Effect of Omeprazole and Cimetidine on Healing of Chronic Gastric Ulcers and Gastric Acid Secretion in Rats

PETER SKOV OLSEN, KIM THERKELSEN and STEEN SEIER POULSEN

Department of Surgery C, Rigshospitalet and Department of Anatomy B, the Panum Institute, University of Copenhagen, Copenhagen, Denmark

SKOV OLSEN, P., THERKELSEN, K. and POULSEN, S.S. Effect of Omeprazole and Cimetidine on Healing of Chronic Gastric Ulcers and Gastric Acid Secretion in Rats. Tohoku J. exp. Med., 1988, 155 (4), 305-310 — The effect of omeprazole and cimetidine on healing of chronic gastric ulcers and gastric acid secretion was investigated in rats. The effect of three doses of omeprazole given orally once daily for 25 days was investigated. In controls median ulcer healing was 19.6% after 25 days. Omeprazole increased median ulcer healing from 36% at 145 µmole/kg/day to 80% at 580 µmole/kg/day. Basal and pentagastrin stimulated gastric acid secretion decreased dose-dependently by nearly 90% at a dose of 580 µmole/kg/day 22-24 hr after the last dose of omeprazole. Cimetidine given twice daily, in a dose that initially inhibits gastric acid secretion by 95%, reduced acid secretion by only 50% 11 hr after the last dose. Median ulcer healing after treatment with cimetidine for 25 days was 41%. This study demonstrates that omeprazole has a more long-acting inhibitory effect on gastric acid secretion compared to cimetidine and accelerates healing of chronic gastric ulcers dose-dependently in rats —— omeprazole; cimetidine; chronic gastric ulcers; gastric acid secretion; rats

Omeprazole is a substituted benzimidazole that acts directly on the parietal cell by blocking the H+, K+-adenosine triphosphatase, the proton pump of the parietal cell (Fellenius et al. 1981). In man and animals omeprazole is a strong and long-acting inhibitor of acid secretion (Larsson et al. 1983; Sharma et al. 1984). A nearly 100% inhibition of gastric acid secretion can be obtained, a property not reported for other inhibitors of acid secretion such as H₂-receptor blockers (Sharma et al. 1984). Due to the strong antisecretory effect of omeprazole this drug might be applicable for treatment of gastric and duodenal ulcers.

Healing rates of approximately 95–100% of duodenal ulcers after 4 weeks of treatment have been reported in man (Cooperative study 1984; Bardhan et al. 1984).
In rats omeprazole prevents the formation of gastric and duodenal erosions and ulcers (Yamamoto et al. 1984). The present experimental study was undertaken to compare the effect of omeprazole and cimetidine on chronic gastric ulcers and gastric acid secretion in rats.

**Materials and Methods**

**Animals**

Male Wistar rats weighing approximately 250 g were used. Before the experiment the rats were fasted overnight with free access to water.

**Gastric ulcer studies**

Chronic gastric ulcers were induced by a slight modification of the acetic acid method (Takagi et al. 1969). Under ether anesthesia a laparotomy was made and a round glass mould (diameter 6 mm) was placed on the serosal surface at the fundo-antral junction of the stomach. Acetic acid 100 μl (17.5 mole/liter) was placed in the mould and removed after 120 sec. A recovery period of seven days was given before treatment was initiated.

Ulcer healing was investigated in rats in groups of 20. Omeprazole was administered in doses of 145, 290 and 580 μmole/kg/day (50, 100 and 200 mg/kg/day) in a volume of 1 ml for 25 days. Omeprazole was given by gastric intubation once daily. Cimetidine was given in a dose of 2,000 μmole/kg/day (500 mg/kg/day) in a volume of 1 ml and administered twice daily by gastric intubation. Controls received saline.

