

FAMOTIDINE FOR THE PREVENTION OF GASTRIC AND DUODENAL ULCERS CAUSED BY NONSTEROIDAL ANTIINFLAMMATORY DRUGS

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Abstract Background. Acid suppression with famotidine, a histamine H₂-receptor antagonist, provides protection against gastric injury in normal subjects receiving short courses of aspirin or naproxen. The efficacy of famotidine in preventing peptic ulcers in patients receiving long-term therapy with nonsteroidal antiinflammatory drugs (NSAIDs) is not known.

Methods. We studied the efficacy of two doses of famotidine (20 mg and 40 mg, each given orally twice daily), as compared with placebo, in preventing peptic ulcers in 285 patients without peptic ulcers who were receiving long-term NSAID therapy for rheumatoid arthritis (82 percent) or osteoarthritis (18 percent). The patients were evaluated clinically and by endoscopy at base line and after 4, 12, and 24 weeks of treatment. The evaluators were unaware of the treatment assignment. The primary end point was the cumulative incidence of gastric or duodenal ulceration at 24 weeks.

Results. The cumulative incidence of gastric ulcers was 20 percent in the placebo group, 13 percent in the group of patients receiving 20 mg of famotidine twice daily ($P=0.24$ for the comparison with placebo), and 8 percent in the group receiving 40 mg of famotidine twice daily ($P=0.03$ for the comparison with placebo). The proportion of patients in whom duodenal ulcers developed was significantly lower with both doses of famotidine than with placebo (13 percent in the placebo group, 4 percent in the low-dose famotidine group [$P=0.04$], and 2 percent in the high-dose famotidine group [$P=0.01$]). Both doses of famotidine were well tolerated.

Conclusions. Treatment with high-dose famotidine significantly reduces the cumulative incidence of both gastric and duodenal ulcers in patients with arthritis receiving long-term NSAID therapy. (N Engl J Med 1996; 334:1435-9.)

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GASTRODUODENAL damage can be seen on endoscopy in 20 to 40 percent of people who take nonsteroidal antiinflammatory drugs (NSAIDs). In epidemiologic studies, the risks of peptic ulcer and death are three to six times higher among people who take these drugs than among those who do not.^{1,2} An effective strategy to prevent these complications is needed.

Endoscopic studies have shown that misoprostol prevents NSAID-associated gastric and duodenal ulcers,³⁻⁵ and in one study the incidence of complications from ulcers was reduced.⁶ However, misoprostol may cause diarrhea and abdominal pain, it has little effect on symptoms of dyspepsia, and it is unsuitable for women of childbearing potential because of its abortifacient action.⁷ Ranitidine can prevent duodenal ulceration in patients taking NSAIDs for arthritis but is relatively ineffective in preventing NSAID-associated gastric ulceration.^{8,9}

Famotidine, a histamine H₂-receptor antagonist, inhibits acid secretion and provides protection against mucosal injury in normal subjects receiving short courses of aspirin or naproxen, with high doses of famotidine more effective than low doses.^{10,11} The efficacy and safety of the drug have not been established in patients with arthritis receiving long-term NSAID therapy.

We compared two doses of famotidine (20 mg twice

daily and 40 mg twice daily) with placebo to test the hypothesis that famotidine provides protection against NSAID-associated gastric and duodenal ulcers.

METHODS

The study was a 24-week, double-blind, parallel-group, randomized comparison of placebo with low-dose famotidine (20 mg twice daily) or high-dose famotidine (40 mg twice daily) as prophylaxis against endoscopically detected gastric or duodenal ulceration. The patients were 18 years old or older and had rheumatoid arthritis or osteoarthritis. They had been receiving standard doses of another NSAID for at least one month and were likely to continue taking this medication for at least six months.

The patients were recruited from the rheumatology and orthopedic clinics at Glasgow Royal Infirmary, Glasgow, Scotland, and University Hospital, Nottingham, England. Patients were not considered eligible for the study if they had taken antiulcer drugs other than antacids within seven days before enrollment or if they were taking 7.5 mg or more of prednisolone daily (or an equivalent dose of another corticosteroid), methotrexate, or antineoplastic drugs. The other main exclusion criteria were lactation, childbearing potential in the absence of contraception, renal failure, diabetes mellitus, and clinically important abnormal values on laboratory tests.

