duration (six days and two weeks), however, sucralfate did not protect the gastric mucosa against ASA (23).

Only two controlled studies have been published on the efficacy of sucralfate in NSAID-induced ulceration; both dealt with efficacy in relation to treatment rather than prevention.

In a study conducted by Manniche and colleagues (15), 67 patients with rheumatic disease and NSAID-induced ulceration were given either ranitidine 150 mg bid or sucralfate 1 g qid for nine weeks. Fifty-one patients had a diagnosis of duodenal ulcer, 14 gastric ulcer, and two had both gastric and duodenal ulcers. The patients in each treatment arm were then further divided into two treatment groups: one NSAID discontinued, and one continued NSAID use. Patients who were not healed by nine weeks were crossed over to the other treatment modality.

The efficacy of these drugs was most apparent in the duodenum, when the NSAID was discontinued. At nine weeks, in patients who stopped their NSAIDs, 92 and 86% of the duodenal and gastric ulcers healed, respectively.

In the group that continued NSAID use, 82% of duodenal but only 20% of gastric ulcers healed. Although this study was well performed, the large number of duodenal ulcers raises the question of whether some of these ulcers were acid-mediated rather than NSAID-mediated. With regard to the efficacy of either ranitidine or sucralfate

Figure 3 Reduction of NSAID-induced gastric mucosal damage with sucralfate. NS Not significant; n Number of patients. (Reproduced with permission from Caldwell JR, Roth SH, Wu WC, et al. *Am J Med* 1987;83 [Suppl 3B]:74-82)

fate on the healing of gastric ulcer, it is difficult to come to a conclusion, due to the small number of subjects who had gastric ulcers.

Caldwell and colleagues (24) evaluated 143 symptomatic patients on long term NSAIDs, of which only 60 had mucosal damage. Patients were randomized to either sucralfate 1 g qid or placebo; the NSAID was continued. In the 60 patients with endoscopic mucosal damage, results were expressed as lesion scores after four weeks of treatment. The lesion scores were unchanged in the placebo group and showed only a small change from baseline in the mean lesion scores (3.5 to 2.46) in those given sucralfate ($P < 0.005$) (Figure 3). When sucralfate was compared to placebo, there was no statistical difference in the mean change of lesion scores.

Sucralfate was effective in decreasing symptoms compared to placebo in patients taking long half-life and non salicylated NSAIDs. Patients taking salicylates and short half-life NSAIDs did not benefit. There was a significant decrease in intensity, but not frequency, of mean symptom scores for all NSAIDs. No correlation was found between mucosal damage and symptom outcome ($P < 0.03$).

In the open-label, six month, follow-up study, sucralfate (1 g bid) was administered (titratable to 1 g qid), as well as antacids for pain. Sucralfate was

evaluated for its effect on symptoms and gastric lesion scores in patients receiving all types of NSAIDs. At the end of the six months there were significant decreases in mean symptom scores for all NSAIDs ($P = 0.001$). Of the original 60 patients with mucosal damage, 36 were monitored and given repeat endoscopies at the end of the study. No significant differences were found in the mean mucosal lesion scores from the end of the double-blind phase to the end of long term therapy. There was no placebo arm in this six month maintenance study.

Side effects: Sucralfate is a nonsystemic drug with a low incidence of side effects. The most common complaint with sucralfate is constipation. It has been shown to decrease the absorption of a variety of drugs including tetracycline, phenytoin, cimetidine and digoxin (25). One study demonstrated raised aluminum levels in patients taking therapeutic doses (ie, 1 g qid) of sucralfate. The significance of raised aluminum levels in relation to Alzheimer's disease remains controversial (26).

Summary: Sucralfate has been shown to be effective compared to placebo in improving symptoms for the milder NSAIDs. It has not, however, shown efficacy in improving NSAID-induced gastric damage compared to placebo. Regardless of whether NSAIDs were continued, sucralfate was found to be as effective as ranitidine in healing

NSAID-induced duodenal ulcers. There are no controlled studies published on the efficacy of sucralfate in the prophylaxis of NSAID-induced mucosal damage or ulceration.

MISOPROSTOL

The prostaglandins have been shown to have antacid, acid antisecretory (27), and mucosal protective effects (28). The mucosal protective effects of the prostaglandins are due to increased mucus and bicarbonate secretion, resulting in an increase in the thickness of the mucus layer. In addition, the prostaglandins appear to maintain or improve gastric mucosal bloodflow, thereby maintaining cell integrity. This action is evident with the E_1 and E_2 prostaglandins.

Misoprostol is a synthetic methyl ester analogue of prostaglandin E_1 , which has been recently approved in Canada for the prophylaxis and treatment of NSAID-induced gastric ulcers. A prostaglandin E_2 analogue, enprostil (Syntex), has undergone clinical trials (29) but has not yet been approved in Canada.

Clinical studies: In clinical studies, misoprostol has been shown to decrease gastrointestinal blood loss significantly in patients with osteoarthritis taking ASA (30). Moreover, misoprostol is the only drug which has been shown to be effective compared to placebo in the prophylaxis and treatment of NSAID-induced gastric ulceration (31). It appears to be effective in the duodenum but this requires further clarification. Misoprostol has also been shown to significantly improve mucosal damage and heal gastric ulcers compared to placebo in patients with rheumatoid arthritis while the NSAID (ASA) was continued (32).

Comparative studies: There has been only one study comparing the mucosal protective effect of misoprostol to cimetidine (33). This double-blind, placebo controlled study demonstrated that misoprostol prevented tolmetin-induced gastric injury in 93.1% of healthy subjects compared to 63% for cimetidine and 26.7% for placebo. Misoprostol was also superior when directly compared to cimetidine (not significant). In the duodenum, both

misoprostol and cimetidine were highly protective compared to placebo.

To study and compare the effects of misoprostol, sucralfate and placebo in the prevention of ASA-induced ulceration, 30 healthy volunteers participated in a double-blind study (23). Volunteers with endoscopically normal mucosa were randomized to receive ASA 650 mg qid with either misoprostol 200 µg qid, sucralfate 1 g qid, or placebo. A therapeutic success was defined as less than 10 hemorrhages or erosions. All patients receiving misoprostol were deemed a success (10 of 10) compared to 20% receiving sucralfate (two of 10) and none of the 10

patients receiving placebo. Overall, misoprostol was found to be significantly superior when compared to placebo and to sucralfate ($P=0.001$).

In an endoscopically controlled study, recently completed by Agrawal and colleagues, misoprostol was found to be superior to sucralfate in preventing the development of gastric ulcers in patients receiving NSAIDs for osteoarthritis over a three month period.

CONCLUSIONS

The efficacy of H₂ receptor antagonists appears to be restricted to the prophylaxis and treatment of NSAID-induced duodenal ulcer disease. Omeprazole may have a place in the future

treatment of NSAID-induced gastric ulcers; however, more studies are necessary to examine this drug's efficacy in both the prophylaxis and treatment of NSAID-induced ulceration. Sucralfate improves symptoms but does not appear to have any effect on improving gastric mucosal damage when compared to placebo. It may, however, be useful in the treatment of NSAID-induced duodenal ulcers. Misoprostol is effective in both the prophylaxis and treatment of NSAID-induced gastric ulcers. Its exact role in the prophylaxis and treatment of NSAID-induced duodenal ulcers remains to be defined.

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