



Is ranitidine therapy sufficient for healing peptic ulcers associated with non-steroidal anti-inflammatory drug use?

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SUMMARY

Long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) increases the risk of serious gastroduodenal events. To minimise these risks, patients often require concomitant acid-suppressive therapy. We conducted a literature review of clinical trials examining use of ranitidine 150 mg twice daily to heal gastroduodenal ulcers (GU) in NSAID recipients. Seven studies were identified. After 8 weeks' treatment with ranitidine, GU healing rates ranged from 50% to 74% and rates of duodenal ulcer (DU) healing ranged from 81% to 84%. Ranitidine was more effective when NSAIDs were discontinued (healing rates reaching 95% and 100%, respectively). The ulcer healing rate with sucralfate was similar to that of ranitidine. However, proton pump inhibitor (PPI) therapy was associated with significantly greater rates of both GU and DU healing than ranitidine;

8-week GU rates were 92% and 88% with esomeprazole 40 mg and 20 mg, respectively (vs. 74% with ranitidine, $p < 0.01$). For omeprazole, 8-week healing rates were 87% with omeprazole 40 mg and 84% with omeprazole 20 mg (vs. 64% for ranitidine, $p < 0.001$), and for lansoprazole the corresponding values were 73–74% and 66–69% for the 30 mg and 15 mg doses, respectively (vs. 50–53% for ranitidine, $p < 0.05$). In the PPI study reporting DU healing the values were 92% for omeprazole 20 mg (vs. 81% for ranitidine, $p < 0.05$) and 88% for omeprazole 40 mg ($p = 0.17$ vs. ranitidine). NSAID-associated GU are more likely to heal when patients receive concomitant treatment with a PPI rather than ranitidine.

Keywords: Non-steroidal anti-inflammatory drugs; gastroduodenal ulcers; proton pump inhibitors; ranitidine

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are primarily prescribed for painful conditions, such as osteoarthritis and rheumatoid arthritis (1), and are among the most widely prescribed medications used today (2). Although the elderly (aged ≥ 65 years of age) receive the bulk of NSAID prescriptions (3), use of NSAIDs is increasing in a wider range of age groups because of the growing use of low-dose aspirin for the prevention of thrombotic conditions (4) and frequent use of over-the-counter NSAIDs for general pain relief (5).

Despite their widespread use and beneficial effects, NSAIDs increase the risk of gastroduodenal ulcers (GU) (6), the consequences of which can sometimes be life-threatening bleeding or perforation (7,8). Advanced age is an independent risk factor for the development of GU (9,10). Not surprisingly, GU are a particular problem among patients suffering from arthritic conditions, the majority of whom are elderly and require long-term NSAID therapy. Research shows that the incidence of serious complications of GU is continuing to rise among older individuals (11).

The most obvious method of controlling NSAID-associated upper gastrointestinal (GI) toxicity is NSAID withdrawal, but consequent deterioration in the underlying condition and increased pain may make this option undesirable (12). Another preventative option involves the use of cyclooxygenase (COX)-2-selective rather than non-selective NSAIDs. Relative to non-selective NSAIDs, COX-2-selective agents are associated with a reduced incidence of serious upper GI adverse events (13,14), but do not eliminate them, particularly in high-risk patients (15,16). Furthermore, concerns about increases in cardiovascular risks have led to re-evaluation of the use of COX-2-selective NSAIDs in clinical practice, and the withdrawal of certain COX-2

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inhibitors from the market. As a result, clinicians are now being urged not to use the remaining marketed COX-2-selective NSAIDs unless absolutely necessary (17). Such restrictions are likely to lead to many patients returning to treatment with a non-selective NSAID.