The recruitment was conducted by two gastroenterologists, who invited all potentially eligible patients with arthritis, regardless of whether they had dyspeptic symptoms, to participate in the study. Patients who accepted the invitation underwent upper gastrointestinal endoscopy.

The study protocol was approved by the ethics committees of the two participating hospitals, and informed consent was obtained from all the patients.

Endoscopic Evaluation

Before the commencement of the study, the two endoscopists attended each other's endoscopic sessions and reviewed still and video images in order to establish standardized reporting criteria for ulcers and other lesions.

At endoscopy, ulcers, erosions, and intramucosal hemorrhages were recorded separately for the esophagus, gastric body, gastric an-

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trum, duodenal bulb, and second part of the duodenum. An ulcer was defined as an excavated mucosal break 3 mm or more in diameter,^{3,5} as measured with biopsy forceps or a custom-made device. Erosions were defined as superficial mucosal breaks, and intramucosal hemorrhages were defined as hemorrhagic lesions without overlying mucosal breaks. The endoscopic findings were used to derive a modified Lanza score of 0 to 4 (0, no lesions, 1 nonulcerated duodenal lesion, or 1 or 2 nonulcerated gastric lesions; 1, 2 to 5 nonulcerated duodenal lesions or 3 to 5 nonulcerated gastric lesions; 2, 6 to 10 nonulcerated lesions; 3, more than 10 nonulcerated lesions; and 4, 1 or more ulcers).⁹ Patients with ulcers were enrolled in a separate study of ulcer healing.

Randomization

Patients without ulcers were stratified according to the type of arthritis and, with the use of a computer-generated schedule, were randomly assigned to receive one 20-mg or 40-mg tablet of famotidine (Pepcid, Merck) twice daily or one placebo tablet twice daily. Co-magaldrox 195/220 (Maalox, Rhone-Poulenc-Rorer) tablets were provided for the relief of dyspepsia. Famotidine is not licensed anywhere for the prevention of ulcers, and the higher dose (40 mg twice daily) exceeds the dose approved for ulcer healing (40 mg once daily).

Assessments

The patients were assessed at base line and after 4, 12, and 24 weeks of treatment. In addition to the endoscopic data, we obtained information on NSAID and other drug therapy, abdominal pain, and arthritis-related physical disability as measured by the Health Assessment Questionnaire (Table 1).¹² The patients underwent a complete physical examination at base line and at the end of the study, and urinalysis and routine hematologic and biochemical tests were performed at each visit. The patients were asked to record abdominal symptoms (pain, heartburn, nausea, and vomiting) and antacid use daily on diary cards. Abdominal pain and joint pain were quantitated on a scale of 1 to 3 (1, mild; 2, moderate; and 3, severe). We assessed compliance with the study regimen by recording tablet counts. At each visit, patients were questioned about adverse events. At the time of the initial endoscopic study, the presence of *Helicobacter pylori* was determined in gastric antral biopsy specimens on the basis of both histologic examination and urease activity. Identification of the organism by either means was considered a positive result.

End Points

The primary end point was the cumulative incidence of gastric or duodenal ulceration at 24 weeks. The secondary end points were Lanza scores for lesser degrees of gastroduodenal injury, the presence or absence of abdominal pain, pain scores, and antacid consumption. The analysis of safety was based on an assessment of adverse events, the score on the Health Assessment Questionnaire, physical examinations, and laboratory tests.

Statistical Analysis

The statistical analyses were performed with the SAS statistical package (version 6.08, Cary, N.C.). The results of an intention-to-treat analysis are presented. A per-protocol analysis was also carried out on patients who could be evaluated, defined as those who took more than 80 percent of both the prescribed NSAID and the study drug, did not take additional full-dose salicylates, and underwent a final endoscopic examination no more than five days after the end of treatment with the study drug.

