

## Treatment of duodenal ulcer with pirenzepine and cimetidine

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*Austrian Multicentre Study\**

**SUMMARY** The purpose of this single blind controlled multicentre trial was to compare the relative effectiveness of pirenzepine and cimetidine in healing endoscopically proven duodenal ulcers. One hundred and twenty six patients with duodenal ulcer were treated with a daily dose of 100 mg pirenzepine (50 mg each before breakfast and before the evening meal), and 128 patients were treated with 1000 mg cimetidine (200 mg with breakfast, lunch, and evening meal and 400 mg at bedtime). Endoscopy was repeated after four weeks by an endoscopist who had not been informed about the treatment. Pirenzepine showed a healing rate of 64.3%, cimetidine one of 73.4%. This difference is not statistically significant (one-sided test:  $\chi_1^2 = 2.48$ ). After four weeks a higher proportion of first ulcers than of recurrent lesions was healed. Pain relief was rapidly achieved with both drugs. A significant trend in favour of cimetidine may, however, not be clinically relevant considering the small difference in the absolute numbers of pain free days and nights. Adverse effects were rare and reversible. We conclude that the efficacy of pirenzepine is similar to that of cimetidine in healing duodenal ulcers.

Although anticholinergics have been used for decades their effectiveness in peptic ulcers is still doubtful,<sup>1</sup> and their clinical use is limited on account of side effects because of the similar affinity of the drug for the muscarinic receptors of both the parietal cells and other organs.

Pirenzepine a newly developed antimuscarinic drug,<sup>2</sup> differentiates between the muscarinic receptors in various organs.<sup>3,4</sup> It appears to possess a high affinity for the parietal cells while only binding weakly with the receptors of other exocrine glands or smooth muscles. A daily dose of 100-150 mg pirenzepine effectively accelerates the healing of duodenal ulcers,<sup>5-7</sup> while a dose of 50-75 mg was not effective.<sup>7</sup> Controlled studies comparing

pirenzepine with cimetidine have shown contradictory results. A Swiss group<sup>8,9</sup> did not find any significant differences in the healing rates of duodenal ulcer treated with either 75 mg pirenzepine, 1000 mg cimetidine or placebo. In contrast, D'Imperio *et al*<sup>10</sup> showed the superiority of 150 mg pirenzepine or 1000 mg cimetidine over placebo in duodenal ulcer, but no difference between the active drugs. Other Italian groups<sup>7</sup> found similar healing rates when comparing 100 mg pirenzepine with 1000 mg cimetidine.

These studies may indicate a dose dependent action of pirenzepine. A controlled trial comprising a sufficient number of cases of duodenal ulcer was therefore conducted to compare the relative effectiveness of 100 mg pirenzepine and 1000 mg cimetidine daily.

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### Methods

#### PATIENTS

The study was conducted as a randomised controlled multicentre trial in 10 centres. After having given

informed consent, a total of 274 patients with endoscopically proven duodenal ulcer entered the trial which was terminated as soon as the originally fixed minimum of 250 evaluable case histories had been obtained.

Twenty cases had to be withdrawn because of exclusion criteria or because the patients had not returned for follow up visits or endoscopic examination. At the end of the study 126 patients had been treated with pirenzepine and 128 patients with cimetidine. The two treatment groups (Table 1) were comparable with regard to age, sex ratio, body weight, history, and smoking habits.

Treatment consisted of 50 mg pirenzepine 15 minutes before breakfast and 50 mg before the evening meal, or 200 mg cimetidine with breakfast, 200 mg with lunch, 200 mg with the evening meal, and 400 mg at bedtime. For pain relief, an aluminium phosphate gel\* was allowed *ad libitum*.

Clinical assessments were made after one, two, and four weeks. Any changes in symptoms and spontaneously reported side effects were recorded. After four weeks gastroscopy was repeated by an endoscopist who had not been informed of the treatment, nor of the results (single-blind design).

