Oxmetidine: clinical pharmacological studies with a new H₂-receptor antagonist

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SUMMARY The gastric antisecretory effects of oxmetidine, a new H₂-receptor antagonist, have been studied in 33 healthy subjects. The relative potency of oxmetidine compared with that of cimetidine depended on the route of administration and the experimental conditions. Oxmetidine intravenously infused was approximately four times as potent as cimetidine, weight for weight, in inhibiting impromidine stimulated gastric acid secretion but was twice as potent when food was used as a stimulus. After oral administration there were no differences in the weight-for-weight potency of oxmetidine and cimetidine, although oxmetidine was twice as potent on a molar basis. These apparent differences according to the route of drug administration are probably due to first pass metabolism of oxmetidine. There were no differences in the duration of action of oxmetidine and cimetidine. Twenty-four hour monitoring of intragastric pH showed that oxmetidine 400 mg twice daily reduced mean hourly 24 hour intragastric pH by 59%, suggesting that a twice daily dosage regimen should be evaluated in the treatment of duodenal ulceration.

Oxmetidine dihydrochloride (Fig. 1) is an example of a new type of H₂-receptor antagonist which is more lipophilic than cimetidine and contains a 5-substituted isocytosine moiety in place of the cyanoguanidine group while retaining the imidazole

showing variation with respect to route of administration and species studied. We have therefore studied the effect of oxmetidine on gastric secretion in man and compared its potency and duration of action with that of cimetidine.

Fig. 1 Structure of oxmetidine dihydrochloride.

ring. Animal pharmacological studies have shown that oxmetidine is a selective H₂-receptor antagonist *in vitro* and a potent inhibitor of histamine-induced gastric acid secretion *in vivo*.¹ However, the potency and duration of action relative to cimetidine were clearly dependent on the experimental conditions

Methods

All studies were carried out on healthy volunteers from whom written informed consent was obtained after detailed explanation of the proposed procedures, which had the approval of the Hospital Ethical Committee.

Thirty-three subjects (32 male and one female) aged 18 to 41 years, mean 25.7 years, were studied.

Twenty-one subjects were studied on more than one occasion and 12 subjects were studied four times. All comparative studies were separated by at least one week.

IMPROMIDINE STIMULATED GASTRIC SECRETION

The effect of the intravenous and intraduodenal administration of oxmetidine and cimetidine was studied during impromidine stimulated gastric secretion.² After an overnight fast a nasogastric tube (14 FR Salem Sump, Sherwood Medical Industries) was passed and positioned in the most dependent part of the stomach under fluoroscopic control. Gastric secretion was collected in 10 minute aliquots throughout by continuous aspiration. The volume of each sample was measured and acid concentration determined by automatic titration to pH 7.0 (Radiometer, Copenhagen). Impromidine 10 µg/kg/h was infused for 60 minutes and peak acid output was calculated as the mean of the last two collections. Oxmetidine 0.8 mg/kg/h was then infused concomitantly for 30 minutes in six subjects. The infusion of impromidine alone was continued for another three hours. In another five subjects, cimetidine 2.0 mg/kg/h was administered using the same experimental design.

To instil drugs directly into the duodenum an additional fine weighted nasogastric tube was passed. Positioning within the duodenum was radiographically confirmed immediately before instillation of oxmetidine or cimetidine 200 mg in 10 ml water. The tube was then withdrawn to minimise the possibility of reflux, and the nasogastric tube clamped for 30 minutes to allow absorption of the drug, the stomach emptied over the next 10 minutes, and regular sampling started after 40 minutes. Infusion of impromidine 10 µg/kg/h continued for up to five hours after dosing.

FOOD STIMULATED GASTRIC ACID SECRETION

The effects of oxmetidine and cimetidine on food stimulated gastric acid secretion were compared in 12 subjects, using a modified intragastric titration technique.^{3,4} After an overnight fast and intubation with a double lumen Salem sump tube, the stomach was emptied and the test meal, total volume 550 ml (pH 5.5, 37°C), instilled. Gastric contents were mixed throughout by continuous hand aspiration and return of 50 ml of the meal; the subjects turned regularly from side to side. For two hours samples were taken every two minutes, the pH measured, and intragastric pH maintained at 5.5 by adjusting the rate of infusion of sodium bicarbonate to the stomach. Gastric acid output

was calculated as the amount of bicarbonate delivered (mmol).

