Alimentary tract and pancreas

Short term treatment of gastric ulcer: a comparison of sucralfate and cimetidine

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SUMMARY A double blind randomised study was undertaken to compare sucralfate and cimetidine in short term treatment of gastric ulcer. The study included 149 patients with endoscopically confirmed gastric ulcerations. Patients with prepyloric ulcers 2 cm or less from the pyloric ring were not accepted for participation in the trial. Ulcer healing was assessed endoscopically at four week intervals. A total of 134 patients completed the study. The cumulative healing rates after 12 weeks were 98% for sucralfate and 94% for cimetidine treated patients. After four and eight weeks, the healing rates were 61% and 94% for sucralfate and 69% and 94% for the cimetidine-treated group respectively. No statistically significant differences in healing rates were seen. The 95% confidence interval was calculated for the difference between the ulcer healing rates of sucralfate and cimetidine. This interval was found to range between +11% and -2% after 12 weeks of treatment—that is, the healing efficacy of sucralfate was calculated to be at most 11% better or 2% worse than that of cimetidine. No significant differences in symptom relief, side effects or antacid intake were found.

Peptic ulcer treatment has for many years been concentrated on reduction of intraluminal acidity. The efficacy of antacid agents in the treatment of gastric ulcer is, however, uncertain.1 Cimetidine, an H2-receptor antagonist with high acid reducing capacity, has recently been demonstrated in a few controlled studies to have a statistically better healing efficacy in gastric ulcer than placebo.2 3

The development of agents acting on the gastric mucosal barrier level, and having cytoprotective properties has provided a new method of combating peptic ulcer disease.

Sucralfate, a basic aluminium salt of sucrose octasulphate, is one of the new cytoprotective agents and has in previous studies given healing rates comparable with those given by cimetidine in the treatment of both duodenal and gastric ulcer.4-7

The main purpose of this study was to compare the healing rates and symptom relief in patients with acute gastric ulcer treated with sucralfate and cimetidine. The study was planned to include a sufficient number of patients to allow the calculation of a short 95% confidence interval for the difference in healing rates.

Methods

Patients

The investigation was as a multicentre, double blind, randomised prospective study with the double dummy technique. Twenty two Swedish hospitals participated in the study. Each hospital should contribute with a minimum of five patients. The study was approved by the ethical committee of the University of Gothenburg and by the Swedish National Board of Health and Welfare.

Inclusion criteria

Patients aged 18 to 70 years with an endoscopically confirmed gastric ulcer were included in the study. Non-bleeding as well as bleeding ulcers were accepted. The minimum ulcer size diameter was 2 mm. Prepyloric ulcers in a position 2 cm or less
from the pyloric ring were not included. All ulcers were biopsied to exclude malignancy.

EXCLUSION CRITERIA
Chronic renal or hepatic disease, known malignancy, pregnancy, and lactation disqualified candidates inclusion. Patients with previous gastric resection or vagotomy or with coexistent duodenal and/or prepyloric ulcers were also excluded, as were patients on continuous medication with anti-inflammatory or anticoagulant drugs. Patients who had received antulcer medication for more than seven days during the last four weeks before diagnosis were not accepted. Psychiatric disease or alcoholism making the patient incapable of cooperating also led to exclusion.

ENDOSCOPY
At inclusion, endoscopy was carried out and the ulcer size and location were noted. The ulcer size was estimated with a measuring probe or open biopsy forceps. At repeat endoscopy, the ulcer was considered to be healed if the ulcer site was totally epithelialised.

TREATMENT
Patients taking part in the study which was in accordance with a preproduced code list randomly allocated to treatment with either sucralfate (Andapsin® Farmos Group AB) 1 g qid or cimetidine (Tagamet® SK&F) 400 mg bd. The maximum delay from endoscopy to start of treatment was five days. The patients received active tablets and dummies packed in plastic blisters daily. They were also given written and verbal instructions to take the sucralfate tablets one half to one hour before meals and not together with antacid tablets. Cimetidine tablets were to be taken together with meals and at bedtime, and not together with antacid tablets. The patients received 30 antacid tablets (Novalucol® Hässle, acid neutralizing capacity 12.5 mmol/tablet) and were instructed to take the tablets only in situations of acute epigastric pain or heartburn. They were given more antacid tablets on request. The patients were also recommended to reduce their consumption of tobacco and coffee.

