Rebound intragastric hyperacidity after abrupt withdrawal of histamine H₂ receptor blockade

C U Nwokolo, J T L Smith, A M Sawyerr, R E Pounder

Abstract
In a series of 24 hour studies, intragastric acidity and plasma gastrin concentration were measured simultaneously in 46 healthy subjects before, during, and 24 to 48 hours after abrupt withdrawal of a histamine H₂ receptor antagonist regimen. For 34 days subjects were given either cimetidine 800 mg at night (n=8), ranitidine 150 mg twice daily (n=10), ranitidine 300 mg at night (n=12), nizatidine 300 mg at night (n=8), or famotidine 40 mg at night (n=8). All subjects responded to H₂ blockade by a decrease in 24 hour intragastric acidity. Withdrawal of H₂ blockade resulted in a significant rise in median nocturnal integrated intragastric acidity in 42 of 46 subjects (+36%; 95% CI +19, +55%) compared with prestudy values, but this rise was not associated with a significant change in the median integrated plasma gastrin concentration (+1%; 95% CI -12, +13%). A statistically significant rise in nocturnal acidity was observed after all regimens, except after dosing with famotidine. After stopping, median daytime integrated acidity and plasma gastrin concentrations in the whole group were raised, but not significantly: values were +15% (95% CI +4, +34%) and +5% (95% CI -2, +12%), respectively. A statistically significant increase in daytime acidity was observed only after dosing with ranitidine. In conclusion, intragastric hyperacidity occurs in most subjects after abrupt withdrawal of a histamine H₂ receptor blocker, but this phenomenon is not associated with hypergastrinaemia.

When the histamine H₂ receptor antagonists were introduced for the management of peptic ulceration, there was concern that they would induce a surge of gastric acid secretion in the days or weeks after their withdrawal.1 Experiments were performed to explore this possibility, but most reported that no rebound hypersecretion could be detected.2-4 It came as a surprise when Fullarton et al11 reported rebound nocturnal hypersecretion of acid occurring after four weeks of treatment with nizatidine 300 mg at night. They found, in a group of eight duodenal ulcer patients, that mean nocturnal acid output was 39.4 mmol/10 hours before treatment, but rose significantly to 74.1 mmol/10 hours when measured two days after stopping. They observed no significant change in daytime intragastric acidity.

The object of this series of experiments was to measure 24 hour intragastric acidity and plasma gastrin concentration before, during, and after five different H₂ antagonist regimens. These experiments were performed in conjunction with an extensive research programme investigating the phenomenon of tolerance during continued H₂ blockade.12-14

Methods

SUBJECTS AND DRUG REGIMENS
Forty six of 48 healthy men completed the study. Their median age was 21 years (range 19 to 24 years), median weight was 74 kg (range 60 to 96 kg), and median height was 1.80 m (range 1.67 to 1.93 m). Twenty four smoked cigarettes (4–20 cigarettes per day). None had been dosed with an antisecretory drug for at least eight weeks before entry to this study.

This study was ‘open label,’ and all the H₂ blockers were supplied by the pharmacy of the Royal Free Hospital, London.

The subjects received no antisecretory drug during the first 24 hour simultaneous study of intragastric acidity and plasma gastrin concentration. They were then randomly assigned to receive one of the following regimens: cimetidine 800 mg at night (Smith Kline & French Laboratories Ltd, n=8),12 either ranitidine 300 mg at night (n=12) or ranitidine 150 mg twice daily (n=10) (Glaxo Laboratories Ltd); nizatidine 300 mg at night (n=8) (Eli Lilly and Co Ltd),13 or famotidine 40 mg at night (n=8) (Thomas Morson Pharmaceuticals).12 The experiments involving cimetidine, nizatidine, and famotidine were extensions of previously published studies investigating ‘tolerance,’ but the ranitidine experiments were not part of the earlier ‘tolerance’ experiments.12 The subjects were dosed with an H₂ receptor antagonist for 34 days, and 24 hour profiles of intragastric acidity and plasma gastrin concentration were measured for assessment of antisecretory activity on day 29 of dosing. The final 24 hour study of acidity and plasma gastrin concentration was begun 24 hours after the last oral dose of each H₂ blocker.

