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Clinical trial

Combined anti-muscarinic and H_2 receptor blockade in the healing of refractory duodenal ulcer. A double blind study

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SUMMARY The purpose of this study was to determine if pirenzepine and cimetidine given together was superior to cimetidine alone in inducing healing of refractory duodenal ulcers which remained unhealed after treatment with cimetidine or ranitidine for at least eight weeks. One hundred and thirty one patients from six centres were randomised to receive either cimetidine (C) 800 mg daily or cimetidine 800 mg plus pirenzepine (C+P) 100 mg daily under double blind conditions for six weeks. The healing rate was similar in both groups, irrespective of the method of calculation. On an intent-to-treat analysis, healing was: C 66%, C+P 57%, and amongst the patients who completed treatment, healing was 70% in both groups. Patients on C and on C+P experienced a similar decrease in daytime and in night time pain. Side effects of treatment, notably dry mouth and blurred vision, were reported more often by patients on combination therapy. Combined treatment with cimetidine plus pirenzepine in patients with refractory duodenal ulcer is unlikely to be beneficial.

Excessive nocturnal vagal drive has been thought to be important in the pathogenesis of duodenal ulcers which do not heal with histamine H_2 receptor blockade. Gledhill *et al*[1] observed that in such patients high dose cimetidine (2 g daily) did not suppress nocturnal acid secretion adequately while a standard dose (1 g daily), given together with atropine 4·8 mg daily, caused marked acid inhibition. They suggested that combined H_2 receptor and antimuscarinic receptor blockade may prove effective in treating patients with refractory duodenal ulcer. As atropine in the doses used frequently caused side effects, it was further suggested that a selective antimuscarinic, such as pirenzepine, would be better tolerated.

The hypothesis that combined cimetidine plus pirenzepine treatment accelerates the healing of duodenal ulcers refractory to H_2 receptor antagonists has been tested in this study.

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Methods

PATIENTS

Six centres in the UK and Eire participated. Outpatients aged 18 years and over were admitted to the study if they had an unhealed duodenal ulcer crater shown at endoscopy after continuous cimetidine 0·8 g–1·0 g daily or ranitidine 300 mg daily for at least eight weeks. Patients were excluded if they had coexistent gastric, prepyloric or pyloric canal ulcer; had previously undergone ulcer surgery other than oversewing of a perforation; serious disease which made attendance difficult; or conditions which contraindicated the use of pirenzepine or cimetidine.

Patients were allocated at random to receive either cimetidine (C) 400 mg (and placebo pirenzepine) twice daily or cimetidine 400 mg plus active pirenzepine (P) 50 mg twice daily on rising and at bedtime. The tablets (cimetidine 200 mg; pirenzepine 50 mg) were all white and of identical appearance. Treatment lasted six weeks but patients were given an extra week's supply of drugs in case appointments

were unavoidably delayed (cimetidine 196 tablets; pirenzepine 98 tablets).

The study was double blind, using a double dummy technique, the drugs being supplied in weekly 'blister' packets. Each day's drugs and each individual dose and its timing was clearly indicated; each 'blister' contained three tablets (two of cimetidine and one of pirenzepine or placebo). All patients received 120 Dijex antacid tablets (neutralising capacity 10 mmol per tablet) for pain relief. No other antiulcer treatment was allowed.

The presence of pain in the last week before entry to the study was noted. All patients were asked to keep a daily record of daytime and of night time pain in diary cards.

The patients were seen again after six weeks. No intermediate visits were booked, although patients were instructed to return immediately if any troublesome problem arose – for example, an increase in pain or development of side effects. Endoscopy was repeated to check for healing, which was defined as the complete disappearance of the ulcer crater regardless of the persistence of erosions or of duodenitis. The presence of pain before entry to the study was compared with that noted in the last week on treatment. Adverse events were recorded: patients were specifically questioned about anticholinergic side effects. Patients were asked to return all unused tablets, which were then counted.

