Gut, 1991, 32, 252-255

Ranitidine in the treatment of non-steroidal anti-inflammatory drug associated gastric and duodenal ulcers

M J Lancaster-Smith, M E Jaderberg, D A Jackson

Abstract

In a multicentre study the effect of ranitidine on healing non-steroidal anti-inflammatory drug (NSAID) associated peptic ulcers was compared in a group of patients who had stopped NSAID treatment with another group who continued with NSAID treatment. A total of 190 patients with confirmed ulcers were randomised to continue or stop NSAID treatment. All patients in addition received ranitidine 150 mg twice daily. Patients were endoscopically monitored at four, eight, and 12 weeks. Gastric ulcers at eight weeks had healed in 63% of those taking NSAIDs compared with 95% of those who had stopped NSAID treatment. For duodenal ulcer the healing rates at eight weeks were 84% in the group continuing NSAIDs compared with 100% in those who stopped NSAIDs. The differences in healing rates were statistically significant for both gastric ulcer ($p=0{\cdot}001$) and for duodenal ulcer ($p=0{\cdot}006$). At 12 weeks, 79% of gastric ulcers and 92% of duodenal ulcers were healed in the group continuing with NSAIDs. All patients with gastric and duodenal ulcers who stopped taking NSAIDs were healed at 12 weeks. The study shows that ranitidine 150 mg twice daily effectively heals NSAID associated peptic ulcers. Healing is more successful when NSAID treatment stops but even if these drugs are continued, substantial healing rates are achievable.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly and universally prescribed group of drugs. In 1986 they accounted for 5% of all National Health Service prescriptions. Approximately 25% of all adverse drug reactions reported to the Committee on Safety of Medicines in the United Kingdom concern reactions attributed to NSAIDs and most of these relate to the alimentary tract.[1]

Gastroduodenal lesions have been reported in more than 30% of patients taking NSAIDs and dyspepsia occurs in up to 60%.[2,3] There is evidence that these drugs may directly induce mucosal lesions or induce lesions by inhibition of prostaglandin synthesis which, in turn, interferes with mucosal protective mechanisms.[4,5] This disruption of mucosal integrity allows back diffusion of gastric acid and in these circumstances suppression of acid secretion protects the gastric mucosa.[6] In addition, some NSAIDs may actually potentiate gastric acid secretion, although this is debatable.[7] It might be expected therefore that suppression of acid secretion would reduce the ulcerogenicity of NSAID treatment. This has led to the common practice of prescribing of NSAIDs and ulcer healing drugs together even though the evidence to support such a policy is incomplete.

The objectives of the present study were to evaluate the efficacy of the H_2 receptor antagonist ranitidine 150 mg twice daily in the healing of gastric and duodenal ulcers and erosions associated with NSAID treatment and to compare healing rates in patients who continued NSAID treatment and those who discontinued NSAID treatment.

Patients and methods

Fifty centres in the United Kingdom took part in the study. Altogether, 321 patients who had taken NSAID treatment for at least 14 days were referred from general practice and hospital departments for upper gastrointestinal endoscopy. They were eligible for entry to the study if they had gastric or duodenal ulcers, or both. Patients were randomised to continue or discontinue NSAID treatment, and those who discontinued NSAID treatment took paracetamol for relief of arthritic symptoms. All patients received ranitidine 150 mg twice daily.

Endoscopy was performed at entry and at four weekly intervals to a maximum of 12 weeks. The following dyspeptic symptoms were evaluated: epigastric pain, heartburn, nausea, and vomiting, and these were graded as none, mild, moderate, or severe. At each four weekly visit study medication was checked and compliance assessed. Pregnant and lactating women and patients with previous upper gastrointestinal surgery, suspicious or confirmed malignancy, dysphagia, ulcers that were bleeding or had recently bled, hepatic or renal impairment, the Zollinger-Ellison syndrome, or a history of alcohol abuse or ingestion of ulcer healing drugs, tricyclic antidepressants, oral steroids, or salicylates were excluded from the study. A study end point was reached if complete re-epithelialisation of an ulcer crater had occurred.

