

Clinical trial

Deduction of duodenal ulcer recurrence by healing with cimetidine plus sulpiride

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SUMMARY The effect of combined treatment with sulpiride plus cimetidine was compared against that of cimetidine alone on the healing of duodenal ulcer and on the subsequent relapse rate. In a double blind study, 35 patients with duodenal ulcer diagnosed by endoscopy were randomly assigned to receive cimetidine 800 mg daily and 38 patients to receive cimetidine 800 mg plus sulpiride 200 mg daily. Sixty patients whose ulcers were healed at three months continued to be observed after stopping treatment and underwent endoscopy to detect recurrences when symptomatic or at three and at six months if asymptomatic. Recurrence was observed in 18 (72%) of 25 patients whose ulcers had healed on cimetidine alone, but in only 11 (38%) of 29 patients whose ulcers healed on cimetidine plus sulpiride.

Cimetidine, a histamine H₂-receptor antagonist, heals the majority of duodenal ulcers within four to six weeks,¹⁻³ but most of these ulcers quickly recur when treatment is discontinued.⁴⁻⁹ The exact mechanism of early recurrence is unclear. Guslandi *et al*^{10, 11} and Arakawa and Kobayashi¹² recently reported that cimetidine treatment results in an inadequacy of the mucosal defensive mechanism. Thus it would seem possible that the concomitant use of cimetidine and drugs that enhance mucosal defensive factors might prevent ulcer recurrence after withdrawal of treatment. Sulpiride, a non-sedative, hypothalamic neuroleptic, increases both mucosal blood flow in the gastroduodenal mucosa¹³ and mucus secretion.¹⁴ This drug has not been shown to be a potent acid lowering agent, although it reduces meal related serum gastrin.¹⁵ Lam *et al*¹⁶ and Mihas and Mihas¹⁷ reported a high ulcer healing rate with an antacid sulpiride combination, and suggested that sulpiride might be a helpful adjunct in ulcer treatment. In the present study, we therefore examined the effect of the combined use of sulpiride plus cimetidine on the recurrence of duodenal ulcer.

Methods

PATIENTS

Seventy three patients with endoscopically verified

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duodenal ulcers entered this double blind controlled trial. Informed consent was obtained from each subject, and the study was carried out in accordance with the Declaration of Helsinki. Endoscopic examinations were carried out less than seven days before starting treatment. All endoscopies were done by the same experienced endoscopist using a forward viewing fiberoptic panendoscope (Olympus GF-P₃). The diameters of the ulcers were measured using the tip of the biopsy forceps. All patients were treated on an outpatient basis. By random allocation 35 patients were assigned to receive treatment with cimetidine only (200 mg three times daily after meals and at bedtime) and 38 patients to cimetidine plus sulpiride (200 mg of cimetidine and 50 mg of sulpiride three times daily after meals and at bedtime). All patients kept a daily record of their consumption of drugs, and attended the hospital once every two weeks. Endoscopy was carried out three months after starting treatment by the same endoscopist, who had no knowledge of the patient's treatment or clinical progress. Healing was defined as a bulb free of an ulcer crater. Patients whose ulcers were not healed at three months were withdrawn from the study. The remaining patients had no further medication, but attended the hospital once every four weeks to check for symptom recurrence. Endoscopy was carried out at the time of symptom recurrence, or at three and six months in those who remained asymptomatic, once again by the same endoscopist who remained unaware of the patient's earlier treatment. The reappearance of an

ulcer crater was considered a recurrence whether symptoms were present or not, but the reappearance of erosions alone was not considered a recurrence.

After being accepted into the study, the patients were interviewed in detail with particular reference to the duration of their illness, cigarette and alcohol consumption, and ingestion of aspirin or non-steroidal, non-salicylate, anti-inflammatory drugs (NSNSAID).

The smoking index was defined as the number of cigarettes smoked per day multiplied by the duration of smoking in years.¹⁸ In calculating the duration of smoking, any continuous pause in smoking lasting more than one year was subtracted. Individuals with a smoking index of over 400 were defined as 'heavy smokers'. Non-smokers were defined as never having smoked. No patients who smoked a pipe and/or cigars only or in addition to cigarettes were included in this study.