The primary end point (i.e., the time to the detection of a gastric or duodenal ulcer) was analyzed with the use of Kaplan-Meier curves for survival, and comparisons among the three groups were made with the log-rank test. The confidence intervals for the Kaplan-Meier curves were estimated with the binomial distribution when possible (without censoring of data) or with Greenwood's formula for the standard error, with the normal approximation.¹³ Changes from base line in Lanza scores, abdominal-pain scores, and joint-pain

Table 1. Base-Line Characteristics of 285 Patients with Arthritis Receiving Long-Term NSAID Therapy and Randomly Assigned to Receive Famotidine or Placebo (Intention-to-Treat Analysis).*

CHARACTERISTIC	STUDY GROUP		
	PLACEBO (N = 93)	LOW-DOSE FAMOTIDINE (N = 95)	HIGH-DOSE FAMOTIDINE (N = 97)
Age (yr)			
Mean	53.4	57.2	55
Range	22-78	18-88	22-83
Duration of arthritis (yr)			
Mean	9.6	12.2	10.1
Range	0-50	0-44	0-47
Health Assessment Questionnaire score†			
Mean	1.3	1.5	1.4
Range	0-2.9	0-2.9	0-2.9
	<i>no. of patients (%)</i>		
Female sex	71 (76)	69 (73)	68 (70)
Current smoker	32 (34)	28 (29)	42 (43)
Rheumatoid arthritis	76 (82)	80 (84)	79 (81)
<i>H. pylori</i> infection‡	46 (49)	48 (51)	48 (49)
Previous ulcer	9 (10)	15 (16)	13 (13)
Moderate or severe joint pain	60 (65)	74 (78)	71 (73)
Abdominal pain§	33 (35)	25 (26)	29 (30)
Heartburn	28 (30)	22 (23)	26 (27)
Nausea	13 (14)	13 (14)	11 (11)
Vomiting	5 (5)	2 (2)	2 (2)
Gastric lesion	29 (31)	40 (42)	32 (33)
Duodenal lesion	8 (9)	9 (9)	13 (13)
NSAID			
Diclofenac	24 (26)	26 (27)	22 (23)
Indomethacin	19 (20)	15 (16)	19 (20)
Naproxen	19 (20)	13 (14)	18 (19)
Ibuprofen	9 (10)	10 (11)	11 (11)
Ketoprofen	5 (5)	5 (5)	5 (5)
Fenbufen	4 (4)	6 (6)	6 (6)
Other¶	14 (15)	23 (24)	20 (21)
Disease-modifying drug			
Sulfasalazine	30 (32)	23 (24)	23 (24)
Gold	6 (6)	14 (15)	18 (19)
Penicillamine	6 (6)	13 (14)	6 (6)
Prednisolone	8 (9)	10 (11)	8 (8)
Hydroxychloroquine	5 (5)	6 (6)	4 (4)

*Patients in the low-dose group received 20 mg of famotidine twice daily, and those in the high-dose group received 40 mg twice daily. There were no statistically significant differences ($P < 0.05$) in any of the characteristics among the groups.

†The score is the average of individual scores, on a scale of 0 to 3, for the ability to dress, rise, eat, walk, reach, grip, shop, vacuum, and garden (0 to 1, some or no difficulty; 1.1 to 2, much difficulty; and 2.1 to 3, in need of several devices or unable to perform the activity).

‡Data were not recorded for three patients in the low-dose group and two in the high-dose group.

§Among the patients with abdominal pain, the pain scores were similar in the three groups.

¶Other NSAIDs, used by fewer than 5 patients in a group, were nabumetone (12 patients), apazone (12), piroxicam (9), flurbiprofen (8), tiaprofenic acid (5), etodolac (4), acetaminophen (3), benorilate (2), tenoxicam (1), and sulindac (1).

scores were compared with the Mantel-Haenszel test (with adjustment for the study center). Changes from base line in scores on the Health Assessment Questionnaire were analyzed with the Kruskal-Wallis test.

The proportional-hazards model was used to assess the effects of potential prognostic factors on the risk of ulceration. These factors included the study center, age, sex, smoking habits, use of alcohol, type of NSAID, duration of prior NSAID therapy, rheumatologic diagnosis, duration of arthritis, presence of erosions or hemorrhagic lesions at the initial endoscopic examination, abdominal pain at base line, his-

tory of peptic ulcer, score on the Health Assessment Questionnaire, second-line treatment with antirheumatoid drugs, prednisolone therapy, peripheral-blood cell counts, and *H. pylori* infection. The results are presented as hazard ratios, which express the increase in the risk that an ulcer will develop.