Overall, the most effective and satisfactory option to help prevent initial occurrence of NSAID-associated GU, heal existing ulcers and prevent ulcer recurrence is co-prescription of a gastroprotective acid-suppressive agent (18–20). This strategy should, in many cases, allow patients to receive long-term NSAID therapy more safely at the most appropriate dose to alleviate their underlying inflammatory condition. Classes of acid-suppressive treatments for NSAID-associated GU include histamine H₂ receptor antagonists (H₂RAs) and proton pump inhibitors (PPIs). PPIs have been shown to be very effective in reducing the risk of developing GU, therefore it may be desirable for patients taking NSAIDs to also take a PPI to prevent ulcers forming (19,21–23). Additionally, cytoprotective agents such as sucralfate can be used to heal GU, and the prostaglandin analogue misoprostol can be used to help prevent NSAID-associated ulcers (12). Notably, misoprostol is the only agent that has been shown to reduce the risk of complications arising from NSAID-associated ulcers (24), but the drug is associated with adverse events such as diarrhoea, abdominal pain and increased uterine contractility (12).

Although it is known that H₂RAs provide less effective acid suppression than PPIs (25), the H₂RA ranitidine has been

widely studied in the treatment of acid-related disorders, including GU and serves as a useful 'yardstick' when comparing the efficacy of various agents. Of the H₂RA class of drugs, ranitidine has also been the agent most extensively studied for the specific indication of healing NSAID-associated ulcers. This review focuses on clinical trials in which ranitidine has been used in the treatment of NSAID-associated GU.

We conducted a search of PubMed using the Medical Subject Headings terms 'NSAID' and 'ranitidine', as well as the text word 'ulcer healing'. The search was limited to manuscripts detailing clinical trials, up to March 2006. Of these, only manuscripts that focused on the use of ranitidine in the treatment of NSAID-associated GU were selected.

RESULTS

Manuscripts Included

Using the search criteria, 33 manuscripts were retrieved from PubMed. Seven of these were selected as being focused specifically on the use of ranitidine 150 mg twice daily (bid) for healing NSAID-associated GU (19,26–31). The main characteristics of the studies are summarised in Table 1. In general, ulcers were considered healed when endoscopy revealed complete re-epithelialisation of the mucosa.

One of the trials identified during our literature search was a 4-week trial performed by Tildesley et al. (29). This was a multinational, multicentre, randomised, double-blind,

Table 1 Studies included in the analysis

<i>Study</i>	<i>Patient population</i>	<i>Ranitidine dose (mg bid)</i>	<i>Comparator dose</i>	<i>Study duration (weeks)</i>
Goldstein et al. (26)	Gastric ulcer and continuous NSAID (<i>n</i> = 399; mean age: 58 years)	150	Esomeprazole (20 mg or 40 mg qd)	8
Campbell et al. (27)	Gastric ulcer and continuous NSAID (<i>n</i> = 692; mean age: 58 years)	150	Lansoprazole (15 mg or 30 mg qd)	8
Agrawal et al. (28)	Gastric ulcer and continuous NSAID (<i>n</i> = 353; mean age: 60 years)	150	Lansoprazole (15 mg or 30 mg qd)	8
Yeomans et al. (19)	Gastric/duodenal ulcer or >10 erosions in the stomach or duodenum and continuous NSAID (<i>n</i> = 541; mean age: 57 years)	150	Omeprazole (20 mg or 40 mg qd)	8
Tildesley et al. (29)	Gastric/duodenal ulcer or >10 erosions in the stomach or duodenum. Continuing or stopping NSAID (<i>n</i> = 243; mean age: 56 years)	150	Placebo without NSAID	4
Lancaster-Smith et al. (30)	Gastric/duodenal ulcer. Continuing or stopping NSAID (<i>n</i> = 190; mean age: 65 years)	150	–	≤12
Manniche et al. (31)	Gastric/duodenal ulcer and continuous NSAID (<i>n</i> = 67; median age RA: 67; non-RA: 71)	150	Sucralfate (1 g qid)	≤9

bid, twice daily; NSAID, non-steroidal anti-inflammatory drugs; qd, once daily; qid, four times daily; RA, rheumatoid arthritis.

placebo-controlled study involving 243 patients with gastro-duodenal damage, 149 of whom had gastric and/or duodenal ulceration of ≥ 5 mm in diameter, associated with current NSAID use. Patients were randomly assigned to receive ranitidine with either continued NSAID use ($n = 99$; $n = 62$ with ulcers), NSAID use discontinued ($n = 94$; $n = 61$ with ulcers) or to placebo with discontinuation of NSAID medication ($n = 50$; $n = 26$ with ulcers).