All patients were randomly allocated to one of the two treatment groups. Randomisation was performed separately for each centre, and every patient received his specially numbered batch of tablets. The following patients were excluded: pregnant women, alcoholics, hospitalised patients, and those with severe diseases besides duodenal ulcer, patients with expected non-compliance as well as patients with stress ulcers after burn or accident, drug induced ulcers, ulcers after gastric resection or vagotomy, ulcers with diameters of more than 3 cm, ulcers occurring during maintenance treatment with cimetidine, pretreatment with effective doses of cimetidine or carbenoxolone for more than three days, as well as patients with severe complications such as haemorrhage or stenosis.

All patients were instructed to record in their diary charts the daily intake of the trial medication, ulcer pain, the daily number of antacids, and any changes in their condition. All remaining tablets had to be returned and were counted. No special diet was recommended, but patients were advised to reduce smoking and avoid alcohol.

#### STATISTICS

The zero hypothesis to be tested was that pirenzepine and cimetidine are equally effective in healing ulcers. The healing rate after four weeks of treatment with cimetidine was assumed to be 75–

Table 1 Comparison of the two treatment groups

	Pirenzepine	Cimetidine
Age (yr): (m ± SD)	46.9±14.6	50.0±13.6
range	19–84	19–81
Sex: male (%)	72	69
female (%)	28	31
Body weight (kg) (m ± SD)	72.2±12.3	71.9±12.3
History: first ulcer (%)	18	18
recurrent ulcer (%)	82	82
Smoker (%)	62	58

90%. A higher efficacy for pirenzepine was considered to be unlikely. A difference in the healing rates of about 10% was expected to be found in this trial. Therefore a one sided formulated  $\chi^2$  test for a 2×2 contingency table was applied. A minimum number of 125 patients in each group was scheduled to achieve a power of ~0.5.

A 2×k contingency table with ordinal classification was used to assess the efficacy of the two drugs as expressed by the concomitant variables 'ulcer pain' and 'antacid consumption'. A  $\chi^2$  test was applied to determine linear trend, and a log linear model was used to compare subgroups (age, first and recurrent ulcers).

#### Results

##### HEALING RATE

After four weeks of treatment with pirenzepine 81 of 126 ulcers (64.3%) were healed. Treatment with cimetidine was effective in healing 94 out of 128 ulcers (73.4%). The healing rates of pirenzepine and cimetidine thus differ by 9.1%. As the  $\chi^2$  value is 2.48 this difference is not statistically significant ( $p>0.05$ ) (Table 2). The healing rate for first episodes of endoscopically proven duodenal ulcer amounted to 74% after treatment with pirenzepine, and to 91% after treatment with cimetidine. With both compounds the healing rate of recurrent ulcers was significantly ( $p<0.05$ ) lower, 62% and 70% respectively, but there was no significant difference between the two treatment groups (Table 3). Grouping patients into 10 year age groups did not reveal any significant influence of age on the healing rate. In neither group could smoking be shown to have an influence on ulcer healing.

##### PAIN RELIEF

Pain relief was achieved with both drugs. In the week before treatment patients had only 1.4±2.3 and 1.0±1.9 days without pain in the pirenzepine group and cimetidine group respectively. Eight per cent of the patients on pirenzepine and 5% of the

\* Phosphalugel®. Dr Kolassa GmbH, Vienna, Austria

**Table 2** Healing rate of duodenal ulcer during a four week treatment with pirenzepine or cimetidine in the 10 participating centres

Centre	Pirenzepine			Cimetidine		
	Patients (no)	Healed		Patients (no)	Healed	
	n	n	%	n	n	%
1	14	6	43	15	7	47
2	5	4	80	5	5	100
3	10	6	60	9	6	67
4	20	13	65	20	16	80
5	3	2	67	2	1	50
6	4	2	50	5	5	100
7	11	4	37	12	10	83
8	4	4	100	5	5	100
9	5	4	80	5	4	80
10	50	36	72	50	35	70
Total	126	81	64.3	128	94	73.4

$\chi_1^2 = 2.48$  NS

patients on cimetidine did not complain about pain at the time of entry into the study. In the fourth week patients were free of pain on  $6.1 \pm 1.7$  days and  $6.3 \pm 1.5$  days respectively. No information was available about pain at night in the pretreatment period. Pain relief at night was parallel to the effect during the day. By the end of the first week, 49 (39%) patients on pirenzepine and 57 (45%) patients on cimetidine had no pain at all at night. In the last week of the trial 94 (75%) pirenzepine treated and 104 (82%) cimetidine treated patients were free of pain for all seven nights of the week.