Consumption of alcohol, aspirin, and NSNSAID was defined as follows:¹⁹

ALCOHOL

(1) Nil – less than 10 g/month; (2) Mild – 10 g/month to less than 60 g/week; (3) Moderate – 60 g/week to less than 60 g/day; (4) Heavy – 60 g or more/day for at least one month.

ASPIRIN AND NSNSAID

(1) Nil – less than one tablet or capsule per month; (2) Mild – one to six tablets or capsules per month; (3) Moderate – two or five tablets or capsules per week; (4) Heavy – six or more tablets or capsules per week for at least two consecutive months.

STATISTICAL ANALYSIS

This was done using the χ^2 test.²⁰ 'Significant' indicates a calculated p value of <0.05.

Results

HEALING OF ULCER

Ulcer healing at three months was similar in both

treatment groups: in 28 of 35 (80.0%) patients on cimetidine alone compared with 32 of 38 (84.2%) patients on cimetidine plus sulphiride. Thirteen patients (seven on cimetidine and six on combined treatment) were withdrawn as their ulcers had not healed.

Heavy smoking retarded healing. Thus healing occurred in all 13 non-smokers, in 16 of 19 (84.2%) patients with a smoking index of 1–400, and in 31 of 41 (75.6%) of patients with a smoking index of over 400 ($p < 0.02$).

ULCER RECURRENCE

Sixty patients with healed duodenal ulcer entered the follow up phase of the trial. Six patients were withdrawn, five (two healed on cimetidine and three on combination treatment) because they refused endoscopy and the sixth (healed on cimetidine) because there was no follow up information.

The results are summarised in Table 1. At six months, of 25 patients treated with cimetidine only, ulcers reappeared in 18 (72.0%). In contrast, ulcers recurred in only 11 of 29 (37.9%) patients who had been on combined cimetidine plus sulphiride ($p < 0.05$). Symptomatic recurrence was more frequent in the former group (in 10 of 25 patients, 40%) than in the latter (five of 29, 17.2%) but not significantly so. The reappearance of duodenal erosions alone in the bulb was observed in five (20.0%) patients treated with only cimetidine but in none of those treated with cimetidine plus sulphiride.

Table 2 shows that the patients in the two groups did not differ significantly with respect to sex distribution, age, duration of illness, size of original ulcer, proportion of cigarette smokers and alcohol consumers, and proportion of habitual aspirin or NSNSAID users.

FACTORS INFLUENCING ULCER RECURRENCE

Ulcers recurred in 29 patients at or within six months, whereas 25 patients continued in remission off treatment. Recurrence was significantly more frequent in heavy smokers. Thus, of the patients

Table 1 Recurrence of duodenal ulcer six months after termination of treatment with cimetidine or cimetidine plus sulphiride

Treatment	Patients (n)	Recurrence (%)		
		Total	Asymptomatic	Symptomatic
Cimetidine	25	18 (72.0)	8	10
Cimetidine+sulpiride	29	11 (37.9)*	6	5

*The difference between the incidences of ulcer recurrence after treatment with cimetidine only, and with cimetidine plus sulphiride was significant ($p < 0.05$).

Table 2 Clinical data of the patients with duodenal ulcer treated with cimetidine or cimetidine plus sulpiride

Data	Cimetidine	Cimetidine plus sulpiride
(n)	25	29
Men:women	20:5	21:8
Age (yr)	48.4±2.2	44.5±2.1
Duration of ulcer (yr)	1.3±0.4	1.6±0.4
Size of original ulcer (mm)		
<-5	5 (20.0)	7 (24.1)
5-10	12 (48.0)	15 (51.8)
10 or more	8 (32.0)	7 (24.1)
Smoking index		
0	6 (24.0)	4 (13.8)
1-400	5 (20.0)	8 (27.6)
400 or more	14 (56.0)	17 (58.6)
Alcohol		
None	12 (48.0)	19 (65.5)
Mild	6 (24.0)	7 (24.2)
Moderate	5 (20.0)	1 (3.4)
Heavy	2 (8.0)	2 (6.9)
Aspirin		
None	22 (88.0)	25 (86.2)
Mild	3 (12.0)	3 (10.4)
Moderate	0 (0.0)	0 (0.0)
Heavy	0 (0.0)	0 (0.0)
NSNSAID		
None	22 (88.0)	23 (79.3)
Mild	2 (8.0)	5 (17.3)
Moderate	1 (4.0)	1 (3.4)
Heavy	0 (0.0)	0 (0.0)