An overall comparison of the three groups of patients was performed, in addition to three pairwise tests. No formal adjustment was made for multiple tests. All tests were two-tailed.

RESULTS

A total of 570 patients were invited to undergo endoscopic screening for enrollment in the trial: 181 patients were unwilling to undergo multiple endoscopic examinations, and 389 accepted the invitation. Of these 389 patients, 104 had gastric or duodenal ulcers at the initial endoscopy and were therefore excluded from the study. The characteristics of the remaining 285 patients are shown in Table 1. A total of 165 patients (58 percent) were from Glasgow, 119 (42 percent) were from Nottingham, and 1 (0.4 percent) was from Leeds. The three treatment groups were well-matched for age, sex, smoking status, use of alcohol, underlying arthritis, and frequency of *H. pylori* infection, as well as for previous ulcer, frequency of joint pain, score on the Health Assessment Questionnaire, and use of individual NSAIDs or disease-modifying drugs.

The per-protocol analysis included 81 patients in the placebo group, 84 in the group receiving 20 mg of famotidine twice daily, and 83 in the group receiving 40 mg twice daily. For this analysis, 12 patients assigned to the placebo group, 11 assigned to the low-dose group, and 14 assigned to the high-dose group were excluded because of a subsequent change to low-dose NSAID therapy or poor compliance with the study drugs.

Cumulative Incidence of Ulcer

Estimates of the cumulative incidence of gastric or duodenal ulceration during the 24-week study period are shown in Table 2 and Figure 1. The cumulative incidence of ulceration, regardless of the site, was lower in both famotidine groups than in the placebo group. However, whereas the higher dose of famotidine was associated with a lower incidence of both gastric and duodenal ulcers, the lower dose was associated with a reduction only in the incidence of duodenal ulcers. The results of the per-protocol analysis were similar (data not shown).

Prognostic Factors

The risk of ulceration was increased by an increase in the peripheral white-cell count (hazard ratio, 1.2 per 1000 cells per cubic millimeter; 95 percent confidence interval, 1.0 to 1.4) and by duodenal erosions and submucosal hemorrhages (hazard ratio, 2.9; 95 percent confidence interval, 1.2 to 6.9). In the placebo group, ulcers developed in 5 of the 8 patients (62 percent) with duodenal lesions at base line, as compared with 19 of the 85 (22 percent) without duodenal lesions. In the low- and high-dose famotidine groups combined, ulcers

Table 2. Cumulative Number and Incidence of Gastric and Duodenal Ulcers at the Completion of the Study (Intention-to-Treat Analysis).

ULCERS*	STUDY GROUP		
	PLACEBO (N = 93)	LOW-DOSE FAMOTIDINE (N = 95)	HIGH-DOSE FAMOTIDINE (N = 97)
Gastric and duodenal			
Cumulative number	24	14	9
Cumulative incidence — % (95% CI)	28 (19–38)	16 (9–24)	11 (4–17)
P value	—	0.05	0.003
Gastric			
Cumulative number	16	11	7
Cumulative incidence — % (95% CI)	20 (11–28)	13 (6–20)	8 (2–14)
P value	—	0.24	0.03
Duodenal			
Cumulative number	10	3	2
Cumulative incidence — % (95% CI)	13 (5–20)	4 (0–8)	2 (0–6)
P value	—	0.04	0.01

*CI denotes confidence interval. P values are for the comparison with the placebo group.

developed in 23 percent of the patients with duodenal lesions at base line and in 11 percent of those without such lesions. There were also trends toward an increased risk of ulceration among patients with *H. pylori* infection (hazard ratio, 1.7; 95 percent confidence interval, 0.8 to 3.5) and a reduced risk among those receiving diclofenac, as compared with all other NSAIDs (hazard ratio, 0.5; 95 percent confidence interval, 0.2 to 1.3).

Analyses of Secondary End Points

At four weeks, 25 patients in the placebo group had gastric Lanza scores of 1 to 4 for gastric lesions, as compared with 18 in the low-dose famotidine group ($P=0.03$) and 12 in the high-dose group ($P=0.01$). The scores for duodenal lesions in the three groups were similar. The results at the 12- and 24-week visits could not be analyzed directly, because they were confounded by the withdrawal of patients with ulcers (Fig. 1).