Manniche et al. (31) conducted a randomised open-label study that compared ranitidine ($n = 32$) with sucralfate 1 g four times daily (qid) ($n = 30$) in patients aged 35–87 years, diagnosed with a GU of > 3 mm diameter. Half of the patients in each treatment group continued with NSAID therapy while the other half was given alternative analgesic treatment. Patients had been receiving NSAID treatment for a mean of > 5 years for rheumatoid arthritis ($n = 38$), osteoarthritis ($n = 24$) or other rheumatic conditions ($n = 5$). If, after 9 weeks of treatment, ulcer healing was not achieved then patients were switched to receive the other anti-ulcer therapy.

In a multicentre, open-label study by Lancaster-Smith et al. (30), 190 patients who were receiving NSAIDs for arthritic conditions and who had at least one gastric and/or duodenal ulcer (DU) of ≥ 5 mm in diameter were randomised to continue ($n = 96$) or stop ($n = 94$) NSAID treatment. All patients were treated with ranitidine for 12 weeks.

The report by Campbell et al. (27) is an analysis of two multicentre, randomised, double-blind trials, one of which is reported separately in the manuscript by Agrawal et al. (28). In these studies, which compared 8 weeks' treatment with ranitidine ($n = 231$), lansoprazole 15 mg once daily (qd) ($n = 232$) or lansoprazole 30 mg qd ($n = 229$), patients had at least one gastric ulcer of ≥ 5 mm in diameter at the start of the study. Patients with multiple gastric ulcers, coexisting DU or coexisting erosive oesophagitis were also eligible to participate in the study. Patients were aged ≥ 18 years and had been receiving a stable daily dose of NSAID treatment for ≥ 1 month before enrolment. The primary indication for NSAID use in both studies was arthritis.

In their multicentre, randomised, double-blind study, Goldstein et al. (26) assessed gastric ulcer healing after 4 and 8 weeks' treatment with ranitidine ($n = 132$), esomeprazole 20 mg qd ($n = 138$) or esomeprazole 40 mg qd ($n = 129$). Again, to be included in the study, patients were required to be aged ≥ 18 years, have at least one gastric ulcer of ≥ 5 mm in diameter at baseline and to have been receiving a stable daily dose of NSAID treatment for ≥ 1 month prior to enrolment. Patients were permitted to have multiple gastric ulcers and concurrent DU, provided that each ulcer was ≤ 25 mm at its greatest diameter. NSAIDs were being used predominantly to treat osteoarthritis ($n = 233$).

In another multinational, multicentre, randomised, double-blind study, Yeomans et al. (19) assessed the efficacy of 4–8 weeks' ranitidine ($n = 174$), omeprazole 20 mg qd ($n = 174$) and omeprazole 40 mg qd ($n = 187$) in patients who had at least one GU of ≥ 3 mm in diameter and/or multiple gastroduodenal erosions. Patients aged between 18 and 85 years who had any condition requiring continuous treatment with daily NSAIDs were assessed for inclusion in the study. Most patients had rheumatoid arthritis ($n = 234$) or osteoarthritis ($n = 182$).

Patients' *Helicobacter pylori* status was assessed by biopsy in four of the studies selected for inclusion in this report (19,26–28). The proportions of patients who were *H. pylori*-positive in each of these studies was 19% (26), 26% (27), 29% (28) and 46% (19).

Ranitidine Healing Rates

The gastric ulcer healing rates associated with the use of ranitidine in patients continuing to take NSAIDs are shown in Figure 1A. Most variation was observed for healing rates at 4 weeks, which ranged from 30% to 67%. Even after 8 weeks, endoscopic examination revealed that approximately one-quarter to one-half of patients treated with ranitidine still had unhealed ulcers (healing rates of 50–74%).

