

# Effect of no treatment, cimetidine 1 g/day, cimetidine 2 g/day and cimetidine combined with atropine on nocturnal gastric secretion in cimetidine non-responders

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**SUMMARY** We have studied nocturnal acid secretion in patients with duodenal ulcer who met predetermined criteria of poor clinical response to cimetidine. Different groups of patients were investigated receiving either no treatment, cimetidine 1 g/day, cimetidine 2 g/day or cimetidine 1 g/day combined with atropine 4.8 mg/day. The results were compared with those obtained from other patients with duodenal ulcer who were studied in our department but who were not classified as according to their clinical response to cimetidine. The results show that despite adequate absorption, cimetidine has a decreased effect at controlling acid secretion in the poor responders and that increasing the dose of drug does not improve response. Control of acid output was, however, dramatically improved when cimetidine was combined with atropine which suggests that patients who do not respond to H<sub>2</sub>-receptor blockade should be treated by a combination of cimetidine with an anticholinergic agent.

Treatment with cimetidine 800 mg or 1 g/day leaves between 13% and 43% of duodenal ulcers unhealed.<sup>1</sup> Although increasing the length of treatment improves healing,<sup>2</sup> some resistant ulcers present a problem in clinical practice. Should they for example be offered an increased dose of cimetidine, alternative medical therapy, or surgery.

During previous studies of 24 hour intragastric acidity<sup>3</sup> in patients with duodenal ulcer we have shown that during the daytime individual responses to cimetidine are similar, but overnight, two distinct patterns of response are seen with one group showing little or no decrease in hydrogen ion activity (H<sup>+</sup>) while the second group become almost anacidic. When analysed retrospectively, the former group of patients were found to have a poor clinical response to treatment.

In the present study we have taken a group of patients who prospectively met criteria of poor response to cimetidine (non-responders) and compared the overnight hydrogen ion activity and acid output with that obtained from unselected duodenal ulcer patients studied previously in our department but who were not classified as being a responder or non-responder. We also studied the

effect on nocturnal acid secretion of doubling the dose of cimetidine from 1 g/day to 2 g/day.

Previous reports have suggested that control of acid secretion may be improved by combination treatment with an anticholinergic agent and cimetidine.<sup>4</sup> We also examined nocturnal gastric secretion after a combination of cimetidine 1 g/day and atropine 4.8 mg/day.

## Methods

### PATIENTS

Patients with duodenal ulcer were defined as having a poor clinical response to cimetidine by meeting one or more of the following endoscopically proven criteria: (1) Failure to heal after cimetidine 1 g/day for six weeks. (2) Relapse within a month of stopping cimetidine 1 g/day for a minimum of six weeks. (3) Relapse on maintenance therapy of 400 mg nocte.

Twelve patients who prospectively met one or more of these criteria were studied over three separate 24 hour periods receiving either no treatment, cimetidine 200 mg tds and 400 mg at 2200 hours (1 g/day) or cimetidine 400 mg tds and 800 mg at 2200 hours (2 g/day). A further 13 patients meeting our criteria were studied over two separate 24 hour periods receiving either no treatment or

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cimetidine 1 g/day.

The results of both these groups were compared with a group of 25 patients with an endoscopically proven duodenal ulcer in remission who had been studied previously in our department and were not selected by any criteria as being a responder or non-responder. Seven non-responders were studied over a third 24 hour period receiving cimetidine combined with atropine 1.2 mg qds with food (4.8 mg/day).

The study design was similar to that used previously from our department.<sup>5</sup> After an overnight fast, patients were admitted to a specially allocated ward at 0730 hours. Standard meals were given at identical times on each study day. The number of cigarettes and drinks consumed were recorded on a data sheet on the first study day and repeated on subsequent occasions. As we were particularly interested in the overnight period, patients were allowed to eat breakfast and lunch before being intubated with a size 10 French nasogastric Salem sump tube. This allowed the patients to eat two of their three main meals without the discomfort of a nasogastric tube.