None of the differences between groups was statistically significant. Values indicate means±SE, and numbers in parentheses indicate percentage of cases.

with a smoking index of over 400, ulcers recurred in 21 of 29 patients (72.4%) compared with in only 10 of 25 patients (40%) who remained ulcer free ($p<0.05$). Sex, age at presentation, duration of illness, size of the original ulcer, cigarette and alcohol consumption, and aspirin or NSNSAID ingestion, however, did not show any significant correlation with ulcer recurrence.

Discussion

The possibility that H_2 -receptor antagonists might enhance the tendency of ulcers to relapse has been considered by numerous investigators,⁵⁻⁹ whereas after healing with drugs that act by other mechanisms such as colloidal bismuth²¹ or sucralfate²² it is rather lower. Although the exact mechanism of possible enhancement of ulcer recurrence after termination of cimetidine treatment is unclear, cimetidine does seem to impair the mucosal defensive mechanism.¹⁰⁻¹² H_2 -receptor antagonists and the mucosal-protective agents have been shown to

Table 3 Factors that may influence recurrence

Factors	Recurrent ulcers	Non-recurrent ulcers
(n)	29	25
Men:women	25:4	16:9
Age (yr)	47.9±2.1	44.5±2.4
Duration of ulcer (yr)	1.6±0.4	1.3±0.3
Size of original ulcer (mm)		
<-5	7 (24.1)	5 (20.0)
5-10	14 (48.3)	13 (52.0)
10 or more	8 (27.6)	7 (28.0)
Smoking index		
0	3 (10.4)	7 (28.0)
1-400	5 (17.2)	8 (32.0)
400 or more	21 (72.4)	10 (40.0)
Alcohol		
None	15 (51.7)	16 (64.0)
Mild	7 (24.2)	6 (24.0)
Moderate	4 (13.8)	2 (8.0)
Heavy	3 (10.3)	1 (4.0)
Aspirin		
None	24 (82.8)	23 (92.0)
Mild	4 (13.8)	2 (8.0)
Moderate	0 (0.0)	0 (0.0)
Heavy	1 (3.4)	0 (0.0)
NSNSAID		
None	24 (82.8)	21 (84.0)
Mild	4 (13.8)	3 (12.0)
Moderate	1 (3.4)	1 (4.0)
Heavy	0 (0.0)	0 (0.0)

The differences of the incidence of heavy smokers with a smoking index of more than 400 between the patients in whom ulcer did or did not recur was statistically significant ($p<0.05$). Values indicate means±SE, and numbers in parentheses are percentage of cases.

prevent ulcer formation by a large variety of ulcer inducing techniques in animals.²³

The known gastrointestinal effects of sulpiride include improvement of blood flow to the gastroduodenal mucosa¹³ and enhancement of mucus secretion.¹⁴ The drug does not affect the basal or histamine stimulated acid output after chronic treatment.¹⁵ Lam *et al*¹⁶ and Mihás and Mihás¹⁷ reported that an antacid sulpiride regimen is very effective in ulcer healing. Lam *et al*¹⁶ suggested that by using a combination of antacid and sulpiride, it would be theoretically possible to control the cephalic and gastric phases of acid secretion which occur with meals. Sulpiride, however, has not been shown to have a potent acid lowering effect.¹⁵ Therefore, it seems likely that its effect on ulcer healing might be because of an improvement of mucosal defensive factors.

In the present study, we found that the combined use of cimetidine and sulpiride reduced recurrence of duodenal ulcers during the six month period after termination of cimetidine treatment, and therefore

the protective effect of sulphiride exists even though the drug was given with cimetidine.

The causes of ulcer relapse have not been established. In the present work, we examined the influence of patient's variables on relapse rate. We found that heavy smoking was closely related to the ulcer recurrence, but no significant correlation between ulcer recurrence and other variables was found. These findings strongly indicate that physicians should encourage their patients to stop smoking, or failing this, reduce their daily cigarette consumption as much as possible.²⁴

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