The effect of the oral administration of cimetidine and oxmetidine 200 mg was compared with placebo (water) in a group of six subjects given two homogenised steak meals, the composition of which has been previously described.⁴ Drugs were administered in solution through the nasogastric tube immediately before instillation of the first meal. Intragastric titration continued for two hours, the subject then rested for one hour, after which a second test meal was given and gastric acid output measured for another two hours.

The effects of intravenous saline, cimetidine 0.5 mg/kg/h, and oxmetidine 0.25 and 0.125 mg/kg/h were compared in another six subjects stimulated by a test meal of Clinifeed 500 (Roussell), containing protein 30 g, fat 11 g, and carbohydrate 70 g in 550 ml water (2100 kJ). Drugs were given by intravenous infusion for one hour before the meal and throughout the study.

TWENTY-FOUR HOUR INTRAGASTRIC ACIDITY

The effects of oxmetidine 400 mg twice daily (at breakfast and bedtime), cimetidine 1.0 g/day (200 mg three times a day with meals and 400 mg at bedtime), cimetidine 400 mg twice daily, and placebo on 24 hour intragastric acidity were compared in six ambulant subjects, using a previously validated technique.⁵ Samples of gastric juice were taken hourly and the pH recorded. Low fat, high protein meals were prepared and standardised over the four study days. The order of drug administration was randomised according to a Latin Square design. For the purpose of analysis all results have been expressed in terms of hydrogen ion activity (mmol/l).

STATISTICAL ANALYSIS

Comparison of the effects of oxmetidine and cimetidine 200 mg by mouth on food stimulated gastric acid output was made by means of a split block analysis of variance. Other data have been analysed by means of Student's *t* test for paired data.

Results

IMPROMIDINE STIMULATED GASTRIC ACID SECRETION

Similar responses were seen in all six subjects during and after the intravenous infusion of oxmetidine (Fig. 2). Oxmetidine 0.8 mg/kg/h for 30 minutes markedly inhibited stimulated gastric acid output. No effect was seen during the first 10 minutes of the infusion and maximum response occurred during the 10 minute collection period

Fig. 2 Effect of oxmetidine on impromidine stimulated gastric acid secretion (mean of six subjects).

immediately after the end of the infusion of the antagonist. At this time, mean gastric acid output was reduced by 96%, volume by 77.1%, and hydrogen ion concentration by 81.6%. Thereafter, gastric acid output gradually returned towards maximally stimulated values.

A similar response pattern occurred in another five subjects who received cimetidine 2.0 mg/kg/h (Fig. 3). Maximum response was seen during the last 10 minutes of the infusion of cimetidine when mean gastric acid output was reduced by 65.1%, volume by 48.2%, and H^+ concentration by 37.5%. Again, there followed a gradual recovery of the gastric secretory response.

In order to examine the duration of action in more detail, response-time curves were plotted using a logit function as an expression of response

($\ln \frac{R}{R_{\max} - R}$ where R is response as a percentage inhibition and $R_{\max} = 100$)

as animal studies have shown that this function correlates well with plasma concentration data. Examination of the terminal phase of the bi-exponential curves, from which response half-life may be calculated, clearly shows no major differences in the duration of action of the antagonists (Fig. 4).

After intraduodenal administration, no differences were seen in the effect of oxmetidine or cimetidine 200 mg with respect to either potency or duration of action (Fig. 5). Maximally stimulated gastric acid secretion was reduced by a mean of 80% by both antagonists due to a reduction in volume and hydrogen ion concentration of the gastric juice.

FOOD STIMULATED ACID SECRETION

Oxmetidine and cimetidine 200 mg by mouth significantly reduced gastric acid output in response to a meal ($P < 0.01$). Total gastric acid output over 90 minutes was reduced by 26.9 and 41.5% respectively, although these values were not significantly different from one another; a smaller but significant difference was seen between placebo and active treatments after the second meal (25.5 and 23.0%, ($P < 0.05$). Maximum inhibition was seen 60 to 120 minutes after drug administration, although the effect of cimetidine appeared to be slightly more rapid. After the second meal, the degree of inhibition decreased with time for both treatments (Fig. 6).

