

# Randomised study of the influence of non-steroidal anti-inflammatory drugs on the treatment of peptic ulcer in patients with rheumatic disease

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**SUMMARY** Sixty-seven patients with rheumatic disease, treated with non-steroidal anti-inflammatory drugs (NSAIDs), entered a controlled trial with a diagnosis of duodenal (n=51), gastric (n=14), or gastric and duodenal (n=2) ulcers. The main objectives of the study were a comparison of ranitidine and sucralfate in ulcer treatment, and to observe the influence of continued NSAID administration during peptic ulcer therapy. Ulcers healed within nine weeks in 52 patients. The mean healing time was similar in 27 patients given ranitidine 150 mg bd (4.9 weeks) and 25 patients given sucralfate 1 g qid (4.6 weeks). In patients with unhealed ulcers after nine weeks of treatment, healing was obtained in seven after further therapy for 3-9 weeks. Of the 30 patients who continued NSAIDs during treatment with either ranitidine or sucralfate, 23 ulcers healed (mean healing time: 5.0 weeks). Of 32 patients in whom NSAIDs were stopped, ulcer healing was documented in 29 (mean healing time: 4.6 weeks). The difference in healing rates was not statistically significant ( $p > 0.10$ ). The outcome of ulcer treatment did not differ in patients with rheumatoid arthritis and patients suffering from osteoarthritis. During a 12 month follow up 14 symptomatic ulcer recurrences were recorded.

Mucosal lesions of the stomach or duodenum are seen frequently in patients taking NSAIDs. The incidence of peptic ulcer has been reported to lie between 17% and 31%<sup>1-3</sup> and elderly patients may be especially susceptible to NSAID associated peptic ulcer perforation.<sup>4</sup> A variety of problems, such as lack of control groups, few prospective studies, multidrug therapy, etc, make it very difficult to reach firm conclusions as to the ulcerogenicity of NSAIDs<sup>5-6</sup> except for unbuffered aspirin, which is considered ulcerogenic.<sup>5,7</sup> In a recent paper, however, it was reported that bleeding complications

from peptic ulcers in patients over 60 years was correlated with use of non-aspirin NSAIDs.<sup>8</sup> The possible influence of NSAIDs on the ulcer healing process has been evaluated in only a few, mainly retrospective studies including a limited number of patients.<sup>9-11</sup>

This study compares the effects of ranitidine or sucralfate on the healing of peptic ulcer in patients with rheumatic disease, half of whom were randomised to continue on NSAID, while the remainder were given alternative analgesic therapy. After ulcer treatment patients were followed up for 12 months.

## Methods

### PATIENTS

Sixty seven consecutive patients from the four participating departments were included, 38 with

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Table 1 Inclusion and exclusion criteria

<b>Inclusion criteria</b>	
Rheumatic disorder continuously treated with NSAID	
Dyspepsia and endoscopically verified gastric or duodenal ulcer	
Ulcer diameter >3 mm	
<b>Exclusion criteria</b>	
Informed consent not obtained	
Operation for peptic ulcer within the last 3 months	
Pregnancy, lactation	
Severe concomitant disease	
Treatment with prednisolone >15 mg/day	
Ulcer perforation or other complications to ulcer disease	
Patient's wish to withdraw	

definite or classical rheumatoid arthritis according to ARA criteria, 24 with osteoarthritis based on clinical and radiological findings and five patients with other diagnoses (degenerative lumbar disc disease three, ankylosing spondylitis one, psoriatic arthritis one). The mean pretrial duration of NSAID treatment was 5.2 years (range 0.3–20) for patients with rheumatoid arthritis and 5.5 years (range 0.1–15) for patients with osteoarthritis or other rheumatic disorders. Twenty six patients were smokers. Inclusion and exclusion criteria are shown in Table 1. The various NSAIDs administered at the time of entry into the study are listed in Table 2. Five patients received penicillamine, 375–625 mg/day, and nine patients prednisolone, 15 mg/day or less.

After endoscopic diagnosis, patients were allocated to one of four treatment regimens according to a block randomisation procedure: (a) Ranitidine, 150 mg bd; continued administration of NSAID. (b) Sucralfate, 1 g qid; continued administration of NSAID. (c) Ranitidine 150 mg bd; withdrawal of NSAID. (d) Sucralfate 1 g qid; withdrawal of NSAID. (Figure.)