ETHICAL CONSIDERATIONS

There is now a generally held view that placebos should not be recommended for use in trials on peptic ulcers.[8,9] Indeed, in many countries it might be considered unethical to continue NSAID treatment after serious gastric and duodenal lesions have been identified. Therefore, and as a result of discussion with consultants concerned in the present study, it was decided not to include a placebo treated control group. It was concluded that such patients would

Department of Medicine, Queen Mary's Hospital, Sidcup, Kent DA14 6LT
M J Lancaster-Smith

Medical Division, Glaxo Laboratories Ltd, Greenford, Middlesex
M E Jaderberg
D A Jackson

Correspondence to:
Dr M J Lancaster-Smith.

Accepted for publication
24 April 1990

be exposed to an unacceptable additional risk.

Approval was obtained from the appropriate ethics committee in all cases and before entry every patient gave informed consent. The trial was conducted in accordance with the Declaration of Helsinki, 1983.

STATISTICAL METHODS

Ulcer analysis

Patients were classified at entry according to whether they had a gastric ulcer but no duodenal ulcer, a duodenal ulcer but no gastric ulcer, or both gastric and duodenal ulcers. Each patient category was analysed separately.

An ulcer was defined as a definite epithelial disruption of the mucosa greater than 0·5 cm in diameter and healing as complete re-epithelialisation of the ulcer crater. Only healed and unhealed patients, as recorded at the follow up endoscopies, were included in the comparison. Data were carried forward for patients who healed before week 12, but data for patients who were withdrawn or failed to attend or who were deemed to be protocol violators during the trial were not carried forward. Thus cumulative healing rates are quoted in this report.

Fisher's exact test was applied to compare the healing rates in the continue NSAID and stop NSAID groups after four, eight, and 12 weeks. All tests were two tailed. Differences between the groups were considered to be statistically significant if p was less than or equal to 0·05.

Prognostic factors

Logistic regression analysis was applied to the healing rates at four, eight, and 12 weeks. The analysis was performed on the ulcer population for those patients with only gastric ulcers and repeated for those patients with only duodenal ulcers. This technique examined the effect of continuing NSAID treatment on ulcer healing while adjusting for the effect of six prognostic factors – arthritic state, age, sex, smoking state at entry, alcohol consumption at entry, and size of ulcer.

Results

Altogether 321 patients were referred and of these, 110 were ineligible for inclusion. The remaining 211 patients had ulcers, of which 21 were subsequently withdrawn due to protocol violations. Both treatment groups were comparable with respect to age, sex, smoking habits, alcohol intake, and duration of arthritic disease (Table I).

TABLE I *Details of patients in study (percentages in parentheses)*

	Non-steroidal anti-inflammatory drugs	
	Continued (n=96)	*Stopped (n=94)*
Mean age (years)	65	65
Age range (years)	25–85	26–89
Men	33 (34)	35 (37)
Women	63 (66)	59 (63)
Non-smoker	69 (72)	67 (71)
No alcohol consumption	50 (52)	35 (37)
Osteoarthritis	67 (70)	73 (78)
Mean duration (months)	80	88
Rheumatoid arthritis	27 (28)	20 (21)
Mean duration (months)	101	104
Osteoarthritis and rheumatoid arthritis	2 (2)	1 (1)

ULCER ANALYSIS

On entry to the study 190 patients had peptic ulcers, of which 84 were gastric and 98 duodenal. Eight patients had both gastric and duodenal ulcers. The distribution of ulcers was comparable in the two treatment groups (Table II).

Gastric ulcers

At each study interval there was a trend for more ulcers to have healed in the group that stopped NSAID treatment compared with those who continued. The healing rates in the group that stopped were 71%, 95%, and 100% at four, eight, and 12 weeks respectively, compared with 54%, 63%, and 79% in those who continued treatment. These differences were significant at eight weeks (p=0·001) and 12 weeks (p=0·004) but not at four weeks (p=0·159) (Fig 1).

Duodenal ulcers

More duodenal ulcers were healed at each stage of the study in the patients who stopped NSAID treatment compared with the group that continued NSAID treatment. The healing rates in those who stopped treatment were 74%, 100%, and 100% at four, eight, and 12 weeks respectively compared with 57%, 84%, and 92% in the group that continued treatment. The four week difference was not significant. The difference at eight weeks was significant (p=0·006), but by 12 weeks such a difference was not detected due to the high healing rates of both regimens (Fig 2).