STATISTICAL ANALYSIS

Based on earlier observations, the anticipated healing rate in patients with refractory duodenal ulcer who were given one to two months' further treatment with standard doses of cimetidine, was roughly 25% or less.[2] We hoped that combined cimetidine plus pirenzepine therapy would result in at least a doubling of the healing rate, about 55%. In order to have a nine in 10 chance of detecting this difference, we aimed to recruit 60 patients in each treatment group. Healing rates were calculated in two ways: first, based on the number of patients who were randomised to receive treatment and were evaluable – that is, intent-to-treat analysis; second, based on the number of patients who completed the treatment.

The statistical tests used for analysis were the χ^2 test to assess healing and pain relief, and paired *t* test and analysis of variance to analyse changes in laboratory values. The 95% confidence intervals of the healing rates in the two treatment groups and of the differences between them was calculated. Results were considered statistically significant when the p value was $<0{\cdot}05$.

The study was approved by the Ethical Committee in each centre and written consent was obtained from each patient.

Results

A total of 131 patients from six centres (3, 6, 12, 27, 28, and 55 patients in the different centres) entered the study but seven patients were excluded from analysis because of protocol violations. The demographic features of the remaining 124 patients in the two treatment groups (C n=59; C+P n=65) are shown in Table 1. Patients in the two groups had comparable mean age and sex ratio. The proportion of smokers, the length of the ulcer history and the duration of preceding cimetidine or ranitidine treatment before inclusion in the study (see below) was also similar. The preceding healing treatment was cimetidine in 103 patients and ranitidine in 15 patients; three patients had had both drugs and the drug used in four patients had not been recorded.

HEALING (Table 1)

Patients whose ulcers did not heal or who were

Table 1 *Comparison of demographic features of patients in the two treatment groups*

	Cimetidine	*Cimetidine + pirenzepine*
Patients (n)	59	65
Male/female	41/18	45/20
Mean age. Years (range)	43 (20–60)	43 (18–70)
Smokers %	76	85
Mean length of ulcer history. Years (range)	9 (1–30)	7 (1–31)
Median duration of preceding H_2 antagonist treatment given for healing. Weeks (range)	16 (8–416)	14 (8–208)

Table 2 *Results*

	Cimetidine	*Cimetidine + pirenzepine*
Patients (n)	59	65
Healed/unhealed	39/17	37/16*
Withdrawals because of:		
Side effects†	2	10
Other reasons	1	1
Healing calculated on intent-to-treat (%)	66	57
95% confidence interval	54%, 78%	45%, 69%
Difference between treatments	9%	
95% confidence interval	−8%, 26%	
Healing calculated on patients completing study (%)	70	70
95% confidence interval	58%, 82%	58%, 82%
Difference between treatments	0·2%	
95% confidence interval	−25%, 25%	

*Endoscopy data missing in one patient who completed six weeks' treatment; †p=0·02.

withdrawn from the study for whatever reason were considered as treatment failures. Two patients on cimetidine (C) and 10 patients on cimetidine plus pirenzepine (C+P) were withdrawn because of side effects (see section on side effects for details). One patient on C was lost to follow up and another patient on C+P was withdrawn from the study because of intercurrent illness.

The healing rate was similar in both treatment groups, irrespective of the method of calculation. By intent-to-treat analysis the healing rate (based on 124 patients) was: C 66%, C+P 57% (p=0·39); and of patients who completed treatment (n=110) it was: C 70%; C+P 70%. The 95% confidence intervals for the treatment differences in the healing rates were, intent-to-treat: −8% to +26%; and completed treatment: −25% to +25%.

EFFECT OF LENGTH OF PRE-ENTRY H_2 ANTAGONIST TREATMENT ON HEALING

It seemed possible that those patients whose ulcers remained unhealed after prolonged cimetidine or ranitidine treatment might be 'more resistant' to cimetidine alone and that combined therapy might prove more effective. But healing rates in patients with shorter (arbitrarily ≤20 weeks) or longer pre-entry H_2 treatment were similar. In patients (n=71) who had healing treatment for ≤20 weeks, healing (of those who completed treatment) was: C 67%, C+P 67% (p=0·86). In the remainder (n=48; data missing in five) who had longer treatment, healing was: C 70%; C+P 76% (p=0·92). Furthermore, when comparing patients who received the same treatment but had different lengths of pre-entry H_2 treatment – that is, ≤20 weeks *v* longer treatment, the healing rates were similar: on C 67% and 70% respectively (p=0·90); on C+P 67% and 76% respectively (p=0·67).