REGISTRATION OF SYMPTOMS, TABLET INTAKE AND SIDE EFFECTS
Current symptoms such as epigastric pain, heartburn, nausea and ulcer hemorrhage were recorded. During the trial, the patients recorded diurnal and nocturnal epigastric pain and heartburn on a special diary card. Missed tablets, antacid intake and daily consumption of tobacco and coffee were also recorded on the diary card. Unexpected symptoms during the study were also recorded by the patient.

FOLLOW UP AND CONTROLS
Each patient had a second contact with the investigator after 14 days, either by telephone or by personal visit. Repeat endoscopy was done after four weeks. If the ulcer was not healed the treatment was continued for another four week period. The maximum duration of treatment was 12 weeks.

LABORATORY TESTS
Laboratory tests were performed at inclusion and at the assessments after four, eight, and 12 weeks of treatment. The tests included haemoglobin, white blood cell count, platelets, creatinine, bilirubin, alkaline phosphatase (ALP), asparate aminotransferase (ASAT), and alanine aminotransferase (ALAT). The serum phosphate concentration was monitored in 54 patients.

STATISTICAL METHODS
The treatment groups were compared with respect to the variables recorded at entry to the study by means of Fisher’s permutation test. If the groups were found initially to differ significantly with respect to any variable correlated to ulcer healing, special statistical measures were to be taken to correct for the differing variable in the main comparison of ulcer healing. Mantel’s test was then used for analysis of the correlation between the entry variable and healing. The Mantel technique in this case means that the correlation between a variable and ulcer healing is first analysed within the sucralfate group and the cimetidine group separately and the results of the two groups are then pooled into one test. A two-sided interval for the difference in healing rates was to be calculated with 95% confidence limits. On the last day of each week during follow up, Fisher’s exact test was used to compare the proportions of patients with epigastralgia. Similar comparisons were made for antacid intake and heartburn.

Results
PATIENT CHARACTERISTICS
Initially, 160 patients were included in the trial. Seven of the participating clinics did not reach the minimum limit of five patients and for this reason 10 patients were blindly excluded from the final evaluation. Another patient was over 70 years old and was also blindly excluded. Of the remaining 149 patients 75 were given sucralfate and 74 cimetidine. Gastric carcinoma was found in four patients in the sucralfate group and six patients in the cimetidine group. Control endoscopy was refused by two patients in each group. One patient in the sucralfate group had profuse ulcer bleeding which led to acute operation...
The patient group and is the groups significant difference was shown in Table 2. A significant difference in mean ulcer size between the groups was found: 7.9 mm in the sucralfate group and 12.6 mm in the cimetidine group (p<0.001). The distribution of ulcer size in the two groups is shown in Table 3. Smoking habits also differed between the groups: in the sucralfate group 47% were smokers, compared with 68% in the cimetidine group (p<0.05).

**Table 1** Causes of withdrawal among 149 gastric ulcer patients treated with sucralfate (1 g qid) or cimetidine (400 mg bd).

<table>
<thead>
<tr>
<th>Cause</th>
<th>Sucralfate</th>
<th>Cimetidine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>75</td>
<td>74</td>
<td>149</td>
</tr>
<tr>
<td>Gastric carcinoma</td>
<td>4</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Refused control endoscopy</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Remain in study</td>
<td>68</td>
<td>66</td>
<td>134</td>
</tr>
</tbody>
</table>