Duodenal ulcer healing rates obtained with ranitidine in patients continuing to take NSAIDs (Figure 1B) were generally higher than those for gastric ulcers. At 4 weeks, DU healing rates ranged from 57% to 74%, increasing to between 81% and 84% at 8 weeks. However, in the study by Tildesley et al. (29) a slightly higher 4-week healing rate was observed for gastric ulcers over DUs (67% vs. 61%).

The study report by Manniche et al. (31) only gives overall GU healing rates by treatment group. These results show comparable healing rates between ranitidine and sucralfate of 84% and 83%, respectively. The respective mean times to ulcer healing were 4.9 weeks and 4.6 weeks. In this same study for the combined treatment groups, a higher percentage of patients who continued NSAID therapy had DU healing (83%) than gastric ulcer healing (50%). For patients who were withdrawn from NSAIDs, respective duodenal and gastric ulcer healing rates were 92% and 86%.

Effect of NSAID Withdrawal on Healing Rates

Use of ranitidine was compared with placebo in the study by Tildesley et al. (29). Discontinuation of NSAID therapy in patients receiving ranitidine resulted in a higher rate of healing for patients with DU but not for those with gastric ulcers, and ranitidine was only associated with a significantly higher 4-week rate of healing than placebo in patients with DU in whom NSAIDs were discontinued (81% vs. 42%; $p < 0.05$). In the study by Lancaster-Smith et al., in which

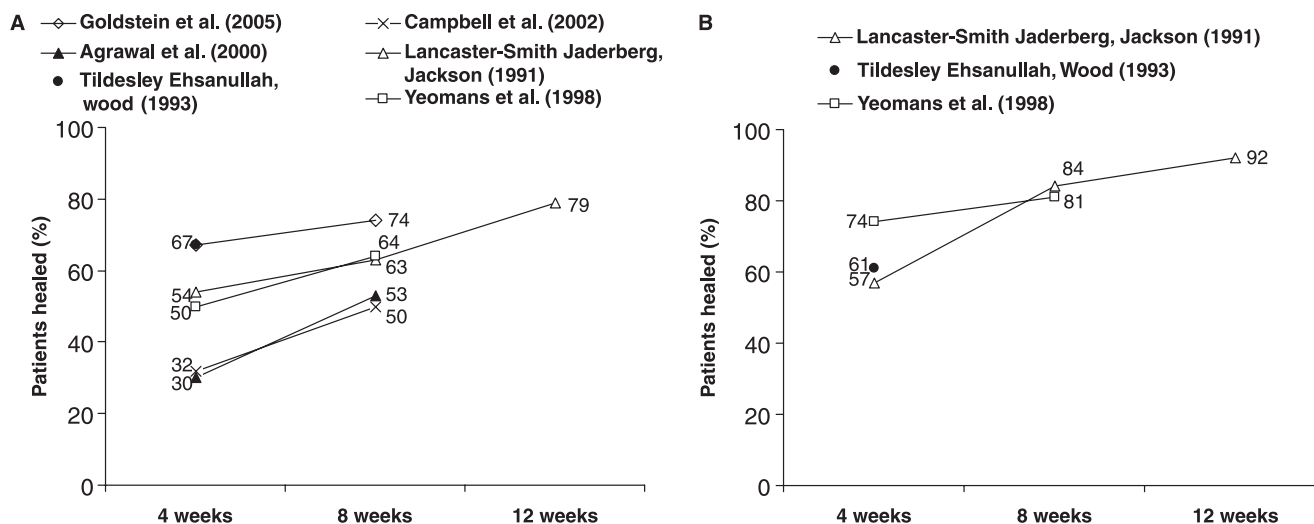


Figure 1 Four-, 8- and 12-week NSAID-associated ulcer healing rates for (A) gastric ulcers and (B) duodenal ulcers in patients taking ranitidine 150 mg twice daily