EFFECT OF SMOKING ON HEALING

Smoking did not appear to affect healing rates. In patients who completed treatment, healing in non-smokers was: C 81%, C+P 67% (p=0·74); and in smokers it was: C 66%; C+P 71% (p=0·76). Amongst patients on cimetidine the differences in healing rates between smokers and non-smokers (81% *v* 66%) were not significant (p=0·42).

HEALING RATES IN TWO GROUPS OF PATIENTS

The healing rates in the 55 patients studied in one centre were compared with those of the remaining 69 patients investigated between the other centres to examine if the overall healing rates had been unduly influenced by the former group. Amongst the 55 patients, of those who completed treatment, healing was: C 65%; C+P 63% (p=0·87); and of the 69 patients, healing was: C 73%; C+P 74% (p=0·79). Thus, within each subgroup the healing rates on both treatments were similar. Though the 55 patients had a lower healing rate compared with the others, the differences were not significant: healing on C 65% (in the 55 patients) *v* 73% (in the remaining 69 patients) (p=0·72); on C+P 63% *v* 74% respectively (p=0·63).

PAIN RELIEF (Table 3)

Patients in both treatment groups had a marked reduction in daytime pain (p<0·001 in both groups) and in night time pain (p<0·001 in both groups) during treatment. Amongst the 110 patients in whom details were recorded, daytime pain was present at entry to the study in: C 66%, C+P 69%; and at the end of treatment in: C 23%, C+P 20%. Similarly, night time pain in the 109 patients in whom details were noted was present at the start of treatment in: C 44%, C+P 54%; and at the end in: C 15%, C+P 6%. Thus, only a few patients had pain after finishing therapy but there was no significant difference in the numbers of patients in the two treatment groups with residual daytime pain (p=0·73) or night time pain (p=0·10).

SIDE EFFECTS AND WITHDRAWALS

Eighteen patients on cimetidine (31%) and 29 patients on combination treatment (45%) had side effects (differences p=0·10; not significant). The most common were: dry mouth (C n=7; C+P n=11); blurred vision (C n=2; C+P n=11); diarrhoea (C n=2; C+P n=4); and tiredness (C n=5; C+P n=3).

Side effects severe enough to lead to withdrawal, however, were significantly (p=0·02) more common in patients on combination therapy (n=10) than

Table 3 *Pain reduction*

	Patients with pain (n)		
	Present	*Absent*	*Not recorded*
Daytime pain			
At start:			
Cimetidine	37	19	3
Cimetidine + pirenzepine	37	17	11
At end:			
Cimetidine	13	43	0
Cimetidine + pirenzepine	11	43	0
Night time pain			
At start:			
Cimetidine	24	31	4
Cimetidine + pirenzepine	29	25	11
At end:			
Cimetidine	8	47	1
Cimetidine + pirenzepine	3	51	0

on cimetidine alone (n=2). Of the latter, one had an anticholinergic effect: a dry mouth; the other patient had epigastric pain, nausea, and tiredness. In contrast, six of 10 patients on C+P had anticholinergic side-effects: blurred vision (n=4) or dry mouth (n=1) or both (n=1). The other four patients were withdrawn because of, respectively: diarrhoea; suspected impotence; nausea and sickness; dizziness and diarrhoea.

Finally, two more patients were withdrawn: one because of failure to attend (on C) and the other because of an unconnected intercurrent illness (on C+P).

COMPLIANCE

Unfortunately, no conclusions could be reached on the amount of cimetidine/pirenzepine used by counting returned tablets because data were missing in 38 patients: 23 patients (C n=9; C+P n=14) did not bring their unused drugs back; and another 15 (C n=6; C+p n=9) claimed to have consumed all their drugs. This seemed unlikely for a seven week supply was given although treatment itself lasted six weeks.

