Large single daily dose of histamine H\textsubscript{2} receptor antagonist for duodenal ulcer. How much and when? A clinical pharmacological study

M DEAKIN, HELEN P GLENNY, J K RAMAGE, JANE G MILLS, W L BURLAND, AND J G WILLIAMS

From the Department of Gastroenterology, Royal Naval Hospital Haslar; Department of Clinical Research and Development, Smith Kline and French Research Ltd, Welwyn, Herts

SUMMARY The effects of single doses of cimetidine 800, 1200, and 1600 mg, given at 2300 h or 800, and 1600 mg at 1800 h, have been studied in patients with duodenal ulcer disease in symptomatic remission, and compared with cimetidine 400 mg bd (0800 h and 2300 h) and ranitidine 300 mg (given at 1800 h) respectively. A dose related reduction in intragastric acidity was seen. All single nocturnal (2300 h) doses of cimetidine produced anacidity overnight. This was not achieved with dosing at 1800 h although the duration of inhibition of gastric acidity was longer. Inhibition of overnight acid and pepsin outputs were similarly dose and timing related, but inhibition of peptic activity was much less after dosing at 1800 h. Cimetidine 1600 mg and ranitidine 300 mg were similar in their effects.

There is growing evidence that the control of nocturnal gastric secretion is the most important factor in the healing of duodenal ulcers.\textsuperscript{1,4} Pharmacological studies have shown that in patients with duodenal ulcer, a single night time dose of cimetidine 800 mg is as effective as 400 mg given twice daily in reducing mean 24 hour hydrogen ion activity, while nocturnal acid secretion is suppressed to a significantly greater extent.\textsuperscript{6} The efficacy of single night time doses of cimetidine or ranitidine in the treatment of duodenal ulcer has been shown\textsuperscript{7,8} and a recent review of data from over 100 clinical studies demonstrated a correlation between the size of the night time dose and the proportion of patients with a healed ulcer after four weeks' treatment.\textsuperscript{7}

The longest period of continuous unbuffered intragastric acidity during a 24 hour period extends from after the evening meal until breakfast. Dosing with the evening meal should result in adequate blood concentration of H\textsubscript{2}-receptor antagonist by the time the buffering effect of the meal is waning.\textsuperscript{9} An improved symptomatic and therapeutic response might therefore be expected if adequate inhibition is obtained for a longer period with earlier dosing.

The present studies were designed to examine the effect of increasing the dose, or altering the time of drug administration, on the extent and duration of suppression of gastric acid and pepsin output by cimetidine.

Methods

SUBJECTS Two double blind studies of 24 hour intragastric acidity, nocturnal acid and pepsin outputs were done in subjects with endoscopically diagnosed duodenal ulcer disease currently in symptomatic remission. The methods used were similar in both studies.

STUDY 1 Ten men (mean age 40 years, range 29–53 years) were studied on five occasions and received: placebo, cimetidine 400 mg bd (0800 h and 2300 h), cimetidine 800 mg, 1200 mg, and 1600 mg at 2300 h as a single daily dose.

STUDY 2 Eight men (mean age 38 years, range 29–46 years) were studied on four occasions and received: placebo, cimetidine 800 mg (at 1800 h), cimetidine 1600 mg (at 1800 h), and ranitidine 300 mg (at 1800 h) as a single daily dose.

Treatment was given according to a randomised
Latin Square allocation. The studies were conducted double blind using a double dummy tablet technique. In both studies dosing started on the evening before the study day. Study days were at least one week but no longer than two weeks apart.

Subjects were admitted to the ward at 1600 h and a sump type nasogastric tube passed. Three identical standard meals comprising 375 ml Clinifeed 500 (Roussel Laboratories Ltd) and one Oxo cube dissolved in 200 ml hot water were given at 1800 h, and 0800 h and 1300 h the following day. Five cups of tea (200 ml) were allowed within the 24 hour period at standard times and tea with two biscuits at 2200 h. Samples of gastric juice were taken for pH measurement at 15 minute intervals for three hours after each meal and then half-hourly. Overnight from 0030 h to 0730 h continuous gastric aspiration was performed by intermittent positive pressure suction pump (Egnel, Switzerland). Gastric juice was collected in hourly aliquots. The volume of each collection was recorded, pH measured and acid concentration determined by automatic titration to pH 7 with 0.1 M NaOH. A sample of each hourly collection was stored at 4°C for assay of pepsin within 18 hours. Pepsin was expressed as peptic activity (IU/l) determined from the rate of degradation of an albumin-bromophenol blue substrate at pH 2.1 The study was discontinued at 1700 h on the day after dosing. Ethical approval for the studies was given by the Royal Naval Medical Research Subcommittee.

DATA ANALYSIS
Hydrogen ion activity (mmol/l) was calculated as \( \log 10 \text{pH} \). Median values for the 24 hours, 1800 to 0030 h (evening), 0130 to 0730 h (overnight), 0800 to 1230 h (morning) and 1300 to 1700 h (afternoon) periods were calculated from the hourly and half hourly results.