Antacids were allowed but not recommended; any antacid consumption was noted in the patient diary. Level of discomfort from ulcer symptoms was

Table 2 List of NSAID administered in the rheumatic disease patients at time of entry into study

Drug	Dose (mg/day)	Patients (n)
Acetylsalicylic acid	2000–4000	5
Azapropazone	600–900	5
Diclofenac	100–200	10
Fenbufen	900	1
Fenoprofen	1800	1
Ibuprofen	800–1600	15
Indomethacin	100–150	9
Ketoprofen	100	1
Naproxen	500–1000	10
Piroxicam	10–20	9
Sulindac	300	1
		67

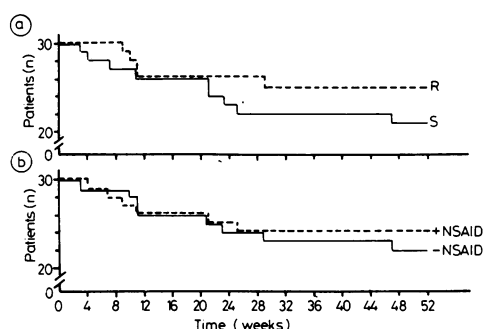


Figure Recurrences of peptic ulcer in 60 rheumatic disease patients according to randomisation at time of entry into study. (a) shows relapses in patients randomised to ranitidine (R) or sucralfate (S); (b) shows relapses in patients randomised to continued administration of NSAID or withdrawal of NSAID during ulcer treatment. The two patients who died during follow up are not shown in this Figure.

recorded daily on a 10 cm long visual analogue scale (0=no discomfort; 10=very severe discomfort). Three patients with severe arthritic pain at night received morphine analogues for a limited period of time; two of them had occasional treatment with opiates before inclusion in the trial.

Ulcer healing was recorded endoscopically every three weeks. The endoscopist had no knowledge of the drugs being taken. If an ulcer had not healed after nine weeks, the treatment was changed to the other antiulcer drug, but NSAID treatment or non-treatment was not changed.

After ulcer healing the patients were followed for 12 months, attending the rheumatological out-patients clinics at regular intervals. Patients in whom NSAIDs had been stopped were free to start such treatment. Patients developing dyspepsia during the follow up period were re-endoscoped to confirm the diagnosis.

#### DURATION OF STUDY AND STATISTICS

The study was planned to include 80 patients. For practical reasons, however, entry was closed after two years when 67 patients had been entered. Chi-square test with Yates's correction for continuity was used. A 5% significance level was chosen.

#### ETHICAL CONSIDERATIONS

We did not think it justified to include a placebo-treated group because of the many effective and well tolerated antiulcer drugs available today.<sup>12</sup> The investigation was approved by the regional ethical committees, and all patients gave their informed consent.

## Results

Of the 67 patients recruited to the study, 51 had a duodenal or prepyloric ulcer, 14 had a gastric ulcer, and two had both duodenal and gastric ulcers. Eleven duodenal ulcers (22%) and five gastric ulcers (36%) were of  $\geq 10$  mm diameter; these were equally distributed in the four treatment groups. Five patients were excluded during the first three weeks of treatment because of lack of cooperation or claims of adverse reactions without any clinical findings (two), cerebral haemorrhage (one), poor general condition (one), and minor but persistent gastrointestinal bleeding (one).

Sixty two patients were available for analysis: 34 with rheumatoid arthritis (15 men; median age 67 (range 43–87) years) and 28 with non-rheumatoid arthritis (24 with osteoarthritis and four with other rheumatic diseases; 12 men; median age 71 (range 35–85) years).

Table 3 shows that the proportion of healed ulcers and the mean healing time were similar in patients given either ranitidine or sucralfate. In 10 patients with persistent ulcer after nine weeks of treatment, continued therapy with the alternative anti-ulcer drug resulted in healing in seven patients after a further three to nine weeks of treatment.

Table 4 shows the results of ulcer treatment in patients who continued on a NSAID in comparison with patients in whom the NSAID was discontinued. There were no differences in the healing rates and the mean healing time between the various subgroups. The 14% difference between NSAID takers and non-takers in overall healing rate is not statistically significant ( $\chi^2=2.23$ ;  $p>0.10$ ).

Median values for the visual analogue scale of ulcer symptoms were 2.8 (range 0–10) at the time of entry; 1.4 (range 0–8) after one week of treatment, and 0.7 (range 0–6) after three weeks. Very few patients had dyspeptic complaints after the initial three weeks of ulcer therapy. Thirty patients, with an equal representation in the treatment groups, reported antacid use equivalent to a neutralising capacity of 15–50 mmol/day (24 patients) and from 50–75 mmol/day in the remainder. Antacid consumption was unusual after the first three weeks of ulcer therapy.