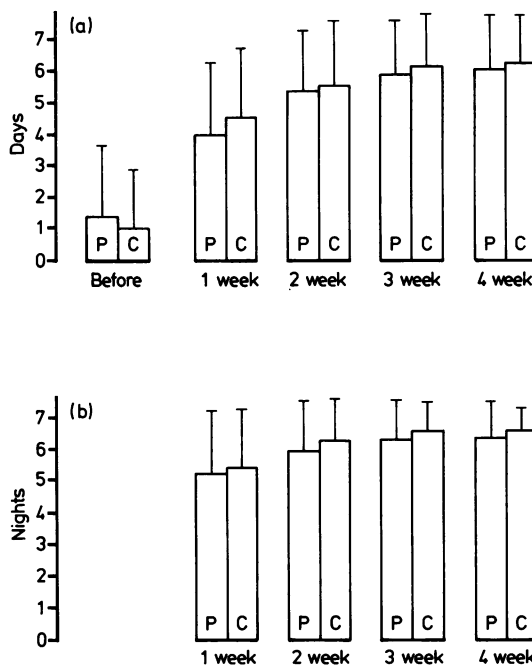
If, however the number of pain free days are counted for each patient individually, and the figures of the first and fourth week are compared with the pretreatment period the linear trend analysis indicates a trend in favour of cimetidine (first week:  $\chi_1^2 = 9.34$ ,  $p < 0.01$ ; fourth week:  $\chi_1^2 = 6.09$ ,  $p < 0.05$ , one-sided). (Figure).

For pain free nights in the fourth week once more a trend in favour of cimetidine ( $\chi_1^2 = 4.11$ ,  $p < 0.05$ ) could be detected.

**Table 3** Influence of recurrency on ulcer healing rate during pirenzepine and cimetidine treatment

	Pirenzepine			Cimetidine		
	n	Healed		n	Healed	
n		%	n		%	
First ulcer	23	17	74	23	21	91
Recurrent ulcer	103	64	62	104*	73	70

\* No information for one patient.



**Figure** Number of days and nights free of pain before and during treatment with pirenzepine (P) and cimetidine (C) (mean  $\pm$  SD)

**ANTACID CONSUMPTION**

Overall intake of antacids was very low. In Table 4 patients are grouped according to antacid consumption per week. During the first week no significant difference between the two drugs was detectable. During the fourth week, however, patients on cimetidine showed slightly lower antacid consumption ( $\chi^2$  trend test:  $\chi_1^2 = 4.61$ ,  $p < 0.05$ ).

**COMPLAINTS AND SIDE EFFECTS**

All spontaneously reported complaints were recorded. Overall incidence of these symptoms was very low. In six patients on pirenzepine and in one

**Table 4** Number of patients classified according to antacid consumption during the first and last week of the trial

Doses of antacid per week	Week 1		Week 4	
	Pirenzepine n	Cimetidine n	Pirenzepine n	Cimetidine n
No antacids	36	49	83	97
$\leq 7$	49	40	28	24
$> 7$	38	37	13	5
No information	3	2	2	2

on cimetidine a dry mouth was observed, and slight impairment of vision occurred four times in the pirenzepine group. These adverse effects disappeared when trial medication was stopped. Only one patient had to be withdrawn from the study because of reversible severe impairment of eye accommodation. One patient on pirenzepine who complained about micturition difficulties had had prostatic hypertrophy before the treatment.

General abdominal symptoms (such as nausea, vomiting, heartburn, diarrhoea or constipation) which appeared during treatment were more likely to be due to the disease itself than to the treatment. Neither of the two drugs influenced the pulse rate blood pressure, appetite or body weight, red blood cells, renal, or liver function tests.