After 25 days of treatment all rats were sacrificed and the stomach and duodenum were fixed in situ by intraluminal injection of formalin 10%. The organs were removed, cut open and suspended on a polyethylene plate in 10% formalin for 24 hr, washed with water and stained with periodic acid-Schiff reagent. The organs were studied under a stereomicroscope and the ulcerated area was photographed. On the photographs the outline of the original ulcer and the part that had not healed could be identified. The size of the original and remaining ulcer was measured planimetrically using a Hewlett Packard 9874 A digitizer (Hewlett Packard Co., Palo Alto, CA, USA). The results were corrected for the magnification of the photographs. The size of the original and remaining ulcer was expressed in mm

**Effect of omeprazole and cimetidine on acid secretion**

Ten rats were equipped with a chronic gastric cannula. Each dose of omeprazole, 145, 290 and 580 μmole/kg/day, was given orally for 3 days, whereafter the effect on acid secretion was investigated. Basal gastric acid secretion was measured for 60 min 22 hr after the last dose of omeprazole. Thereafter the rats received pentagastrin 50 μg/kg s.c. (Peptavlon®; ICI, Macclesfield, UK) and acid secretion was collected for 60 min. Rats given cimetidine had gastric acid secretion measured after three days of treatment. Basal gastric acid secretion was measured for 60 min 10 hr after the last dose of cimetidine. Thereafter the rats received pentagastrin 50 μg/kg s.c. and acid secretion was collected for 60 min.

**Laboratory analysis**

The hydrogen ion concentration in gastric acid secretion was determined by titration with NaOH using an autotitrator ABU-12 (Radiometer, Copenhagen, Denmark). From the hydrogen ion concentration and volume the acid output was calculated.

**Statistical analysis**

Statistical evaluation of the data was done by the Mann-Whitney's test for unpaired observations. Probability values ≤ 0.05 were considered significant. Analysis of variance
was performed by Kruskal-Wallis test. Bonferroni's test was used for multiple comparisons. All results are given as medians and total ranges.

**RESULTS**

Chronic gastric ulcers were induced in 100 rats. Five rats died 2–6 days after ulcer induction because of perforation. In the remaining rats the contours of the original and remaining ulcer could readily be identified and measured. In controls the median ulcer healing was 19.5%, total range 10–56%. In rats receiving omeprazole none of the ulcers had healed completely after 25 days of treatment (Fig. 1). Omeprazole however, increased median ulcer healing dose-dependently from 36% at 145 \( \mu \) mole/kg/day to 80% at 580 \( \mu \) mole/kg/day. Median ulcer healing after treatment with cimetidine was 41% (Fig. 1).

Each dose of omeprazole decreased basal and stimulated gastric acid secretion compared with controls. No difference in pentagastrin-stimulated acid secretion was found when the dose of omeprazole increased from 145 \( \mu \) mole/kg/day to 290 \( \mu \) mole/kg/day. Omeprazole at a dose of 580 \( \mu \) mole/kg/hr decreased stimulated acid secretion significantly compared with controls as well as the two lower doses of omeprazole. Cimetidine reduced acid secretion by approximately 50% (Table 1).

![Fig. 1. Effect of omeprazole and cimetidine on healing of chronic gastric ulcers in rats. The size of the regenerated mucosa is given in percent of the size of the original ulcer. Horizontal bar indicate the median. Cimetidine was given in a daily dose of 2,000 \( \mu \) mole/kg.](image)

a, \( p < 0.01 \) compared with controls; b, \( p < 0.01 \) compared with 145 \( \mu \) mole/kg/day; c, \( p < 0.01 \) compared with 290 \( \mu \) mole/kg/day.
In the present study chronic gastric ulcers were induced in rats by destruction of the outer muscular layer by acetic acid. Several experimental models have been used for evaluation of anti-ulcer agents such as the indometacin ulcer model (Kasuya et al. 1979). These methods induce merely superficial ulcerations with a rapid spontaneous healing mainly by contraction of the outer muscular layer (Rosin et al. 1976). If the outer muscular layer is destroyed the healing is slow which makes the model applicable for testing a possible effect of anti-ulcer drugs. This has previously been demonstrated for chronic duodenal ulcers induced by cysteamine as well as acetic acid in rats (Ishibashi et al. 1979; Poulsen et al. 1985).