At 1900 hours a 19 gauge butterfly cannula was inserted into a forearm vein and blood taken throughout the overnight period in 12 patients receiving the 1 g/day regimen and four patients receiving the 2 g/day regimen. After separation in a lithium heparin tube and storage at  $-20^{\circ}\text{C}$ , plasma was sent to Wickam Laboratories for estimation of plasma cimetidine by high pressure liquid chromatography.<sup>6</sup> The stomach was emptied by manual suction at 0100 hours and continuous mechanical aspiration applied overnight until 0700 hours. Suction was interrupted every 20 minutes to ensure tube patency. Each hour volume of gastric juice was measured and a 5 ml sample taken for pH estimation using a glass electrode calibrated with buffers of pH 4.0 and 7.0 before each batch of measurements. The sample was then titrated to pH 7.0 with 0.1 molar sodium hydroxide using an autoburette (Radiometer, Copenhagen) and acid output was then calculated.

Measurements of pH were converted to hydrogen ion activity for statistical analysis. Paired Student's *t*

tests compared means from the same group of patients receiving any two different treatments and unpaired Student's *t* tests compared means from any two different groups of patients receiving identical treatments. Comparisons between more than three treatments were analysed by analysis of variance.

## Results

In each study, one third of the non-responders failed to heal on the full dose, one third relapsed on maintenance and one third relapsed within a month of stopping treatment. There were no differences in results of volume, acid output or H<sup>+</sup> activity when each group was analysed separately. No differences were noted in smoking habits recorded on diary cards between the non-responders and the unselected duodenal ulcer patients.

### COMPARISON OF CIMETIDINE 1 G/DAY WITH 2 G/DAY

In the 12 patients receiving no treatment, cimetidine 1 g/day and cimetidine 2 g/day, mean hourly nocturnal (0100–0700 hours) H<sup>+</sup> activity (Table 1) decreased from 45 mmol/l with the 1 g/day dosage regimen ( $p < 0.05$ ) and to 31 mmol/l with the 2 g/day regimen ( $p < 0.05$  compared with no treatment and NS compared with the 1 g/day regimen). Mean hourly nocturnal acid output (Table 1) decreased by 41% with cimetidine 1 g/day ( $p < 0.05$  compared with the no treatment day) and by 51% with cimetidine 2 g/day ( $p < 0.05$  compared with the no treatment day and NS compared with cimetidine 1 g/day). Mean hourly nocturnal volume of secretion (Table 1) decreased with both cimetidine 1 g/day and 2 g/day but neither of these decreases reached statistical significance. Doubling the dose of cimetidine resulted in doubling of the peak plasma level as shown in Figure 1.

### COMPARISON OF NON-RESPONDERS WITH UNSELECTED DUODENAL ULCER PATIENTS

Mean hourly nocturnal H<sup>+</sup> activity is shown in Fig. 2. There was no significant difference in H<sup>+</sup> activity between the two groups on the no treatment day. After cimetidine, mean hourly H<sup>+</sup> activity

Table 1 Mean nocturnal hydrogen ion activity, acid output and volume of secretion in 12 non-responders receiving either no treatment, cimetidine 1 g/day or cimetidine 2 g/day. Percentage decrease shown in brackets.

	No treatment	Cimetidine 1g/day	Cimetidine 2g/day
Nocturnal volume (ml/h)	81	64 (21)	54 (33)
Nocturnal acid output (mmol/h)	7.3	4.3 (41)*	3.6 (51)*
Nocturnal H <sup>+</sup> activity (mmol/l)	45	33 (27)*	31 (31)*

