*Clinical trial***Effect of smoking on duodenal ulcer healing with cimetidine and oxmetidine**

R GUGLER,* H-G ROHNER, P KRATOCHVIL, G BRANDSTÄTTER, and H SCHMITZ

From the Department of Medicine, University of Bonn, Germany; St. Barbara-Hospital, Gladbeck, Germany; and the Second Department of Medicine, Landeskrankenhaus Graz, Austria

SUMMARY The effect of oxmetidine 800 mg/day, a new histamine H₂-receptor antagonist, on duodenal ulcer healing was compared with cimetidine 1000 mg/day in a two-centre double-blind trial. Ninety-nine patients completed the study. After four weeks, ulcers were healed in 74% of the cimetidine-treated patients and in 78% of the oxmetidine-treated patients ($p>0.05$). Healing rates after eight weeks increased to 90% in the cimetidine group and to 94% in the oxmetidine group. Healing rates after four weeks were, however, different in the two centres ($p<0.01$): in centre 1 88% of the cimetidine-treated, but 63% of the oxmetidine-treated patients healed, in centre 2 rates were 60% (cimetidine) and 92% (oxmetidine). Analysis of patient data revealed that in the two centres treatment success was inversely correlated ($p<0.01$) with the percentage of smokers in each treatment group. Smoking significantly influences duodenal ulcer healing with histamine H₂-receptor antagonists.

The histamine H₂-receptor antagonist cimetidine is a potent drug used for duodenal ulcer healing.¹ Despite a remarkably low incidence of side-effects, there is some concern that cimetidine might interfere with endocrine, immunological, and drug metabolic processes.² Oxmetidine is a newly developed histamine H₂-receptor antagonist which differs from cimetidine by containing an isocytosine ring instead of a cyanoguanidine group as a side chain (Fig. 1). Studies in man have indicated that oxmetidine is more potent than cimetidine on a molar basis, but has a similar duration of effect.^{3,4} Given in a dose of 400 mg bid oxmetidine reduced 24-hours gastric acidity to a similar degree as cimetidine 1 g daily.⁵ This study was designed to assess its ability to heal duodenal ulcers compared with cimetidine.

Methods**PATIENTS**

One hundred patients with endoscopically documented duodenal ulcers were entered into the

Fig. 1 Chemical structure of cimetidine and oxmetidine.

* Address for correspondence: Professor Dr R Gugler, Department of Medicine, University of Bonn, 5300 Bonn-Venusberg, Federal Republic of Germany.

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trial from consecutive cases referred to two medical centres: St. Barbara-Hospital, Gladbeck, Germany; and Medical Department II, Landeskrankenhaus Graz, Austria. Patients were considered for inclusion in the study if on endoscopy a duodenal ulcer with a minimum size of 3 mm in one diameter (to be measured with the open branch of a biopsy forceps or the standard Olympus measuring device) was diagnosed. Patients were excluded from consideration if they were over 70 years of age, if they had significant cardiac, pulmonary, hepatic, or renal (serum creatinine greater than 2.0 mg/dl) disease, if they had clinically significant laboratory abnormalities after routine screening, if they had complications of their ulcer (perforation, bleeding, delayed gastric emptying), if they had prior upper gastrointestinal surgery, or if they had received cimetidine during the eight weeks before entry into the study. Patients were informed about the nature of the study, and their written consent was obtained.

MANAGEMENT

After being accepted into the trial, the patients were randomly assigned to one of the two treatment regimens. They were carefully instructed on the dosage schedule of the study medication and on the use of diary cards for registration of ulcer pain; symptom recording was done separately for day and night. They were also asked to report their daily consumption of antacid tablets. The patients were seen by their treating physicians every two weeks, and details of their general well-being and of specific symptoms were noted on follow-up forms.

In each patient endoscopy was performed by the same endoscopist before entry into the study and after four weeks of treatment; endoscopy was again repeated after eight weeks if the ulcer had not healed after four weeks.