#### PATIENT'S COMPLIANCE

Patients' compliance was estimated by counting the unused tablets. The proportion of patients with exact intake of medication was higher in the pirenzepine than in the cimetidine group (Table 5).

#### Discussion

As the pharmacokinetic properties of pirenzepine and cimetidine differ considerably with regard to half-life<sup>11 12</sup> and absorption,<sup>12 13</sup> we felt that the two drugs required specific schedules and different intake frequencies. Pirenzepine was given twice daily, before breakfast and the evening meal, cimetidine was given four times a day with every meal and at bedtime. If double dummies had been used the seven tablets required per day might have had a bearing on patients' compliance.

In a single blind design, endoscopy was performed by an endoscopist who was not informed of the medication nor the clinical condition of patients. To avoid psychological influence by the trade mark, the packages handed to the patients were labelled with the generic name. In addition, we applied the most rigorous statistical standards, not only by using one-sided tests, but also by comparing trends in ulcer pain and antacid consumption. Separate randomisation for each centre has also helped to overcome the problems of interpreting the results.

This trial suggests that pirenzepine and cimetidine are similarly effective in healing duodenal ulcers. The healing rate is well in the range of 57–90% as can be seen from controlled studies carried out with cimetidine,<sup>14 15</sup> and well above the placebo healing rate in Vienna<sup>16</sup> of 32% after four weeks.

Our data fit into the hypothesis, recently summarised by Bianchi-Porro,<sup>7</sup> that ulcer healing may be accelerated only by a daily dose of 100 to 150 mg pirenzepine. Double blind studies using 100 mg pirenzepine or more daily have shown a significant improvement in ulcer healing.<sup>5 6</sup>

The ineffectiveness of pirenzepine in healing ulcers as shown in the Swiss comparative trial<sup>8 9</sup> might be explained by the low daily dose of only 75 mg pirenzepine. In addition, the number of patients (22 in each treatment group) was too small to allow a valid conclusion as to which treatment was superior; in fact the group of patients treated with cimetidine did not differ significantly from that treated with placebo.

As might be expected, 150 mg pirenzepine daily have been shown to be as effective as 1 g cimetidine (healing rate 72% and 75% respectively) and significantly better than placebo (36%), but this quantity causes considerable anticholinergic side effects.<sup>7</sup> In our trial, however, side effects were mild. The typical anticholinergic adverse reactions to pirenzepine were fully reversible, but careful monitoring of patients with accommodation disorders or prostate hypertrophy is suggested.

We consider the pirenzepine dose of 50 mg twice daily to be optimal as there is no essential difference in the healing rates of 100 mg and higher doses, but side effects occur less frequently. Furthermore, 150 mg pirenzepine were not more effective than 100 mg in inhibiting gastric acid secretion stimulated by modified sham feeding.<sup>17</sup>

Rapid pain relief was achieved with both drugs by day and by night. This was reflected by low antacid consumption in both groups. The statistical trend in favour of cimetidine seems to be small and of little clinical relevance. It might be accounted for in part by the fact that patients taking four doses of a drug daily tend to use less additional medication than patients on only two doses.

Pirenzepine was taken more regularly than cimetidine. This better compliance is due to the smaller number of doses, but is of importance in therapy. Omitting one dose of pirenzepine means reducing the daily dose to 50% while with cimetidine only 20% (or 40% at night) of the dose is omitted.

Pirenzepine, a drug with antimuscarinic action on the gastric mucosa may bring about a new assessment of anticholinergics in the treatment of peptic

Table 5 Proportion of patients with exact intake of medication (exact number  $\pm$  1 tablet per week)

	Exact intake of medication		
	1 week	2 week	3 and 4 week
Pirenzepine	75.9%	73.3%	68.8%
Cimetidine	63.2%	65.5%	43.4%

ulcers. Pirenzepine is a novel compound on account of its higher affinity to the muscarinic acetylcholine receptors in the gastric mucosa and because it does not affect the central nervous system (as does atropine) owing to its insolubility in lipids.

The results of the trial suggest that pirenzepine may be a valuable drug in healing duodenal ulcer.

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