About 30 percent of the patients had abdominal pain at base line (Table 1). At the end of the study, 29 percent of the patients in the placebo group had abdominal pain, as compared with 19 percent of the patients in the low-dose famotidine group and 17 percent of those in the high-dose group. Among the patients with pain, the abdominal-pain scores and mean daily use of antacids during the study were similar in the three groups.

Safety Profile and Dropout

Both doses of famotidine were well tolerated. Patients dropped out of the study because of the development of ulcers (withdrawal per protocol, Fig. 1), the occurrence of adverse events, or other reasons, as shown in Table 3. In the high-dose famotidine group, there was a small but statistically significant reduction in the mean platelet count at the completion of the study, from 321,000 to 309,000 per cubic millimeter ($P=0.02$).

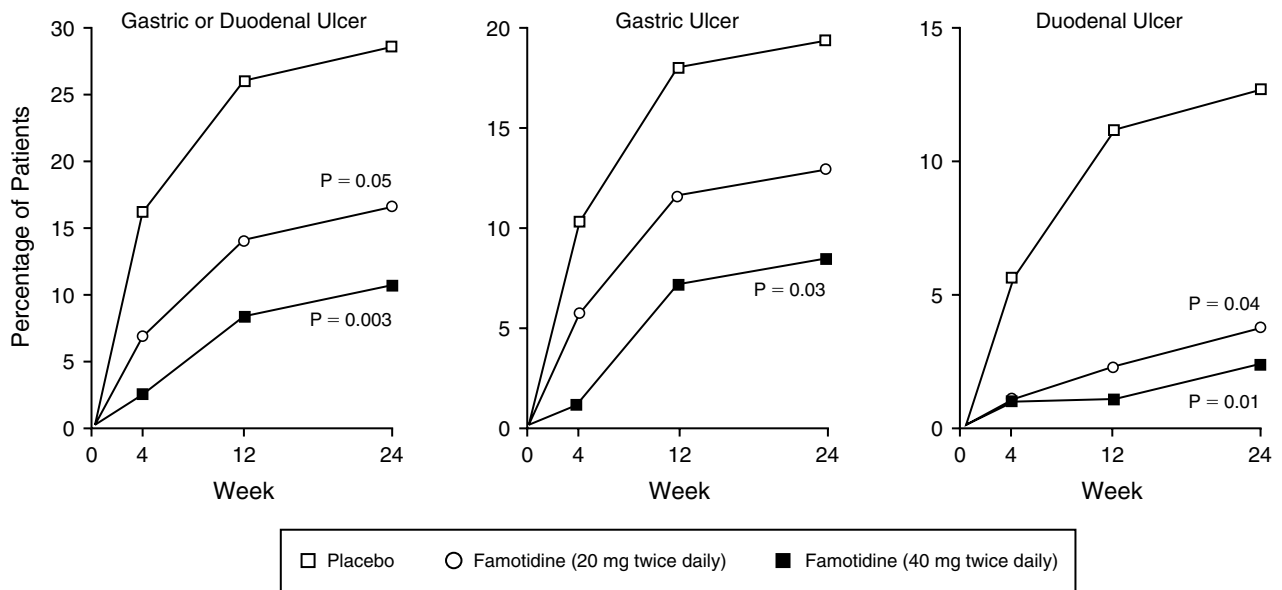


Figure 1. Cumulative Incidence of Gastric and Duodenal Ulcers at 4, 12, and 24 Weeks in Patients with Arthritis Receiving Long-Term NSAID Therapy, According to the Group Assignment.

Data are from the intention-to-treat analysis. P values are for comparisons with the placebo group.

There were no other important changes in the results of laboratory tests in any group.