Blood and urine samples were obtained at each visit to the clinic and the following laboratory tests were performed: haemoglobin, erythrocyte count, haematocrit, WBC total and differential, platelet count, serum sodium, potassium and chloride, BUN, serum creatinine, and uric acid, transaminases, lactate dehydrogenase, alkaline phosphatase, bilirubin, glucose and protein in urine, and urine sediment.

MEDICATION

Oxmetidine and cimetidine tablets of identical appearance were packed into blisters of six tablets, with two tablets to be taken after breakfast and at bedtime, and one tablet each to be taken after lunch and after dinner. Oxmetidine daily dose was 800 mg, and the dosing schedule was 400 mg (2×200 mg tablets) after breakfast and at bedtime. Cimetidine

daily dose was 1000 mg, with 200 mg (one tablet) after meals and 400 mg at bedtime. The respective 'empty' places in the blisters were filled with placebo tablets. Antacid tablets (Gelusil) were allowed *ad libitum* for the relief of ulcer pain.

CALCULATIONS

Statistical evaluation of results was performed with Student's *t* test for differences between means. Differences in healing rates in relation to treatment group, treatment centre, and smoking habits were analysed by three-dimensional contingency table tests^{6,7} for the following sequences: 1. treatment – centre – success; 2. treatment – centre – smoking; 3. treatment – smoking – success. Three-dimensional tables were preferred over four-dimensional tables because of too small cell frequencies in the latter.

Results

One patient treated with oxmetidine was withdrawn from the trial when he developed a rash possibly related to drug intake after three weeks of therapy. Seven months after treatment, the rash still persisted, and the dermatologist's diagnosis of urticaria factitia excluded a drug-related disease. All remaining 99 patients completed the trial, with 50 patients receiving cimetidine and 49 receiving oxmetidine. The relevant patient characteristics of the two treatment groups are listed in Table 1. The two groups were comparable with regard to age, sex, duration of ulcer disease, ulcer size (largest diameter), macroscopic appearance, form, smoking habits and drinking habits.

After four weeks of treatment, the ulcer had healed in 37 (74%) of the cimetidine-treated patients and in 38 (78%) of the oxmetidine-treated patients (Fig. 2); this difference is not significant ($p>0.05$). After eight weeks, ulcers were healed in an additional seven patients in the cimetidine- and eight patients in the oxmetidine-treated group, giving a total healing rate of 45 (90%) of the

Table 1 Clinical data of all patients participating in trial

	Cimetidine	Oxmetidine
No.	50	49
Age (yr)	44.5±14.3*	45.2±13.8
Male/female	43/7	35/14
Duration of ulcer disease (yr)	9.7±11.4*	9.4±9.9
Ulcer		
Size (mm)	7.6±4.1*	7.6±4.0
Form (linear/round)	4/46	9/41
Smokers (no.)	34	35
Alcohol drinkers (no.)	24	27

* Mean ± SD

Fig. 2 Percent duodenal ulcer healing of all patients after four weeks' and eight weeks' treatment with cimetidine (CIM) and oxmetidine (OXM). N; number of patients healed.

Fig. 3 Percentage duodenal ulcer healing in each centre after four weeks' treatment with cimetidine (CIM) and oxmetidine (OXM). N; number of patients healed.

cimetidine and 46 (94%) of the oxmetidine group, thus leaving a total of eight patient unhealed.

When four weeks' healing response was analysed separately for the two centres involved, major differences became apparent (Fig. 3). In Gladbeck the ulcers healed in 88% of the cimetidine-treated and in 63% of the oxmetidine-treated patients. In Graz 60% of the cimetidine- but 92% of the oxmetidine-treated ulcers healed. The difference between treatment groups in relation to the different centres was significant ($p < 0.01$).

Patient characteristics analysed separately for Gladbeck and Graz are listed in Table 2. Age, sex, duration of disease, ulcer size and form, and patients consuming alcohol were equally distributed

between the two treatment groups in Gladbeck as well as in Graz. Ulcer size differed greatly between the two centres, probably because of differences in methods of estimation, but in both centres ulcer size was identical in the two treatment groups. Smoking habits, however, differed substantially between the groups in both centres. In Gladbeck, 58% of cimetidine- and 96% of oxmetidine-treated patients were smokers, in Graz, 76% of the cimetidine- and 48% of the oxmetidine-treated patients smoked.