\* $p < 0.05$  compared with no treatment

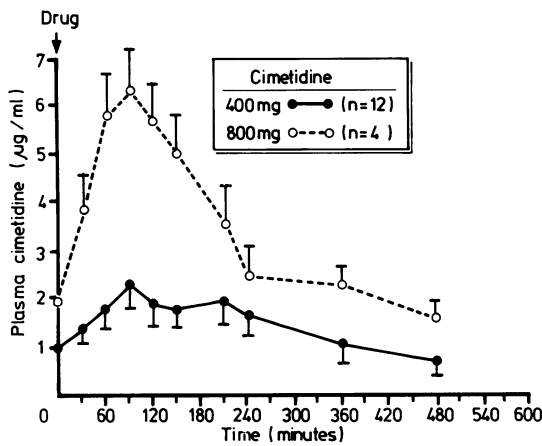


Fig. 1 Plasma cimetidine ( $\pm$ SEM) levels in four patients receiving cimetidine 2 g/day and in 12 patients receiving cimetidine 1 g/day.

decreased in both groups but the decrease in the unselected duodenal ulcer patients was significantly greater than in the non-responders ( $p < 0.01$ ).

Mean hourly acid output is shown in Fig. 3. On the no treatment day, acid output was 6.5 mmol/h in the non-responders compared with 4.3 mmol/h in the unselected duodenal ulcer patients (NS). After cimetidine, mean hourly acid output decreased to

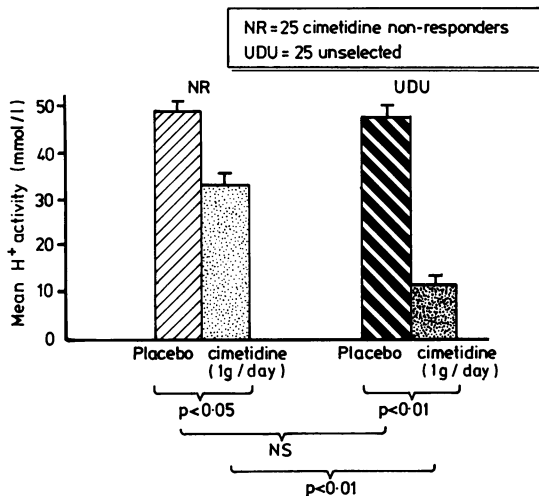


Fig. 2 Mean nocturnal hydrogen ion activity ( $\pm$ SEM) in 25 non-responders receiving either no treatment (placebo) or cimetidine 1 g/day and in 25 unselected duodenal ulcer patients receiving either no treatment (placebo) or cimetidine 1 g/day.

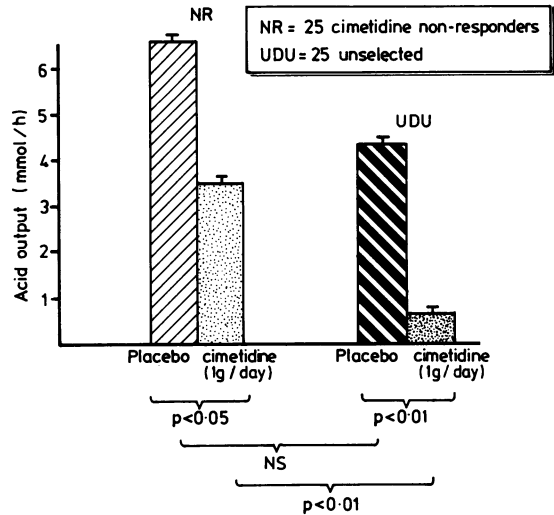


Fig. 3 Mean nocturnal acid output ( $\pm$ SEM) in 25 non-responders receiving either no treatment (placebo) or cimetidine 1 g/day and in 25 unselected duodenal ulcer patients receiving either no treatment (placebo) or cimetidine 1 g/day.

3.5 mmol/h in the non-responders ( $p < 0.05$ ) and to 0.7 mmol/h in the unselected duodenal ulcer patients ( $p < 0.01$  compared with the no treatment day and  $p < 0.01$  compared with the non-responders receiving cimetidine). Mean hourly nocturnal volume of secretion was 74 ml/h in the non-responders on the no treatment day compared with 55 ml/h in the unselected duodenal ulcer patients (NS). After cimetidine, volume did not decrease significantly in the non-responders but decreased to 29 ml/h in the unselected duodenal ulcer patients ( $p < 0.01$  compared with the no treatment day and  $p < 0.05$  compared with the non-responders receiving cimetidine) (Fig. 4).