DISCUSSION

The results of this study show that treatment with a high dose of famotidine significantly reduces the cumulative incidence of both gastric and duodenal ulcers in patients with arthritis receiving long-term NSAID therapy. As in previous studies of patients with NSAID-induced ulcers,¹⁴ many of our patients did not have abdominal pain or dyspepsia. Among those who did, however, there was a trend toward a reduction in dyspepsia among the patients taking famotidine. A strength of the study was that since only two physicians performed the endoscopic examinations, the likelihood of differences in the endoscopic evaluations was minimized. The design of previous studies of the efficacy of ranitidine in preventing NSAID-induced lesions may have militated against the detection of a protective effect against gastric ulcers, because the studies were relatively small and of short duration, with low event rates.¹⁵ Some of these factors may also explain the lack of a protective effect of famotidine in another study.¹⁶

One might speculate that NSAID-related duodenal ulcers are more likely to be dependent on acid than gastric ulcers — hence, the greater ability of histamine-receptor antagonists to prevent duodenal ulcers. Although much of the gastroduodenal damage associated with NSAIDs is due to the inhibition of prostaglandin synthesis, acid plays an important part,¹⁷ and in studies in humans, high doses of acid-inhibiting drugs were needed to achieve substantial protection against acute gastric damage.^{10,18}

At a standard dose of 20 to 40 mg daily, which is approved for the healing of ulcers, famotidine is well tol-

erated,^{19,20} although there are fewer data on the higher dose we used (40 mg twice daily). We found the higher dose to be well tolerated. Of the adverse events listed in Table 3, only three might have been related to famotidine: abdominal pain, rash, and diarrhea.

One of the prognostic factors that influenced the development of ulcers was the leukocyte count. We included the leukocyte count as a prognostic factor because studies in animals have suggested that neutrophils have a role in NSAID-associated gastric damage.²¹ Our results are consistent with this hypothesis. In addition, base-line lesions in the duodenum were predictive of both duodenal and gastric ulceration. One possible explanation for this association is that duodenal lesions were a marker for *H. pylori* infection, although this infection appeared to be a separate risk factor in the multivariate analysis. Although the influence of *H. pylori* infection was not statistically significant, it may have been weakened by the exclusion of patients with ulcers at the base-line assessment, the majority of whom had *H. pylori* infection.²²

In a recent six-month study of misoprostol,⁶ there was a reduction in ulcer complications in patients being treated with NSAIDs, which is consistent with the reduced incidence of endoscopic lesions found in previous studies of misoprostol.³⁻⁵ Since in our study the cumulative incidence of ulcers in the placebo group at 4, 12, and 24 weeks was similar to that reported in the placebo groups in endoscopic studies of misoprostol³⁻⁵ and the reductions in gastric and duodenal ulcers in both famotidine groups were also similar to the reductions associated with misoprostol³⁻⁵ it is likely that famotidine would have a similar effect on ulcer complications.

In conclusion, high doses of famotidine were well tol-

Table 3. Adverse Events and Other Reasons for Withdrawal from the Study (Intention-to-Treat Analysis).

REASON	STUDY GROUP		
	PLACEBO (N = 93)	LOW-DOSE FAMOTIDINE (N = 95)	HIGH-DOSE FAMOTIDINE (N = 97)
Adverse event			
Severe knee pain	1	0	0
Myocardial infarct	1	0	0
Thrombocytopenia	1	0	0
Abdominal pain	0	1	0
Pneumonitis	0	1	0
Cerebrovascular accident	0	1	0
Pharyngitis	0	1	0
Rash	0	1	0
Esophageal ulcer	0	1	0
Angina	0	0	1
Diarrhea	0	0	1
Unwilling to continue	6	5	12
Discontinuation of NSAID therapy	1	0	0
Loss to follow-up	1	2	0
Other	2	1	2
Total	13	14	16

erated and effective in preventing both gastric and duodenal ulcers in patients with arthritis receiving long-term NSAID therapy.