use of ranitidine was investigated in the absence of a comparator (30), discontinuation of NSAIDs improved healing of gastric ulcer and DU. After 8 weeks of treatment, gastric ulcers had healed in 95% of patients who had stopped NSAID therapy compared with 63% in patients continuing NSAIDs ($p = 0.001$). For DU, the healing rates were 100% and 84% in patients who had ceased or continued NSAIDs, respectively ($p = 0.006$). Similar trends were observed for gastric ulcers and DUs treated with ranitidine or sucralfate in the trial by Manniche et al. (31). In this study, GU healing rates were 77% in patients who continued to take NSAIDs and 91% in patients in whom NSAIDs were withdrawn ($p > 0.10$).

Comparator Healing Rates

Manniche et al. (31) found that the rate of GU healing obtained with sucralfate was similar to that obtained with ranitidine (83% and 84%, respectively). These rates were obtained in a mixture of patients who continued to take NSAID medication and those who discontinued NSAID therapy.

Of the six manuscripts included in this report, four compared ranitidine with PPIs; one using esomeprazole (20 mg or 40 mg qd) (26), one using omeprazole (20 mg or 40 mg qd) (19) and two using lansoprazole (15 mg or 30 mg qd) (27,28). Four- and 8-week healing rates for ranitidine vs. esomeprazole, omeprazole and lansoprazole are shown in Figure 2.

Compared with the ranitidine treatment group at both the 4- and 8-week assessments, gastric ulcer healing occurred in significantly higher proportions of patients treated with either the 20 mg dose of esomeprazole or the 40 mg dose (Figure 2A). At the end of the 8-week treat-

ment period, the healing rate was 74% with ranitidine compared with 88% with esomeprazole 20 mg ($p < 0.01$) and 92% with esomeprazole 40 mg ($p < 0.001$).

Statistical analysis of the 8-week data showed a significant difference in favour of both omeprazole doses for healing gastric ulcers and for omeprazole 20 mg for healing DU, relative to ranitidine (Figure 2B). After 8 weeks of treatment with the 20 mg omeprazole dose, gastric ulcer healing occurred in 84% of patients and DU healing was observed in 92% of patients compared with 64% of gastric ulcer ($p < 0.001$) and 81% of DU ($p < 0.05$) patients treated with ranitidine. Numerically higher healing rates were observed with both doses of omeprazole relative to ranitidine after 4 weeks of treatment.

In the two papers that investigated ranitidine in comparison with lansoprazole, both doses of the PPI were found to be significantly more effective than ranitidine for providing healing of gastric ulcers after both 4 and 8 weeks of treatment (Figure 2C). The 8-week gastric ulcer healing rates were 73% (28) and 74% (27) in patients treated with lansoprazole 30 mg, relative to respective healing rates of 53% ($p < 0.01$) and 50% ($p < 0.001$) for patients treated with ranitidine.

Effect of *H. pylori* On Healing Rates

The rates of *H. pylori* infection were 19% in the paper comparing ranitidine and esomeprazole (26), 26% and 29% in the two papers comparing ranitidine and lansoprazole (27,28), and 46% in the study comparing ranitidine and omeprazole (19). Campbell et al., Goldstein et al. and Yeomans et al. all reported that *H. pylori*-positive patients were more likely to be healed during 8 weeks of treatment than *H. pylori*-negative patients. Yeomans et al. reported that