During the 12 months follow up 14 of 32 patients randomised to withdrawal of NSAIDs, resumed this treatment whereas 15 of 30 patients randomised to continued NSAIDs gave up the same. Symptomatic ulcer recurrences were documented in 14 patients (eight smokers), nine of whom took NSAIDs at the time of relapse. The recurrences were evenly distributed in the four randomisation groups (Figure). Ulcer re-healing was shown endoscopically in 10 of these patients after three to six weeks of treatment with either of the two ulcer regimens. Two patients died during the follow up, but death could not be associated with complications of the peptic ulcer disease.

There were very few and non-specific complaints of adverse reactions possibly related to ranitidine or sucralfate. Routine laboratory screening tests did not show any abnormalities, except for a transient rise in S-creatinine in one patient.

## Discussion

Withdrawal of salicylates and other NSAIDs is generally recommended to a patient with a peptic ulcer. This trial has shown that ulcer treatment can be accomplished in spite of continuous administration of NSAIDs. The patients received a broad spectrum of NSAIDs and five were given aspirin, which is likely to cause more mucosal damage than the other NSAIDs.<sup>13</sup> The conclusions of our study would be unchanged, even if the five aspirin takers had been excluded from the analyses.

Sucralfate, a non-absorbable 'cytoprotective drug' with proven efficacy in the treatment of peptic ulcer<sup>14</sup> was compared with ranitidine, a potent H<sub>2</sub>-receptor blocker.<sup>15</sup> Both drugs can be expected to heal 85–90% of peptic ulcers after eight weeks of treatment. The randomisation procedure guaranteed an even distribution of patients in the four treatment groups as well as a balanced representation of the two major rheumatic disorders, rheumatoid arthritis and osteoarthritis, within these groups. It is therefore permissible, in later calculations, to combine the diagnostic and/or treatment groups as appropriate.

Virtually, the same healing rate and mean healing time were found for ranitidine and sucralfate. The

Table 3 Results of peptic ulcer treatment with ranitidine or sucralfate for up to nine weeks in 62 patients with rheumatic disease.

	Ranitidine			Sucralfate		
	Patients (n)	Healed (n)	Mean time to healing (weeks)	Patients (n)	Healed (n)	Mean time to healing (weeks)
RA	18	15 (83%)	4.6	16	12 (75%)	4.0
OA	14	12 (86%)	5.3	14	13 (93%)	5.1
Total	32	27 (84%)	4.9	30	25 (83%)	4.6

RA: Rheumatoid arthritis; OA: Osteoarthritis.

Table 4 Influence of NSAID on peptic ulcer treatment in 62 patients with rheumatic disease. No statistically significant differences between maingroups or subgroups.

	Continued NSAID				Withdrawal of NSAID			
	Ratio of healed ulcers		Meantime to healing (weeks)		Ratio of healed ulcers		Meantime to healing (weeks)	
	GU	DU	GU	DU	GU	DU	GU	DU
Small ulcers (diam <1.0 cm)	1/2 (50%)	14/15 (93%)	9.0	4.0	3/3 (100%)	12/12 (100%)	3.0	3.0
Large ulcers :diam ≥1.0 cm)	2/4 (50%)	6/9 (67%)	7.5	6.0	3/4 (75%)	11/13 (85%)	8.0	5.7
Subtotal	3/6 (50%)	20/24 (83%)			6/7 (86%)	23/25 (92%)		
Total: GU+DU	23/30 (77%)		5.0		29/32 (91%)		4.6	

GU: Gastric ulcer; DU: Duodenal ulcer.

proportion of healed ulcers rose from 31/62 (50%) at three weeks to 52/62 (84%) at nine weeks. This corresponds with results from studies involving non-rheumatic patients. Non-steroidal anti-inflammatory drug takers with gastric ulcers tended to heal more slowly, or not at all within nine weeks, but seven of 10 persistent ulcers did heal after a total of 12–18 weeks of treatment.

Asymptomatic ulcer recurrences were not registered. This is in accordance with the entry criteria of dyspepsia. Excluding the two patients who died during follow-up, the recurrence rate was 0.23 (95% confidence limits: 0.13–0.36). This is probably a minimum estimate as can be judged from studies in non-rheumatic patients<sup>16</sup> which, however, often include asymptomatic ulcers found at endoscopy at fixed intervals during the follow-up period.

From the results of this study, we suggest that NSAIDs should not be stopped if a peptic ulcer is diagnosed in a patient with active rheumatic disease. According to our experience, ulcer therapy can be carried through effectively in parallel with anti-inflammatory treatment. Our data show that ranitidine and sucralfate have equal ulcer-healing efficacy and that there is no difference regarding the outcome of ulcer treatment in patients with either rheumatoid arthritis or osteoarthritis.

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