**Table 2** Comparison of patient characteristics at entry to the study between 68 gastric ulcer patients treated with sucralfate (1 g qid) and 66 treated with cimetidine (400 mg bd).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sucralfate</th>
<th>Cimetidine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)±SD</td>
<td>54±11.9</td>
<td>56.5±9.7</td>
<td>ns</td>
</tr>
<tr>
<td>Sex: males/females</td>
<td>35/33</td>
<td>32/34</td>
<td>ns</td>
</tr>
<tr>
<td>Smokers</td>
<td>32 (47%)</td>
<td>45 (68%)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Patients taking NSAID*</td>
<td>16 (23%)</td>
<td>22 (33%)</td>
<td>ns</td>
</tr>
<tr>
<td>Patients drinking alcohol</td>
<td>43 (63%)</td>
<td>44 (67%)</td>
<td>ns</td>
</tr>
<tr>
<td>Patients drinking coffee</td>
<td>54 (79%)</td>
<td>58 (88%)</td>
<td>ns</td>
</tr>
<tr>
<td>Ulcer history:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with first episode</td>
<td>30 (44%)</td>
<td>32 (48%)</td>
<td>ns</td>
</tr>
<tr>
<td>Patients with relapse</td>
<td>38 (56%)</td>
<td>34 (52%)</td>
<td>ns</td>
</tr>
<tr>
<td>Duration of current symptoms (weeks)±SD</td>
<td>8±5.0</td>
<td>8.2±8.9</td>
<td>ns</td>
</tr>
<tr>
<td>Duration of ulcer disease (years)±SD</td>
<td>6.5±5.9</td>
<td>5.1±8.1</td>
<td>ns</td>
</tr>
<tr>
<td>Latest ulcer (years)±SD</td>
<td>4±7.5</td>
<td>3±2±6.3</td>
<td>ns</td>
</tr>
<tr>
<td>Size of current ulcer (mm)±SD</td>
<td>7.9±5.7</td>
<td>12.6±9.8</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Patients with more than one ulcer</td>
<td>12 (18%)</td>
<td>11 (17%)</td>
<td>ns</td>
</tr>
<tr>
<td>Symptoms at entry to study:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>59 (87%)</td>
<td>45 (68%)</td>
<td>ns</td>
</tr>
<tr>
<td>Heartburn</td>
<td>37 (54%)</td>
<td>23 (35%)</td>
<td>ns</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>19 (28%)</td>
<td>22 (33%)</td>
<td>ns</td>
</tr>
</tbody>
</table>

*NSAID=Non-steroidal anti-inflammatory drugs

**Table 3** Estimated ulcer size in 134 gastric ulcer patients treated with sucralfate (1 g qid) or cimetidine (400 mg bd).

| Ulcer size (mm) | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10-14 | 15-19 | 20-24 | 25-29 | 30-34 | >40 |
|-----------------|---|---|---|---|---|---|---|---|-------|-------|-------|-------|-------|------|-----|
| Sucralfate      | 1 | 8 | 18 | 1 | 11 | 4 | 5 | 0 | 11    | 3     | 5     | 0     | 1     | 0    |
| Cimetidine      | 1 | 5 | 2  | 7 | 5  | 4 | 3 | 1 | 16    | 12    | 3     | 1     | 4     | 2    |

**Healing rate**

Ulcer size significantly influenced the healing rate. In the sucralfate treated group healing rate for ulcers smaller than 6 mm was 73% and for ulcers larger than 6 mm healing rate was 51% at four weeks treatment (p>0.05). Corresponding figures in the cimetidine group were 85% and 53% (p<0.01).

After eight weeks of treatment the small ulcers in the sucralfate group were healed in 92% and in the cimetidine group in 95%. The corresponding figures for the larger ulcers were 96% and 93% respectively. The ulcer size did not significantly affect ulcer healing after eight weeks of treatment neither in the sucralfate nor in the cimetidine group. As healing was significantly affected by ulcer size in the cimetidine group after four weeks of treatment the difference in ulcer size between the treatment groups was taken into consideration when calculating the healing rates after four weeks, using Mantel's test. As will be seen from Table 4 the adjusted healing rates at four weeks is 61% for sucralfate and 69% for cimetidine. The cumulative healing rates after eight weeks were 94% for both the sucralfate group and the cimetidine treated group. After 12 weeks, the healing rates for sucralfate were 98% and for cimetidine 94%. Table 4 and Figure 1. Smoking did not have any significant correlation to ulcer healing in either of the groups after four, eight or 12 weeks of treatment.