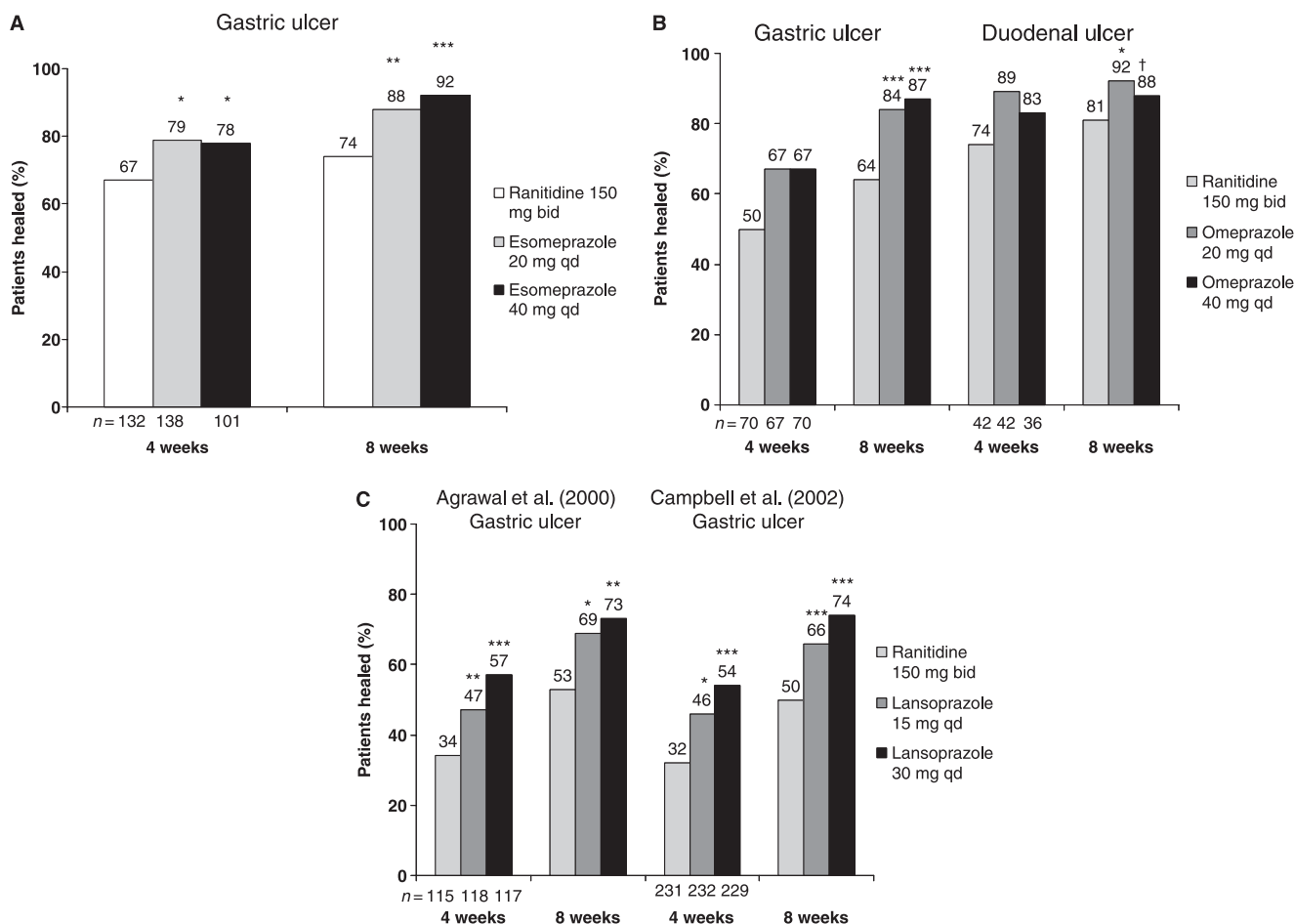


Figure 2 Four- and 8-week gastric and duodenal ulcer healing rates in studies comparing ranitidine 150 mg twice daily (bid) with the proton pump inhibitors (A) esomeprazole once daily (qd) (26), (B) omeprazole (qd) (19) or (C) lansoprazole (qd) (27,28). The manuscript by Campbell et al. (27) includes the study by Agrawal et al. (28) as part of a pooled analysis with a separate study. *p < 0.05, **p < 0.01, ***p < 0.001, †p = 0.17

GU were healed after 8 weeks of treatment in 83% of *H. pylori*-positive and 75% of *H. pylori*-negative patients receiving omeprazole 20 mg, 82% and 71% of the respective groups of patients receiving omeprazole 40 mg, and 72% and 55% of those receiving ranitidine (p = 0.05 for the overall likelihood of successful healing in *H. pylori*-positive vs. *H. pylori*-negative patients).