Nocturnal volume, acid and pepsin outputs were calculated as the sum of the seven hours overnight (0030 to 0730 h) and pepsin concentration as the mean over this period. Data have been summarised as the median with 25th and 75th percentiles for descriptive purposes. The effect of treatment compared with placebo has been calculated from median values. Treatment differences between each of the nocte doses of cimetidine and cimetidine bd (study 1) were examined by a Friedman two way analysis of variance followed by two sided Wilcoxon’s paired comparison tests; parametric tests (analysis of variance and \( t \) test) were applied to all other variables (study 1). A Wilcoxon’s paired comparison test was

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Fig. 1  Intragastric pH against time showing mean (+ or – SEM). Values for 10 subjects receiving placebo (——), cimetidine 400 mg bd (———), cimetidine 800 mg nocte (· · · · ·) and cimetidine 1200 mg nocte (· · · · ·). Standard meals (M) were taken at 1800, 0800 and 1300 h and cups of tea (T) as indicated. Tablets were taken at 0800 and 2300 h.
used to examine for statistical significance in study 2. The pH profiles for each treatment have been presented in graphical form as the mean pH with standard error of the mean.\(^1\)\(^4\)

**Results**

**Intragastric pH**

The mean 24 hour intragastric pH profiles for placebo, cimetidine 400 mg bd, cimetidine 800 mg nocte and cimetidine 1200 mg nocte are shown in Figure 1 and the pH profiles for placebo, cimetidine 800 mg and cimetidine 1600 mg nocte (2300 h – study 1) in Figure 2. The extent of the change in intragastric pH overnight was dose related. Cimetidine 1600 mg led to achlorhydria overnight in all subjects. This was terminated by the stimulus of rising for breakfast but with a delay in the pH fall after this meal. The effects of cimetidine 400 mg and 800 mg were less profound and of shorter duration.

The mean 24 hour pH profiles for placebo, cimetidine 800 mg, cimetidine 1600 mg and ranitidine 300 mg when given at 1800 h (study 2) are shown in Figure 3. In contrast with the period of overnight achlorhydria after dosing at 2300 h, the effect on intragastric pH was less profound but of longer duration. No change in intragastric pH was seen for the hour after ingestion and the effects were transiently overcome by the stimulus of the evening snack (2200 h). Cimetidine 800 mg when given at 1800 h did not maintain effective control of intragastric pH throughout the night. The effects of cimetidine 1600 mg and ranitidine 300 mg were similar.

**Intragastric hydrogen ion activity**

The median hourly hydrogen ion activities are given in Table 1 together with the percentage inhibition relative to placebo for the 24 hour period and periods within the study day.

**Study 1: 2300 h dosing**

Over the whole 24 hour period all treatments caused a significant decrease in hydrogen ion activity (p<0.01). Cimetidine 400 mg bd decreased median hourly hydrogen ion activity to a greater extent than cimetidine 800 mg (p<0.05) but there was no statistically significant difference between cimetidine 400 mg bd and cimetidine 1200 mg or cimetidine 1600 mg.
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Study 1: 2300 h dosing
The inhibition of nocturnal acid and pepsin output by cimetidine 400 mg was significantly less than cimetidine 800 mg nocte (p<0.05), cimetidine 1200 mg and 1600 mg nocte (p<0.01). Single night time doses of cimetidine 1200 mg and 1600 mg produced almost complete inhibition of acid and pepsin outputs and of pepsic activity overnight.

Study 2: 1800 h dosing
Reductions in night time acid and pepsin outputs were less than after dosing at 2300 h; this effect was most clearly shown for pepsin output and pepsic activity. After dosing at 1800 h intragastric pH remained acidic and significant pepsic activity persisted. The effects of cimetidine 1600 mg and ranitidine 300 mg were comparable.

Discussion
The extent or duration of inhibition of gastric secretion necessary to induce healing of duodenal ulcers is not known. Clinical studies have shown, however, that a twice daily dosage regimen of an H₂ receptor antagonist is as effective as a qid regimen and furthermore that a large single night time dose is as effective as a bd dose. Thus, 24 hour control of

Overnight the effects of cimetidine 800 mg, 1200 mg, and 1600 mg nocte were significantly greater than cimetidine 400 mg (p<0.05, p<0.01, p<0.01 respectively) but there was no significant difference between any of the higher doses.

Cimetidine 1600 mg had a significant effect during the morning after administration (40%, p<0.01) but the effect was not as great as that after the morning dose of cimetidine 400 mg (67%). The effects of cimetidine 800 mg or 1200 mg were not significant relative to placebo during the morning period. There were no significant drug effects during the afternoon of the day after any of the night time only doses.

Study 2: 1800 h dosing
The effects of cimetidine 1600 mg and ranitidine 300 mg on 24 hour, evening and overnight intragastric acidity were similar and not statistically different but these doses decreased hydrogen ion activity to a greater extent than cimetidine 800 mg (p<0.05). None of the doses had a significant effect relative to placebo during the morning or afternoon after administration.