A further problem was that patients assigned to cimetidine returned more tablets than those on combination treatment. Those given C returned a median (range) of: cimetidine 28 (0–75) tablets; placebo pirenzepine 14 (0–30) tablets. In contrast, those on C+P returned: cimetidine 12 (0–168) tablets; pirenzepine six (0–84) tablets. Bearing in mind the nature of the packaging which would have prevented patients selectively using only some tablets and discarding the others, it is difficult to explain these findings.

Finally, more antacid was apparently used by patients on combination treatment. Those on cimetidine returned a median (range) of 102 (0–120) tablets compared with 88 (0–120) tablets in patients on combination treatment. But it is difficult to draw firm conclusions as 44 patients (C n=20; C+P n=24) did not return their unused Dijex antacid tablets.

HAEMATOLOGY AND BIOCHEMISTRY

No abnormality which could be attributed to the drugs was seen in either treatment group.

Discussion

The combined administration of H_2-receptor antagonist cimetidine or ranitidine with pirenzepine produces greater acid suppression than that achieved by either agent alone.[3–6] It is therefore to be expected that such combined treatment would result in more rapid ulcer healing: indeed in the only previous study[7] markedly higher healing was reported. Dal Monte *et al*[7] randomised patients whose ulcers remained active after four months of antiulcer treatment (the first two months on cimetidine 1 g daily and the last two months on pirenzepine 150 mg daily) to further treatment with either full dose cimetidine (C) or pirenzepine (P) (as before) or to combined treatment with cimetidine 400 mg plus pirenzepine 75 mg daily (C+P). After one month healing occurred in: C 0%, P 0%, C+P 80%; and at six months healing occurred in approximately one third of patients in the first two groups. In contrast (and against expectations), in our study healing was similar in both groups: C 66%; C+P 57% by intent-to-treat analysis and C 70%, C+P 70% of those who completed treatment.

The failure to produce a higher healing rate on combination treatment (C+P) may have been due to a number of reasons. One possibility, based on observations of Gledhill *et al*[1] is that C+P may benefit only those patients whose nocturnal acid secretion cannot be suppressed by high dose cimetidine (2 g). We did not preselect our patients in this way, partly because it was impractical and partly because we felt it unnecessary as Gledhill *et al*'s[1] findings suggested this pathophysiological abnormality was present in most refractory duodenal ulcer patients. This cannot be the full explanation, however, because Dal Monte *et al*[7] did not preselect patients in this manner but reported very high healing rates on combined treatment with C+P.

A second possibility is that combined treatment may be useful only in those patients whose ulcers persist despite prolonged H_2 receptor antagonist treatment, the supposition being that such patients' acid secretion may be cimetidine resistant but susceptible to suppression by C+P; and that even a slight additional acid suppression at this stage may accelerate healing. In our study, however, healing rates in those who had H_2 antagonist treatment for 20 weeks or less before entry to the study were similar to those whose ulcers persisted despite much longer treatment. Differences in smoking habits, a third possibility, did not account for our results, for healing rates were not significantly different in smokers and in non-smokers.

A fourth possibility is lack of compliance in patients on combined treatment which, theoretically, may have prevented getting higher healing rates in this group. Unfortunately, useful conclusions on compliance cannot be drawn from our data. Similar proportions of patients in both treatment groups had pain at the start and therefore had an incentive to take their treatment; and the observation that more patients on combined treatment suffered side effects indicates that they did at least try to take their tablets.

A final possibility is a confounding effect. In an earlier study[2] healing occurred in only eight of 57 (14%) patients with refractory ulcer kept on cimeti-

dine 1 g daily. We anticipated a similar healing rate in this study; instead, healing occurred in 70% (of those who completed the study). This was not a distortion produced by results from one centre for the same high healing rates in both treatment groups were observed in all centres.

In conclusion, the results of this study suggest that adding pirenzepine to cimetidine to heal duodenal ulcers refractory to H_2 receptor antagonists alone, confers no advantage.

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