The 95% confidence intervals for the difference in healing rates are also shown in Table 4. The figures are calculated with respect to sucralfate, which means that after 12 weeks of treatment the healing efficacy of sucralfate might be at most 11% better or 2% worse than that of cimetidine.

**Symptom relief and antacid intake**

Of the 134 patients who completed the study, 64 in the sucralfate and 63 in the cimetidine group kept a proper record of their symptoms and antacid intake during the study. Epigastric pain, heartburn and antacid intake were compared between the groups every seventh day during the first eight weeks of...
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Table 4  Cumulative healing rates in 134 gastric ulcer patients treated with sucralfate (1 g qid) or cimetidine (400 mg bd)

<table>
<thead>
<tr>
<th></th>
<th>Success rate 4 weeks</th>
<th>ns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healing rate</td>
<td>68%</td>
<td>66%</td>
</tr>
<tr>
<td>Healing rate</td>
<td>463%</td>
<td>62%</td>
</tr>
<tr>
<td>Healing rate</td>
<td>894%</td>
<td>94%</td>
</tr>
<tr>
<td>Healing rate</td>
<td>1298%</td>
<td>94%</td>
</tr>
</tbody>
</table>

Fig. 1 Cumulative healing rate in 134 gastric ulcer patients treated with sucralfate (1 g qid) or cimetidine (400 mg bd). Sucralfate was administered to 68 patients and 66 patients were treated with cimetidine.

Fig. 2 Gastric ulcer patients complaining of epigastric pain during treatment with sucralfate (1 g qid) or cimetidine (400 mg bd). Figures are calculated from diary cards from 64 patients in sucralfate and 63 patients in cimetidine treated group. After 28 days of treatment, only 25 patients in each group were still under treatment. The number of patients with diurnal epigastric pain is shown in the left hand diagram and the number with nocturnal epigastric pain in the right hand diagram.

treatment, using Fisher's exact test. After eight weeks, only five patients were still under treatment. The number of patients complaining of diurnal or nocturnal epigastric pain is shown in Figure 2. There was a rapid fall in patients complaints of diurnal epigastric pain in both treatment groups. No significant difference between the groups was noted during the study.

As shown in Figure 2, patients with nocturnal epigastric pain were few and it is not possible to estimate the effect of the treatment on this symptom in this material.

The number of patients taking antacid tablets is shown in Figure 3. On the twenty first day of treatment, seven patients in the sucralfate group and 17 patients in the cimetidine group used antacid tablets (p<0.05). The antacid intake decreased during the study and the curves approximately follow the curves for diurnal epigastric pain.

Laboratory findings
Statistically significant changes in laboratory values were not observed. Serum phosphate was monitored in 54 patients (29 on sucralfate treatment) and was not found to change during the treatment.

Unwanted effects
The unwanted effects registered are shown in Table 5. No serious reaction was observed and no patient was withdrawn from the study because of side effects.

Discussion
Mucosal lesions in the upper gastrointestinal tract are believed to be due to an imbalance between mechanisms maintaining the integrity of the mucosa
and aggressive factors such as acid, pepsin, and bile salts. Reduction of intraluminal acidity has until recently been a primary aim of the treatment of peptic ulcer disease. Antacids, anticholinergics, and \( \text{H}_2 \)-receptor antagonists are all effective in the treatment of duodenal ulcer.\(^\text{11-14}\) In the treatment of gastric ulcer, however, antacids or anticholinergics have not given convincing results as regards ulcer healing or symptom relief.\(^\text{1}\)

Cimetidine, the first clinically used \( \text{H}_2 \)-receptor antagonist, has only in a few controlled studies given significantly better results than placebo in the treatment of gastric ulcer.\(^\text{2, 3}\) Gastric ulcer patients have not been shown to have an increased acid secretion capacity.\(^\text{15}\) Thus, acid is not the only and perhaps not even the most important factor in gastric ulcer disease. Therefore recent research has focused on changes in the mucosal defence mechanisms.