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REFERENCES

- Barrier CH, Hirschowitz BI. Controversies in the detection and management of nonsteroidal antiinflammatory drug-induced side effects of the upper gastrointestinal tract. *Arthritis Rheum* 1989;32:926-32.
- Hawkey CJ. Non-steroidal anti-inflammatory drugs and peptic ulcers: facts and figures multiply, but do they add up? *BMJ* 1990;300:278-84. [Erratum, *BMJ* 1990;300:764.]
- Graham DY, Agrawal NM, Roth SH. Prevention of NSAID-induced gastric ulcer with misoprostol: multicentre, double-blind, placebo-controlled trial. *Lancet* 1988;2:1277-80.
- Bardhan KD, Bjarnason I, Scott DL, et al. The prevention and healing of acute non-steroidal anti-inflammatory drug-associated gastroduodenal mucosal damage by misoprostol. *Br J Rheumatol* 1993;32:990-5.
- Graham DY, White RH, Moreland LW, et al. Duodenal and gastric ulcer prevention with misoprostol in arthritis patients taking NSAIDs. *Ann Intern Med* 1993;119:257-62.
- Silverstein FE, Graham DY, Senior JR, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1995;123:241-9.
- Walt RP. Misoprostol for the treatment of peptic ulcer and antiinflammatory-drug-induced gastroduodenal ulceration. *N Engl J Med* 1992;327:1575-80.
- Ehsanullah RSB, Page MC, Tildesley G, Wood JR. Prevention of gastroduodenal damage induced by non-steroidal anti-inflammatory drugs: controlled trial of ranitidine. *BMJ* 1988;297:1017-21.
- Robinson MG, Griffin JW Jr, Bowers J, et al. Effect of ranitidine on gastroduodenal mucosal damage induced by nonsteroidal antiinflammatory drugs. *Dig Dis Sci* 1989;34:424-8.
- Daneshmend TK, Prichard PJ, Bhaskar NK, Millns PJ, Hawkey CJ. Use of microbleeding and an ultrathin endoscope to assess gastric mucosal protection by famotidine. *Gastroenterology* 1989;97:944-9.
- Aabakken L, Bjornbeth BA, Weberg R, Viksmoen L, Larsen S, Osnes M. NSAID-associated gastroduodenal damage: does famotidine protection extend into the mid- and distal duodenum? *Aliment Pharmacol Ther* 1990;4:295-303.
- Sherrer YS, Bloch DA, Mitchell DM, Young DY, Fries JF. The development of disability in rheumatoid arthritis. *Arthritis Rheum* 1986;29:494-500.
- Kalbfleisch JD, Prentice RL. *The statistical analysis of failure time data*. New York: John Wiley, 1980.
- Skander MP, Ryan FP. Non-steroidal anti-inflammatory drugs and pain free peptic ulceration in the elderly. *BMJ* 1988;297:833-4.
- French PC, Darekar BS, Mills JG, Wood JR. Ranitidine in the prevention of non-steroidal anti-inflammatory drug-associated gastric and duodenal ulceration in arthritic patients. *Eur J Gastroenterol Hepatol* 1994;6:1141-7.
- Simon TJ, Berger ML, Hoover ME, Stauffer LA, Berlin RG. A dose-ranging study of famotidine in prevention of gastroduodenal lesions associated with non-steroidal anti-inflammatory drugs (NSAIDs): results of a U.S. multicenter trial. *Am J Gastroenterol* 1994;89:A1644. abstract.
- Rowe PH, Starlinger MJ, Kasdon E, Hollands MJ, Silen W. Parenteral aspirin and sodium salicylate are equally injurious to the rat gastric mucosa. *Gastroenterology* 1987;93:863-71.
- Daneshmend TK, Stein AG, Bhaskar NK, Hawkey CJ. Abolition by omeprazole of aspirin induced gastric mucosal injury in man. *Gut* 1990;31:514-7.
- Rohner HG, Gugler R. Treatment of active duodenal ulcers with famotidine: a double-blind comparison with ranitidine. *Am J Med* 1986;81(4B):13-6.
- Savarino V, Mela GS, Scalabrini P, Di Timoteo E, Magnolia MR, Celle G. Continuous 24-hour intragastric pH monitoring in the evaluation of the effect of a nightly dose of famotidine, ranitidine and placebo on gastric acidity of patients with duodenal ulcer. *Digestion* 1987;37:103-9.
- Wallace JL, Keenan CM, Granger DN. Gastric ulceration induced by non-steroidal anti-inflammatory drugs is a neutrophil-dependent process. *Am J Physiol* 1990;259:G462-G467.
- Hudson N, Taha AS, Sturrock RD, Russell RI, Hawkey CJ. The influence of *Helicobacter pylori* colonisation on gastroduodenal ulceration in patients on non-steroidal anti-inflammatory drugs. *Gut* 1992;33:Suppl:S42. abstract.