Intravenous infusion of oxmetidine 0.125 mg/kg/h, 0.25 mg/kg/h, or cimetidine 0.5 mg/kg/h, reduced meal stimulated gastric acid

Fig. 3 Effect of cimetidine on impromidine stimulated gastric acid secretion (mean of five subjects).

Fig. 4 Mean responses (inhibition of gastric acid output) vs time curves after the intravenous infusion of omeprazole (●—●) and cimetidine (○—○).

output by a mean of 30.9, 69.1 and 69.6% respectively compared with placebo.

TWENTY-FOUR HOUR INTRAGASTRIC ACIDITY
Compared with placebo, the cimetidine 1.0 g/day regimen reduced mean hourly hydrogen ion activity

from 15.9 ± 3.0 ($\pm$ SEM) mmol/l to 7.12 ± 0.55 mmol/l (55.2%, $P < 0.05$), cimetidine 400 mg twice daily to 7.31 ± 1.30 mmol/l (54.0%, $P < 0.05$), and omeprazole 400 mg twice daily to 6.58 ± 0.79 mmol/l (58.6%, $P < 0.05$). Differences between the three treatment regimens were not significant, and

Fig. 5 Effect of intraduodenal administration of oxmetidine (.....) or cimetidine (—) 200 mg on stimulated gastric acid output (mean of three subjects).

Fig. 6 Percentage inhibition of gastric acid output in each 30 minute period after instillation of a test meal (mean of six subjects $\pm$ SEM).

all three produced a reduction in intragastric acidity throughout the whole study period (Fig. 7). An increase in hydrogen ion activity was seen at 1800 hours just before the evening meal and this

response was reduced during treatment with cimetidine 1.0 g/day, although variance in the data meant that this effect was not significantly different from the other treatments. No other differences were seen in the pattern of the responses over the 24 hour study period. The reduction in gastric acidity was greater overnight than during the day with all treatment regimens.

OTHER EFFECTS

No side-effects were either observed or reported during these studies and no clinically significant changes were seen in any haematological or biochemical parameters.

Discussion

After intravenous infusion, oxmetidine was approximately eight times as potent as cimetidine on a molar basis (four times on a weight for weight basis) as an inhibitor of impromidine stimulated gastric acid secretion. However, after intraduodenal administration, no difference was seen in the effect of 200 mg doses of each compound. These apparent differences in relative potency, according to the route of drug administration, are the result of the pharmacokinetic handling of oxmetidine. The systemic availability of an oral dose of oxmetidine is approximately 50%.⁶ This is probably as a result of first pass metabolism; biliary elimination of oxmetidine has been demonstrated with 37% of the

administered dose appearing in the bile as a glucuronide conjugate.⁷ The similarity in potency of orally administered oxmetidine and cimetidine was confirmed by the results of the food stimulated studies. In these studies cimetidine produced less inhibition than had been reported previously⁴ but this may be explained by small numbers and individual variations in response.

To study duration of action, it is important either to examine the duration of the response to equipotent doses of the drugs to be compared, or to study the rate of change if a linear relationship between time and response can be derived. The use of the logit function allows the duration of response to be examined in this way. This method has the disadvantage that it relies on that part of the response curve which is measured with the least accuracy—that is, percentage inhibitions of less than 50%—and comparisons are also only strictly comparable within subjects. Within these limitations, there was no significant difference in the duration of action of oxmetidine and cimetidine. This was supported in the food studies where a comparable maximum response occurred with no difference in the response to a second meal some hours later.