In this study the median ulcer healing in untreated rats was approximately 20% after 25 days. Treatment with omeprazole for 25 days dose-dependently increased median ulcer healing from 36% at 145 μmole/kg/day to nearly 80% at 580 μmole/kg/day. However, none of the ulcers had healed completely after 25 days of treatment. Compared to other anti-ulcer agents such as H2-receptor antagonists omeprazole is a more potent and long-acting inhibitor of acid secretion (Brimblecombe et al. 1978). It might be postulated however, that a more pronounced inhibition of acid secretion by omeprazole might only have a marginal benefit on ulcer healing compared to other drugs. In humans with duodenal ulcer healing rates of 75–80% have been reported after treatment with H2-receptor antagonists or sucralfate for 4 weeks (Ippoliti and Peterson 1979). In preliminary studies in patients with duodenal ulcer healing rates of approximately 94–98% after 4 weeks of treatment with omeprazole have been found (Rohner et al. 1986; Smallwood et al. 1986). In patients with gastric ulcers healing rates averaged 65–70% after 4 weeks of treatment with omeprazole (Darle et al. 1986; Hütttemann 1986). We have previously compared the effect of omeprazole and 

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (μmole/kg/day)</th>
<th>Basal acid secretion (μmole H+/30 min)</th>
<th>Pentagastrin stimulated acid secretion (μmole H+/30 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>—</td>
<td>74 (45–103)</td>
<td>279 (141–381)</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>145</td>
<td>43 (25–77)a</td>
<td>83 (67–143)a</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>290</td>
<td>32 (17–52)b</td>
<td>74 (74–109)a</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>580</td>
<td>11 (7–19)c</td>
<td>29 (22–42)c</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>2,000</td>
<td>35 (14–40)b</td>
<td>128 (76–249)b</td>
</tr>
</tbody>
</table>

Results are given as medians and total ranges. *p<0.01 compared with controls; **p<0.05 compared with omeprazole 145 μmole/kg/day; ***p<0.01 compared with omeprazole 290 μmole/kg/day.
Omeprazole, Cimetidine and Gastric Ulcers in Rats

We administered cimetidine twice daily in a dose of 1,000 μg/kg. This dose inhibits gastric acid secretion initially by approximately 95% (Poulsen et al. 1986), but this inhibitory effect slowly decreases and after 11 hr, just before the next dose, acid secretion is only inhibited by 50%. The median ulcer healing was 41% after 25 days of treatment with cimetidine given orally. We found a median ulcer healing of 80% after 25 days of treatment at a dose of omeprazole, given once daily as a bolus, that inhibits basal and stimulated gastric acid secretion by approximately 90%. This difference in healing rates is probably caused by differences in pharmacology between cimetidine and omeprazole. When cimetidine and omeprazole are given by gastric intubation to rats the antisecretory effect of omeprazole is longer than cimetidine due to accumulation in the parietal cell from which it leaves much more slowly than it disappears from the blood (Epstein et al. 1964; Larsson et al. 1985). This results in a long-acting inhibitory effect on acid secretion as shown in this study, where acid secretion was inhibited by 85-90%, 22-24 hr after 580 μmole/kg × day of omeprazole. The doses of omeprazole used in our study are considerably higher than the doses known to produce nearly complete inhibition of acid secretion for 24 hr in man (Howden et al. 1984). Investigation of the antisecretory effect of omeprazole after single dose administration in rats showed that the antisecretory effect was not so long in rat as in man and dog (Howden et al. 1984). Our study demonstrates that it is possible to inhibit gastric acid secretion effectively for 24 hr in rats with a single dose of omeprazole.

In conclusion this study has shown that omeprazole can accelerate healing of chronic gastric ulcers in rats. At the highest dose of omeprazole used a nearly complete 24 hr inhibition of acid secretion was found. Omeprazole seems to be more effective than other known anti-ulcer agents. The experimental results suggest that omeprazole might be a more effective drug than cimetidine in treatment of patients with gastric ulcer.

Acknowledgments

Omeprazole was provided by AB Hässle, Möln达尔, Sweden.

References

3) Cooperative study (1984) Omeprazole in duodenal ulceration: Acid inhibition,