Gastric and duodenal ulcers

Three of the eight patients who had both gastric and duodenal ulcers failed to attend for follow up visits. Of the remaining five patients, three discontinued NSAID treatment and were healed within eight weeks. One of the two patients who continued taking NSAIDs was completely healed at four weeks and the other remained unhealed throughout the trial.

PROGNOSTIC ULCER FACTORS

The logistic regression analysis showed no significant differences between prognostic factors for those patients with gastric ulcer except a confirmation of the difference in healing rates

TABLE II *Diagnosis at entry to study*

	Non-steroidal anti-inflammatory drugs		
Type of ulcer	*Continued*	*Stopped*	
Gastric No (%)	37 (39)	47 (50)	84 (44)
Duodenal No (%)	55 (57)	43 (46)	98 (52)
Gastric+duodenal No (%)	4 (4)	4 (4)	8 (4)
Total	96	94	190

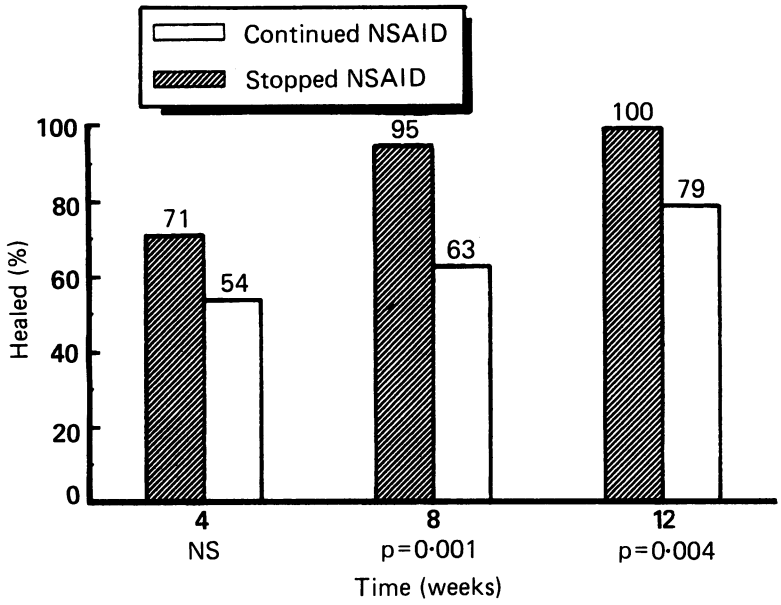

Figure 1: Healing rates in patients with gastric ulcers. NSAID=non-steroidal anti-inflammatory drugs.

between the two treatment groups at eight weeks (p=0·0007), described above. The logistic regression analysis, however, showed that the odds on patients with osteoarthritis having their duodenal ulcer healed by the end of the fourth week taking ranitidine was significantly better than for those patients with rheumatoid arthritis or a combination of the two diseases (p=0·03). The duodenal ulcer healing rates at eight and 12 weeks were too high to enable meaningful evaluation of the prognostic factors. No particular NSAID was associated with persistent ulceration or slower healing rates.

GASTROINTESTINAL SYMPTOMS SCORE ANALYSIS

Symptom scores from the 190 ulcer patients were analysed. Epigastric pain, heartburn, nausea, and vomiting improved appreciably in both treatment groups during the study. Epigastric pain was the most common complaint (55%). The occurrence of this symptom decreased greatly at subsequent visits whether patients continued or stopped NSAID treatment; 96% of patients in the group that stopped and 89% in the group that continued recorded mild or no pain after four weeks' treatment with ranitidine. Of the patients for whom severe pain was recorded on entry to the trial, more than 90% showed an improvement at subsequent visits whichever study group they were in.