The effect of smoking on healing results within this trial is shown in Fig. 4. Sixty-eight per cent of all patients treated with cimetidine and 71% of all patients treated with oxmetidine were smokers. Ninety-two per cent of treatment failures with

Table 2 Clinical data of participating patients analysed separately for two centres involved

	Gladbeck		Graz	
	Cimetidine	Oxmetidine	Cimetidine	Oxmetidine
No.	25	24	25	25
Age (yr)	42.8 ± 16.0*	42.1 ± 12.3*	46.2 ± 12.6*	48.1 ± 14.8*
Male/female	23/2	19/5	20/5	16/9
Duration of ulcer disease (yr)	8.1 ± 9.6*	7.4 ± 8.4*	10.1 ± 10.2*	10.1 ± 10.2*
Ulcer				
Size (mm)	10.8 ± 3.4*	11.0 ± 3.3*	4.3 ± 1.4*	4.7 ± 1.7*
Form (linear/round)	2/23	4/20	2/23	5/20
Smokers (no.)	15	23	19	12
Alcohol drinkers (no.)	12	13	12	14

* Mean ± SD

Fig. 4 Percentage smokers in the cimetidine-treated and in the oxmetidine-treated patients of all patients of the study, of treatment failures after four weeks, and of all patients in Gladbeck and in Graz. N; number of smokers. Total: total number.

cimetidine (12 out of 13) and 91% of treatment failures with oxmetidine (10 out of 11), however, were smokers. Smoking, therefore, was inversely correlated to a significant degree ($p < 0.01$) with ulcer healing under cimetidine and oxmetidine (Table 3). In each centre, smoking was distributed differently between the two treatment groups ($p < 0.01$). When healing rates were compared separately for smokers and non-smokers, no difference was found between cimetidine and oxmetidine in each centre ($p > 0.83$).

ADVERSE EFFECTS

Two patients (one on cimetidine, one on oxmetidine) experienced diarrhoea during the first week of the trial, but did not have to be withdrawn. One patient on cimetidine reported difficulties in concentrating during the second week. One patient on oxmetidine experienced mild lacrimation during the first two weeks on oxmetidine.

Table 3 Treatment results in relation to smoking

Results tested for	p Value
Difference in healing rates between cimetidine and oxmetidine in Gladbeck and Graz	<0.01
Difference in number of smokers between treatment groups in Gladbeck and Graz	<0.01
Influence of smoking on healing rates in the two centres	<0.01
Difference in healing rates between treatment groups in smokers and non-smokers	0.83
Difference in healing response between cimetidine and oxmetidine after exclusion of the variables 'smoking' and 'treatment centre'	0.68

LABORATORY TESTS

There were no significant changes in haematological indices throughout the trial. Five patients on oxmetidine developed significantly (greater than double the upper normal value) raised serum transaminases, and four patients had mild (less than double) rises in serum transaminases. Of the cimetidine-treated patients one developed significantly raised serum transaminases during the trial. As a number of these patients were known to be moderate to heavy drinkers, the precise role of the investigated drugs in causing these abnormalities is difficult to judge. At subsequent follow-up examinations in all these patients the transaminase levels had returned to normal. In 31 patients of the cimetidine group serum creatinine values increased at week four over the baseline value, but in another 12 patients serum creatinine decreased. In the oxmetidine group, serum creatinine increased in 11 patients and decreased in 10 patients. Serum creatinine of the total group changed from a mean of 1.07 ± 0.22 mg/dl at the beginning to 1.22 ± 0.33 mg/dl after four weeks in the cimetidine group ($p < 0.001$), and from 1.10 ± 0.31 to 1.19 ± 0.37 mg/dl in the oxmetidine group ($p > 0.05$).