Nocturnal Acid and Pepsin Output
The median values for the night time acid and pepsin outputs and peptic activity are shown in Table 2.
Intragastric acidity is not necessary to heal duodenal ulcers and control of night time acidity would seem to be the single most important factor. A single daily dose has the added theoretical advantage of improving patient compliance and a larger dose may overcome the relative pharmacological resistance to H₂ receptor antagonists seen overnight in some patients who fail to heal on a smaller dose, in a bd regimen.

Twenty four hour studies of gastric secretion have been useful previously in designing dosing regimens of antisecretory drugs. Such studies have traditionally reported results as hydrogen ion activity rather than pH. We have chosen to use both as pH will bring out the differences between higher doses, whereas hydrogen ion activity tends towards zero once pH is greater than 5, and intragastric pH after higher doses of H₂ receptor antagonists can be in the 6–9 pH range. Pepsin is known to be important in the pathogenesis of duodenal ulcers and peptic activity is pH related, falling once intragastric pH is above 4 with irreversible loss of activity at pH 6–5 to 7. It has been shown that some patients with duodenal ulcers secrete pepsins that are still active at higher pH than conventionally considered and the mucolytic properties of these pepsin species may be important. Therefore, in assessing the effectiveness of a drug regimen a low hydrogen ion activity will indicate when the intragastric pH is unlikely to support high intragastric peptic activity but the continuing presence of unchanged pepsin should not be discounted.

What therefore is the optimal dose of cimetidine when used as a once nightly dose? After a dose of 800 mg or above, when given at 2300 h, intragastric hydrogen ion activity was almost completely inhibited in this study and night time acid output was virtually nil. Fall in night time peptic activity, however, correlated with intragastric pH change. The percentage of overnight samples of pH >6 was similar after both cimetidine 400 mg and 800 mg (46% and 51% respectively). Intragastric pepsin concentration was not reduced further by cimetidine 800 mg than by the 400 mg dose. After cimetidine 1200 mg and 1600 mg there was a further fall in pepsin concentration as a greater number of samples...
reached a pH >6 (81% and 84% respectively). Therefore, in terms of nocturnal intragastric acidity, cimetidine 800 mg would appear to be the optimum night time dose for cimetidine as long as healing is dependent on raising intragastric pH above the optimum for pepsin and not on denaturing the enzyme. Even with the 800 mg dose the quantity of pepsin reaching the duodenum is minimal as volume changes were considerable.

Increasing the dose of cimetidine to 1600 mg produces a longer duration of action; hydrogen ion activity was reduced by 40% during the morning after administration. This was, however, not as effective as the morning dose of cimetidine 400 mg (given bd), represents a very small change in intragastric pH and is unlikely to be of clinical importance.

During a 24 hour period, the longest single period of intragastric acidity that remains unbuffered by meals includes the evening and night time periods. Theoretically the effectiveness in healing or in symptomatic control might be improved if the period of sustained inhibition were more prolonged. After dosing at 1800, however, the pattern of control of intragastric activity was different: the response to cimetidine 800 mg and 1600 mg was more prolonged but less profound than after dosing at 2300 h, with some acidity persisting overnight. The close correlation of healing with overnight inhibition of acidity suggests that this would be a disadvantage in the treatment of duodenal ulcers.

When treatment is given at 1800 h, the effect of tea and biscuits at 2200 h and tea at 2400 h is dramatic as can be seen from Figure 3. The ease with which H₂ blockade can be overcome by food has been noted previously and these patient data reinforce the suggestion that patients with duodenal ulcer might be advised to take only a light meal some time before the bedtime dose of cimetidine.

Despite considerable decrease in nocturnal acid output after a dose of cimetidine at 1800 h the decrease in nocturnal pepsin output was less marked than after 2300 h dosing when cimetidine 1600 mg effected almost complete inhibition. Median nocturnal pepsin concentration was decreased by 53.6% and 86.9% when cimetidine 800 mg and 1600 mg respectively were given at 2300 h whereas there was little change when the dose was given at 1800 h (23.5% and 20% respectively). As previously noted inhibition of pepsin correlated with the increase in intragastric pH. After dosing at 1800 h intragastric pH change was moderate and unlikely to have caused significant denaturation of pepsin. This suggests that H₂ receptor antagonists have an indirect effect on pepsin secretion which is secondary to pH and
volume changes. The clinical significance of greater inhibition of in vitro peptic activity overnight has not been determined but may be an advantage.

In conclusion, we have shown that evening and overnight intragastric acidity is inhibited by dosing with an H2 receptor antagonist at 1800 h, but dosing at 2300 h is likely to be more effective in the management of duodenal ulcers because nocturnal anacidity is achieved and inhibition of peptic activity is greater. Significant inhibition of peptic activity by denaturation seems to occur only under anacidic conditions.

Cimetidine 800 mg nocte (2300 h) produced almost complete suppression of nocturnal acidity in the group of patients studied, although 1600 mg did increase intragastric pH further. This higher dose may be of benefit to those patients in whom pharmacological resistance to this dose has been demonstrated.12 Treatment should, however, be taken on retiring as earlier dosing does not adequately control nocturnal intragastric acidity or peptic activity.

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