COMBINATION THERAPY WITH CIMETIDINE AND ATROPINE (Table 2)

Mean nocturnal H<sup>+</sup> activity decreased by 39% with cimetidine 1 g/day (NS) and by 69% with the combination ( $p < 0.05$  compared with placebo).

Mean hourly nocturnal acid output decreased by 83% with the combination ( $p < 0.01$  compared with the mean value of this group of patients on the no treatment day and  $p < 0.01$  on cimetidine). Mean hourly nocturnal volume of secretion decreased from 81 ml/h on the no treatment day, to 56 ml/h receiving cimetidine (NS) and to 16 ml/h receiving the combination ( $p < 0.01$  compared with this group of patients on the no treatment day and  $p < 0.01$  receiving cimetidine). All seven patients in this

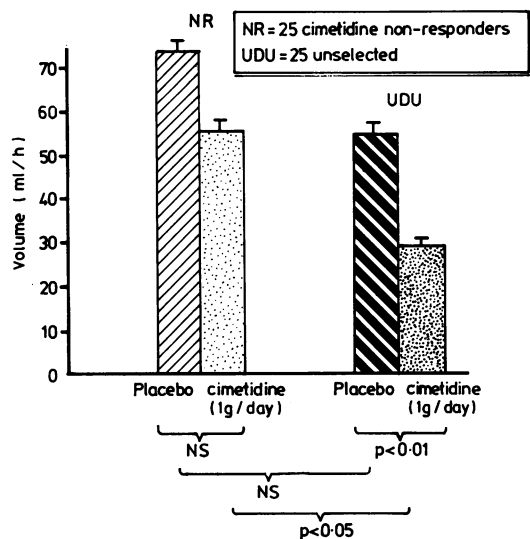


Fig. 4 Mean nocturnal volume of secretion ( $\pm$ SEM) in 25 non-responders receiving either no treatment (placebo) or cimetidine 1 g/day and in 25 unselected duodenal ulcer patients receiving either no treatment (placebo) or cimetidine 1 g/day.

group complained of dry mouth and blurring of vision with the dose of atropine used.

## Discussion

Any definition of cimetidine resistance must include dosage and duration of treatment.<sup>7</sup> It could be argued that a cimetidine non-responder is one whose ulcer fails to heal with a conventional course of cimetidine and not one who relapses within a month of stopping treatment. Patients who relapse early, however, present a considerable management problem. Although our non-responders were a mixed group, when we analysed our data, there were no differences in results between patients with different definitions of poor response.

Poor inhibition of acid output might be expected to be associated with low plasma drug concentrations. Our plasma cimetidine concentrations are, however, no different from the blood cimetidine

concentrations reported after a 400 mg dose of cimetidine in nine healthy subjects.<sup>8</sup> Increasing the dose results in a corresponding increase in the peak plasma concentration of cimetidine.

Our finding of no benefit from increase in the dose of cimetidine to 2 g/day agrees with a previous report<sup>9</sup> which showed nocturnal acid secretion is inhibited by a similar degree with either cimetidine 400 mg nocte or 800 mg nocte in patients with duodenal ulcer. Our observation is also supported by similar healing rates reported in trials comparing cimetidine 0.8 g/day with either 1 g/day,<sup>10</sup> 1.2 g/day,<sup>11</sup> 1.6 g/day,<sup>12</sup> or 2 g/day.<sup>13</sup> Ranitidine which on a molar basis is approximately five times more potent than cimetidine has also been found to produce similar healing rates to cimetidine.<sup>14</sup>

Two reports<sup>15,16</sup> have shown an increased basal acid output in cimetidine non-responders but this has not been confirmed by others.<sup>17</sup> Although we found an increased nocturnal acid output in non-responders compared with the unselected duodenal ulcer patients, this did not reach statistical significance.