DISCUSSION

Our review is focused on ranitidine, at a dose of 150 mg bid, because this therapy is widely used for treating GU associated with NSAIDs and a sufficient number of primary healing studies have been conducted with this agent to support such a review. The overall findings of the review show that ranitidine has similar efficacy to sucralfate for healing GU, but provides less effective ulcer healing than PPIs during continuous NSAID therapy. Ulcers heal most readily with ranitidine when NSAIDs are discontinued. After 8 weeks of treatment during continuous NSAID therapy,

PPIs are capable of producing GU healing rates that are up to 20% greater than rates obtained with ranitidine.

Healing rates associated with ranitidine treatment were found to vary markedly between studies, with Goldstein et al. (26) and Tildesley et al. (29) reporting 4-week gastric ulcer healing rates in patients continuing NSAID therapy that were more than twice those reported by Campbell et al. (27) and Agrawal et al. (28). Additionally, the 8-week gastric ulcer healing rate reported by Goldstein et al. was more than 20% greater than those reported with ranitidine in these other two studies. The reasons for this are unclear because all of these studies used the same ulcer definition (≥5 mm in diameter), but were most likely related to differences in the patient populations.

Although there are few published studies examining the use of other H₂RAs in NSAID-associated ulcer healing, healing rates have been reported in association with compounds such as famotidine, nizatidine and cimetidine. In a study by Hudson et al. (32), famotidine 40 mg bid was assessed for NSAID-associated GU healing in arthritic

patients either continuing to take or discontinuing NSAID therapy. Over the relatively long 12-week treatment period, the healing rate was 89% in patients continuing NSAID therapy. It should, however, be noted that the standard famotidine dose is 20 mg bid rather than 40 mg bid. In another study involving patients with NSAID-associated GU, three different regimens of nizatidine therapy led to over 90% of patients being healed at 8 weeks (33). In addition, cimetidine 800 mg/day led to a 49% peptic ulcer healing rate at 4 weeks and a 81% healing rate at 8 weeks in patients with GU associated with continuous NSAID use (34). It should be noted that inclusion criteria for these studies allowed for patients with quite small ulcers (as small as about 3 mm in diameter), which may have rendered them easier to treat than in a number of the studies included in this review that specified an ulcer diameter of ≥ 5 mm. Additionally, the absence of placebo or other control groups in these studies of other H₂RAs limits interpretation and detracts from the relevance of the results.

The degree of gastroduodenal damage caused by NSAIDs is highly dependent upon intragastric pH (35–37). It is well established that H₂RAs provide less effective acid suppression over a 24-h period than PPIs (38). The increased healing rates observed with PPI therapy relative to ranitidine in the studies included in this review are consistent with GU healing being directly related to the degree of acid suppression obtained with acid-suppressive drugs (39).

The contribution made by *H. pylori* to the risk of NSAID-associated ulcers is still controversial (40). Historically, *H. pylori* infection has been shown to be a risk factor for the development of GU (41). However, *H. pylori* may have a mixed role in NSAID-associated ulcer healing as infection increases the acid-suppressive effect of PPIs (42) and also seems to stimulate synthesis of prostaglandin E₂ by promoting mucosal inflammatory cell infiltration (43). In contrast, NSAIDs act to depress prostaglandin levels (44), thereby compromising protection of the gastroduodenal mucosa against gastric acid (45). The results of the relevant studies included in this review suggest that successful healing of GU may occur most readily in *H. pylori*-positive patients, regardless of the type of treatment. However, the extent of the risk or benefit associated with *H. pylori* infection for patients taking NSAIDs has yet to be fully established (19).

CONCLUSION

The results of this review show that, in patients with NSAID-associated GU, for whom discontinuation of NSAID therapy is not appropriate, PPIs, which offer more substantial acid suppression than H₂RAs, are associated with higher rates of ulcer healing than ranitidine at the standard dose of 150 mg bid.

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