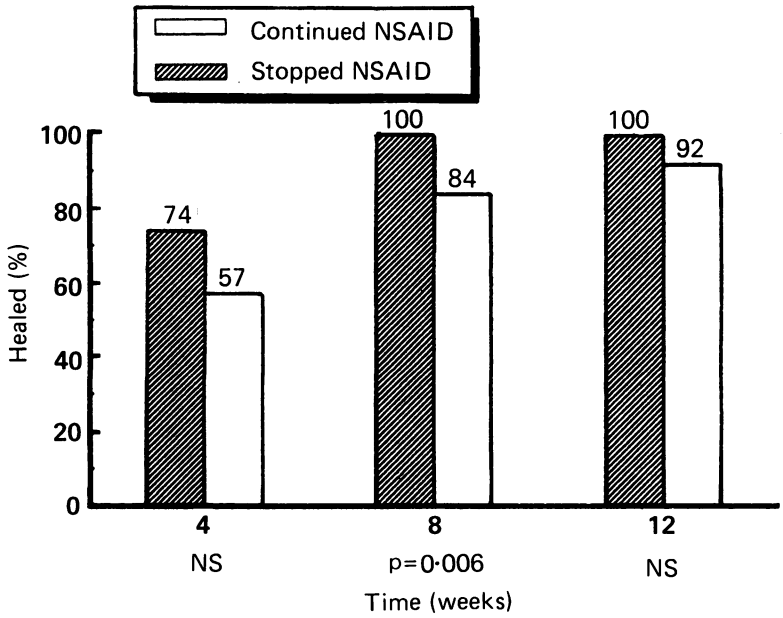

Figure 2: Healing rates in patients with duodenal ulcers. NSAID=non-steroidal anti-inflammatory drugs.

SAFETY EVALUATION

A total of 22 (7%) patients out of 321 referred reported 32 adverse events. Ten per cent in the group continuing NSAID treatment experienced 24 events; 4% in the group that stopped experienced eight events. Eight deaths were recorded. The death of an 83 year old woman in this study may be attributed to NSAID treatment. It is clinically evident that this patient, with a visible vessel in the ulcer crater, was not eligible for inclusion in the study. The remaining deaths in the study were not attributed to NSAIDs or the trial drugs.

Discussion

The high healing rates at four and eight weeks for both gastric and duodenal ulcers in patients who discontinued NSAID treatment were comparable to those found in many trials of H_2 receptor antagonist drugs in patients with peptic ulcers not associated with NSAID treatment.[10 11] When the NSAID was stopped for the duration of treatment 100% of duodenal ulcers healed after eight weeks and 100% of gastric ulcers healed after 12 weeks. These results therefore do not support the concept that NSAID associated ulcers – even after NSAIDs have been withdrawn – are less responsive to ulcer healing drugs than ulcers not originally associated with NSAID treatment.

By contrast, continuing NSAID treatment after endoscopic diagnosis of an ulcer reduced the healing rates of both gastric and duodenal ulcers. But, despite patients continuing to take the NSAID, healing rates in this group were still relatively high, with 79% and 92% respectively of gastric and duodenal ulcers healing after 12 weeks' treatment. These results are comparable to healing rates of 77–81% at eight to nine weeks for patients taking NSAIDs and ulcer healing treatment together in small[9 12] or uncontrolled studies.[13 14] Furthermore, in all of these studies the 70% or better healing rates for patients continuing to take NSAIDs compares favourably with rates of less than 40% found for ulcer healing with placebo treatment.[10 11]

That duodenal ulcers heal successfully in patients who continue to take NSAIDs is perhaps predictable as ranitidine given prophylactically reduces the incidence of duodenal ulceration in arthritic patients taking NSAIDs.[15] In the same study gastric ulceration was not prevented by ranitidine, suggesting that acid might be a less important factor in the pathogenesis of NSAID induced gastric ulcer.

The present study, however, suggests that the

suppression of acid secretion may be accompanied by healing of pre-existing gastric ulcers despite continuing NSAID treatment. Furthermore, the study showed progressive rates of gastric ulcer healing with time, and it seems possible that extending ranitidine treatment beyond three months might have achieved still higher rates of healing.

The estimation of symptom improvement was not the major objective in this study, as patients were eligible for entry whether or not symptoms of dyspepsia were present. In addition, symptoms were not monitored daily but were assessed retrospectively at each clinic visit. Although difficult to analyse adequately after the fourth week of treatment, there was a general, pronounced alleviation of symptoms irrespective of whether the NSAID was continued or not.

The H_2 receptor antagonists available have a good record for tolerance and low incidence of adverse events.[16] On the other hand NSAIDs are associated with a high incidence of adverse events. This study, not surprisingly, detected a higher frequency of adverse events in patients continuing NSAID treatment than in those who stopped treatment.

NSAID associated gastric and duodenal ulcers can be treated effectively with ranitidine 150 mg twice daily, and when NSAID treatment is withdrawn rates of healing are strictly comparable to those reported for ulcers not associated with these drugs.[10 11] Although healing is slowed by continuing NSAID treatment, substantial rates of healing may still be achieved.