The relative potency of the two antagonists when given by intravenous infusion depended upon the experimental conditions. Against impromidine stimulated gastric acid secretion oxmetidine was four times as potent as cimetidine on a weight for weight basis, while during food stimulated gastric acid secretion this difference was reduced to approximately twice. Similar differences in esti-

mates of relative potency against different secretory stimuli have been reported for ranitidine and cimetidine.⁸

Previous studies with cimetidine have shown that 24 hour monitoring of intragastric pH provides a useful means of assessing the effect of multiple dosing under relatively physiological conditions with patients fully ambulant and eating a normal diet.^{5,9} The pattern of 24 hour intragastric acidity seen in these studies was similar to that seen previously. Treatment with cimetidine 1.0 g/day, cimetidine 400 mg twice daily, or oxmetidine 400 mg twice daily resulted in a decrease in mean hydrogen ion activity throughout the study period. The effect with all treatments was less marked by day when regular meals and normal activity resulted in mean hydrogen ion activity of less than 10 mmol/l on many occasions during the placebo treatment study day. Oxmetidine 400 mg twice daily reduced intragastric acidity at least as well as either dose of cimetidine. After all three treatment regimens, 50% of the gastric samples had a pH of 2.5 or more, while 20% were $\geq$ pH 4.

Oxmetidine was well tolerated in all subjects and no untoward signs or symptoms were reported. In another series of studies, oxmetidine in bolus doses of 50–200 mg intravenously had no effect on circulating serum prolactin, in contrast with marked but transient increases seen in the same subjects after the intravenous administration of similar doses of cimetidine.¹⁰ Animal toxicity studies have shown no effects of oxmetidine on prostate, seminal vesicle, or testes weight and specific binding studies with ³H dihydrotestosterone have

shown it to have less than 1/100 of the activity of cimetidine, itself only a very weak anti-androgen (P C Sivel, personal communication). These findings, together with its potent anti-secretory activity in man, suggest that oxmetidine should be evaluated in the treatment of duodenal ulcer disease and that a twice daily dosage regimen of cimetidine or oxmetidine may produce sufficient reduction in gastric acidity to allow ulcer healing.

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References

- 1 Blakemore RC, Brown TH, Durant GJ, *et al.* SK&F 92994: a new histamine H_2 receptor antagonist. *Br J Pharmacol* 1980; **70**:105P.
- 2 Hunt RH, Mills JG, Beresford J, Billings JA, Burland WL, Milton-Thompson GJ. Gastric secretory studies in humans with impromidine (SK&F 92676)—a specific histamine H_2 receptor agonist. *Gastroenterology* 1980; **78**:505–11.
- 3 Fordtran JS, Walsh JH. Gastric acid secretion rate and buffer content of the stomach after eating. Results in normal subjects and in patients with duodenal ulcer. *J Clin Invest* 1973; **52**:645–7.
- 4 Pounder RE, Williams JG, Russell RCG, Milton-Thompson GJ, Misiewicz JJ. Inhibition of food-stimulated gastric acid secretion by cimetidine. *Gut* 1976; **17**:161–8.
- 5 Pounder RE, Williams JG, Milton-Thompson GJ, Misiewicz JJ. Effects of cimetidine on 24-hour intragastric acidity in normal subjects. *Gut* 1976; **17**:133–8.
- 6 Mills JG, Melvin MA, Griffiths R, Hunt RH, Burland WL, Milton-Thompson GJ. SK&F 92994—a new histamine H_2 receptor antagonist. *Gut* 1980; **5**:A462.
- 7 Gugler R, Somogyi A. The biliary excretion of histamine H_2 -receptor antagonist cimetidine and oxmetidine. *Clin Pharmacol Ther* 1981; **29**:249–50.
- 8 Konturek SJ, Obtulowicz W, Kwiecien N, Sito E, Mikes E, Olesky J. Comparison of ranitidine and cimetidine in the inhibition of histamine, sham-feeding, and urea-induced gastric secretion in duodenal ulcer patients. *Gut* 1980; **21**:181–6.
- 9 Pounder RE, Williams JG, Milton-Thompson GJ, Misiewicz JJ. 24-hour control of intragastric acidity by cimetidine in duodenal ulcer patients. *Lancet* 1975; **2**:1069–72.
- 10 Sharpe PC, Melvin MA, Mills Jane G, Burland WL, Groom GV. Prolactin responses to histamine H_2 receptor antagonists. *Acta Endocrinol(Kbh)* 1980; **95**:308–13.