The mucosal epithelium is protected from damage by mucus release, bicarbonate secretion, epithelial cell renewal from the deep mucosal cell proliferative zone, mucosal blood flow, intact cellular membranes and synthesis and release of prostaglandins.\(^\text{16}\) Cytoprotection has been defined as the ability of drugs to protect the gastric mucosa from necrotic damage by a variety of aggressive agents like alcohol, boiling water, acid, and overdistension.\(^\text{10-18}\)

Sucralfate has long been thought to heal ulcers by forming a protective barrier over eroded mucosa. This barrier is impermeable to acid, binds bile salts and inhibits pepsin activity.\(^\text{19}\) Recent investigations have shown that sucralfate also possesses cytoprotective properties, probably via stimulation of the local synthesis and release of prostaglandins. Mucosal blood flow, epithelial cell renewal and the formation of mucus is thereby enhanced.\(^\text{5, 20}\) This, together with the absence of known interactions, extremely low toxicity and side effects\(^\text{21}\) makes this drug highly interesting in the treatment of gastric ulcer.

Sucralfate and cimetidine have earlier only in a few studies been compared in the treatment of gastric ulcer. The healing rates for both drugs have been reported between 40–60% after four and 75–85% after eight weeks of treatment.\(^\text{7, 22-23}\) Only Marks\(^\text{9}\) has treated patients for 12 weeks and he reported 83% healing rate for sucralfate and 89% for cimetidine. In all the above cited studies sucralfate has been administered in a dose of 1 g qid and cimetidine in a dose of 200+200+200+400 mg with exception for Martins study\(^\text{23}\) in which the patients received cimetidine 300 mg qid. Significant differences in healing rate or symptomatic relief between the treatment groups could not be demonstrated in any of these studies, corresponding well to our present study. The healing rates in our study were in both groups slightly higher than in the above cited studies both after four, eight and 12 weeks of treatment. This may be because of differences in the ulcer population or the ulcer size.

When presenting the results of an ulcer healing study comparing different drug treatments, most authors declare the drugs equally effective if there is no significant difference between the drugs. It is often forgotten that, even if the p value is greater than 0.05, there is a risk of falsely accepting two treatments as equally effective although the true difference in healing rates may be large.\(^\text{24, 25}\) A more reliable comparison of efficacy is the 95% confidence interval for the difference in healing rates between the drugs.\(^\text{10}\) This means that the probability that the true difference between healing rates is not within this interval is less than 5%.

It is not unusual that a single comparison among a large number of statistical calculations on the same material may show a significant difference. This can be referred to random and therefore the isolated significant difference in patients taking antacid
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tablets on day 21 cannot be regarded as clinically relevant. The overall intake of antacid was very low and did not reach the acid neutralising capacity that is necessary for ulcer healing. Although antacid compounds give relief of acute symptoms, we find it preferable to minimise antacid intake in gastric ulcer therapy when other drugs like sucralfate or cimetidine are used. Antacids have unwanted effects and may also interfere with the bioavailability of other drugs, including cimetidine. Large amounts of antacid taken together with sucralfate might also interfere with the sucralfate-protein binding capacity. The unwanted effects recorded in our study are similar to those previously reported and no serious adverse reactions were noted.

Succralfate and cimetidine are both effective in the short term treatment of gastric ulcer. The 95% confidence interval for the difference in ulcer healing efficacy between sucralfate and cimetidine ranges from +11% to −2% – that is, the healing efficacy of sucralfate is at most 11% better or 2% worse than that of cimetidine.

We wish to thank Farmos Group AB and SK&F CO for the supply of drugs during the study. We also thank the endoscopy assistants at our hospitals, who have helped us with both clinical and administrative work, Anders Odén, PhD who has done the statistical calculations and Mrs Maj-Lis Fröjd, at the Surgical Department in Trollhättan, who typed the manuscript.

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