We thank the following physicians for contributing to and participating in the trial: W R Burnham, M G Bramble, D S Rampton, W S Hislop, R D Montgomery, J H B Saunders, P D Fairclough, A G Vallon, R J Salem, J McLoughlin, J N Blackwell, J Dawson, C S Humphrey, D L Dowling, A D Walls, K R Hine, M G Ashton, R J Dickinson, D R Foster, K G Wormsley, D E Sibson, C O Record, C M Bate, A J Levi, S N Booth, J D Kinlock, A K Banerjee, J MacIntyre, E T Swarbrick, R T Orchard, M B McIllmurray, D A Griffiths, D L Carr-Locke, D R Sutton, A D Irving, V Melikian, C White, R J Russel, R Ferguson, J P Bolton, M O Rake, K R Palmer, P M Smith, A D Beattie, J R Ball, I C Forgacs, R J Walker, K G Porter, and G E Foster.

1 CSM update. Non-steroidal anti-inflammatory drugs and serious gastrointestinal reactions. *BMJ* 1986; **292**: 614.
2 Coles LS, Fries JF, Kraines RG, *et al.* From experiment to experience: side effects of non-steroidal anti-inflammatory drugs. *Am J Med* 1983; **74**: 820–8.
3 Geczy M, Peltier L, Wolbach R. Naproxen tolerability in the elderly; a summary report. *J Rheumatol* 1987; **14**: 348–54.
4 Hawkey CJ, Rampton DS. Prostaglandins and the gastrointestinal mucosa: are they important in its function, disease or treatment? *Gastroenterology* 1985; **89**: 1162–88.
5 Bennett A, Collins P, Taveres I. Human gastric mucosal damage by anti-inflammatory drugs. *Dig Dis Sci* 1986; **31** (suppl): 483.
6 Hogan D, Thomas F, Isenberg J. A single dose of cimetidine prevents aspirin induced gastric damage in man. *Dig Dis Sci* 1986; **31** (suppl): 481.
7 Levine RA, Schwartzel EM. Effects of indomethacin on basal and histamine stimulated human gastric acid secretion. *Gut* 1984; **25**: 718–22.
8 Peterson WL, Elashoff J, Placebos in clinical trials of duodenal ulcer: the end of an era? *Gastroenterology* 1980; **79**: 585–8.
9 Loludice T, Saleem T, Lang J. Cimetidine in the treatment of gastric ulcer induced by steroidal and non-steroidal anti-inflammatory agents. *Am J Gastroenterol* 1981; **75**: 104–10.
10 Kelly KA, Malegelada J-R. Medical and surgical treatment of chronic gastric ulcer. In: Isenberg JI, Johansson C, eds. *Clinics in gastroenterology. Vol 13. Peptic ulcer disease.* London: Saunders, 1984: 621–34.
11 Thomas JM, Misiewicz G. Histamine H2-receptor antagonists in short and long term treatments of duodenal ulcer. In: Isenberg JI, Johansson C, eds. *Clinics in gastroenterology. Vol 13. Peptic ulcer disease.* London: Saunders, 1984: 501–41.
12 Manniche C, Malchow-Moller A, Andersen JR, *et al.* Randomised study of the influence of non-steroidal anti-inflammatory drugs on the treatment of peptic ulcer in patients with rheumatic disease. *Gut* 1987; **28**: 226–9.
13 Croker JR, Cotton PB, Boyle AC, Kinsella P. Cimetidine for peptic ulcer in patients with arthritis. *Ann Rheum Dis* 1980; **39**: 275–8.
14 Bijlsma JWJ. Treatment of NSAID-induced gastrointestinal lesions with cimetidine: an international multicentre collaborative study. *Aliment Pharmacol Therap* 1988; **25**: 85–96.
15 Ehsannullah RSB, Page MC, Tildesley G, Wood JR. Prevention of gastroduodenal damage induced by non-steroidal anti-inflammatory drugs: controlled treatment of ranitidine. *BMJ* 1988; **297**: 1017–21.
16 Penston JG, Wormsley KG. Adverse reactions and interactions with H2-receptor antagonists. *Medical Toxicology* 1986; **1**: 192.