SYMPTOMATIC RESPONSE

The effect of cimetidine and oxmetidine treatment on ulcer pain is shown in Fig. 5. Both treatment forms equally reduced symptoms during day and night, and no differences were observed between the two centres. Consumption of antacid tablets was reported by a total of 11 patients (seven cimetidine, four oxmetidine) during the initial two weeks of the trial, but only by three patients (two cimetidine, one oxmetidine) during the following two weeks. The

Fig. 5 Number of patients with pain during the day and at night before therapy and after two and four weeks' therapy in the cimetidine- and oxmetidine-treated groups.

differences between treatment groups were not significant.

Discussion

The effect of the new histamine H_2 -receptor antagonist, oxmetidine, on duodenal ulcer healing was compared with cimetidine in a two-centre double-blind trial in 99 patients. The oxmetidine dose of 800 mg was selected on the basis of experimental antisecretory data in normal subjects and in duodenal ulcer patients.^{3-5, 8} These studies suggest that, by the intravenous route, oxmetidine is about four times as potent as cimetidine, whereas by the oral route oxmetidine is only slightly superior, probably due to intestinal or liver first-pass metabolism.

In the present study, oxmetidine produced a four week ulcer healing rate of 78%, which is almost identical with that of 74% by cimetidine, and these figures are similar to those commonly reported for cimetidine and for other drugs with proven efficacy in healing duodenal ulcers.⁹⁻¹⁰ Healing rates after eight weeks were 94% and 90%, respectively, leaving 10% or less of all ulcers unhealed under these H_2 -receptor antagonist regimens. Our results indicate that oxmetidine twice daily is as effective as cimetidine in the conventional dosage regimen of 1000 mg divided into four doses. These results also correspond to healing rates achieved with the other new histamine H_2 -receptor antagonist, ranitidine.¹¹⁻¹²

The difference in mean ulcer size in the two centres points to the difficulty of measuring ulcers even by use of special measurement devices. Ulcer size was, however, identical in the two treatment groups in each centre, so that influence of ulcer size on treatment results with cimetidine and oxmetidine is excluded.

Symptomatic relief provided by oxmetidine was

also similar to cimetidine, although the meaning of these figures is limited by the lack of information on the spontaneous regression rate of symptoms. Consumption of antacids was low in both treatment groups confirming the good symptomatic response to oxmetidine and cimetidine.

Adverse effects observed in this study under oxmetidine and cimetidine were mild and temporary in all cases, except for one patient on oxmetidine who showed a skin disorder probably not related to the drug but serious enough to exclude further participation. Transient rises in serum creatinine and serum transaminases are documented under cimetidine.¹²⁻¹⁴ In the course of the present study, rises in serum transaminases occurred in six patients, but was transient in all cases. A significant increase in serum creatinine level was also recorded here in the cimetidine treatment group. The laboratory changes were not associated with any clinical symptoms and did not require withdrawal of patients from the study.

Smoking has been claimed to play an important role in the production as well as in the retardation of healing of duodenal ulcers, although definite proof has not yet been presented.¹⁵⁻¹⁸ A recent report points to smoking as an important factor for healing of duodenal ulcer with ranitidine.¹⁹ Our study stresses the role of smoking for ulcer healing by a coincidentally opposite allocation of smokers and non-smokers to the treatment groups in each centre. This explained the surprising initial finding that in Gladbeck cimetidine was significantly better than oxmetidine, whereas in Graz oxmetidine was significantly better than cimetidine. Only when healing rates were determined separately for smokers and non-smokers in the individual centres, were differences in healing between cimetidine and oxmetidine no longer present. These findings raise the question as to whether or not abstaining from smoking is as important for the medical

management of duodenal ulcer disease as is the prescription of drugs which inhibit gastric acid secretion. If we have to use antisecretory drugs for ulcer healing, smokers may require greater doses than non-smokers or longer treatment periods with a standard dose. Individual treatment regimens for duodenal ulcer should at least in part be influenced whether the patient is a smoker or not.

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