There may be several explanations why volume of secretion was not significantly affected by cimetidine in the non-responders. Our collection techniques may have been variable but are no different from those used previously when studying the unselected duodenal ulcer patients whose volume decreased markedly with cimetidine. Kirkpatrick and Hirschowitz<sup>18</sup> reported an increased residual volume in non-responders which may have been because of the delayed gastric emptying. If the stomach is incompletely emptied at the start of continuous collection, nocturnal volume of gastric juice might contain residual secretion present before collection began. Although we could not discount this possibility, considerable care and attention was given to avoid these inaccuracies. Cimetidine may increase reflux which would explain the lack of effect on volume. During the study few samples were bile stained, however, and any changes because of reflux should have become apparent in the unselected duodenal ulcer patients.

When cimetidine was combined with atropine, there were dramatic reductions in H<sup>+</sup> activity, acid output and volume of secretion. This additional

Table 2 Mean nocturnal hydrogen ion activity, acid output and volume of secretion in seven non-responders receiving either no treatment, cimetidine 1 g/day or cimetidine 1 g/day combined with atropine 4.8 mg/day. Percentage decrease shown in brackets.

	No treatment	Cimetidine 1g/day	Cimetidine 1g/day and atropine 4.8mg/day
Nocturnal volume (ml/h)	81	56(31)	16(80)**
Nocturnal acid output (mmol/h)	6.9	3.9(43)	1.2(83)**
Nocturnal H <sup>+</sup> activity (mmol/l)	42	26(39)	13(69)*

\*\* p<0.05 compared with cimetidine  
\* p<0.05 compared with no treatment

benefit of an anticholinergic agent has also been reported by others<sup>19</sup> although most studies suggest that improved control of acid output is achieved by a reduction in volume rather than acidity.<sup>20 21</sup>

In a previous study from our department,<sup>21</sup> no additional reduction of acidity was seen when atropine 2.4 mg/day was combined with cimetidine 1 g/day. This finding agreed with Peterson *et al*<sup>19</sup> who found that the addition of clonidine bromide to cimetidine did not improve control of acidity. We recently confirmed our previous observations in an unpublished study using atropine 2.4 mg/day combined with cimetidine 1 g/day in 11 non-responders. Patients during this latter study did not complain of side effects which prompted us to increase the dose to 4.8 mg/day in the present investigation. It has been widely held that the optimum effective dose of an anticholinergic to control acid secretion could only be found by 'titration' against side effects in each individual patient.<sup>22</sup> Feldman *et al*,<sup>20</sup> however, found that poldine 15 mg gave the same inhibition of acid secretion as a 45 mg dose. In contrast, our present study showed an additional benefit from the larger dose of atropine. Poldine is a quaternary compound which may explain these discrepancies although other pharmacological differences between these agents may be responsible.

How then should cimetidine resistant ulcers be treated? The aetiology of duodenal ulcer suggests an imbalance between excessive acid and pepsin secretion and a defective mucosal barrier. Greater inhibition of acid secretion occurs with 150 mg of ranitidine compared with 400 mg of cimetidine<sup>23</sup> although comparable healing rates are reported in duodenal ulcer trials. Three uncontrolled studies have claimed ranitidine healed cimetidine resistant ulcers<sup>24-26</sup> but prolonging the length of treatment with cimetidine is also known to increase the number of ulcers which heal.<sup>2</sup> We have shown control of acid secretion is better achieved by adding an anticholinergic agent to cimetidine but all our patients complained of undesirable side effects at the dose used. The antimuscarinic agent pirenzepine appears to have fewer systemic side effects and when given intravenously has been reported to dramatically reduce acid secretion when combined with cimetidine.<sup>4</sup> This combination has been used with some success in the Zollinger Ellison Syndrome<sup>27</sup> and we would suggest this form of therapy offers a logical approach to therapy for non-responders and deserves clinical evaluation.

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