EXPERIMENTAL DESIGN
The subjects were studied using the Royal Free Hospital protocol,15 with minor changes as specified below. The subjects began fasting at 1330 hours, and were provided with a standard light supper at 1815 hours. They had nothing to eat or drink until 2130 hours, when a 10 FG Salem Sump nasogastric tube (Argyle Medical, Crawley, West Sussex) was positioned in the stomach; its position was checked by a water recovery test. Aliquots (5–10 ml) of intragastric contents were aspirated hourly throughout the study, and the pH of each aliquot was measured immediately to the nearest 0·01 pH unit by means of a glass electrode and digital pH meter.
Figure 1: 24 hour median hourly intragastric acidity before dosing (•—•), on day 29 of dosing (—•—•), and 24 hours after stopping cimetidine 800 mg at night (—•••), in eight healthy subjects. N=night cap, B=breakfast, C=coffee, L=lunch, T=tea, D=dinner.

Figure 2: 24 hour median hourly acidity before dosing (•—•), on day 29 of dosing (—•—•), and 24 hours after stopping ranitidine 150 mg twice daily (•••••), in 10 healthy subjects.

Figure 3: 24 hour median hourly intragastric acidity before dosing (•—•), on day 29 of dosing (—•—•), and 24 hours after stopping ranitidine 300 mg at night (—•••••), in 12 healthy subjects.

(Radiometer, Copenhagen). The electrode was calibrated with standard buffers (pH 7.00, 4.01, and 1.09; Radiometer, Copenhagen) before and after every six samples in each hourly batch of aspirates.

Every hour from 2300 hours to 2300 hours the next day (apart from 0100, 0300, 0500, and 0700 hours) blood was taken via a venous cannula for assay of the plasma gastrin concentration. The blood was collected in lithium heparin tubes which contained 0.2 ml aprotinin (Bayer UK Ltd, Newbury). The tubes were centrifuged immediately, and the plasma transferred to plastic tubes and frozen to −20°C. All the plasma samples from each subject were analysed for gastrin in one batch, by radioimmunoassay using the antibody GAS 179 in Professor Bloom’s laboratory at the Royal Postgraduate Medical School London. The subjects were fully ambulant around the ward during the study. The food and environmental conditions for all studies were identical to
Rebound intragastric dosing. After famotidine 40 mg, p value subjects.

**TABLE II** Median integrated nocturnal (2400–0800 hours) intragastric acidity (mmol.l/l) in 46 healthy subjects before, during, and after dosing with an H₂ antagonist regimen

<table>
<thead>
<tr>
<th>Medication</th>
<th>Day 0</th>
<th>Day 29</th>
<th>Day 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine (800 mg, nocte)</td>
<td>84</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>Ranitidine (150 mg, bd)</td>
<td>472</td>
<td>472</td>
<td>472</td>
</tr>
<tr>
<td>Nizatidine (300 mg, nocte)</td>
<td>501</td>
<td>501</td>
<td>501</td>
</tr>
<tr>
<td>Famotidine (40 mg, nocte)</td>
<td>561</td>
<td>561</td>
<td>561</td>
</tr>
</tbody>
</table>

p value compared with before dosing *=0.05; †=0.01 (Wilcoxon rank sum test).

**TABLE II** Median integrated daytime (0900–2300 hours) intragastric acidity (mmol.l/l) in 46 healthy subjects before, during, and after dosing with an H₂ antagonist regimen

<table>
<thead>
<tr>
<th>Medication</th>
<th>Day 0</th>
<th>Day 29</th>
<th>Day 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine (800 mg, nocte)</td>
<td>87</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td>Ranitidine (150 mg, bd)</td>
<td>410</td>
<td>410</td>
<td>410</td>
</tr>
<tr>
<td>Nizatidine (300 mg, nocte)</td>
<td>389</td>
<td>389</td>
<td>389</td>
</tr>
<tr>
<td>Famotidine (40 mg, nocte)</td>
<td>263</td>
<td>263</td>
<td>263</td>
</tr>
</tbody>
</table>

p value compared with before dosing *=0.05; †=0.01 (Wilcoxon rank sum test).

those used in earlier experiments at the Royal Free Hospital. The standard meals (bedtime snack, breakfast, coffee, lunch, tea and dinner) were eaten at 2245, 0815, 1045, 1315, 1545, and 1815 hours, respectively. The bedtime doses of medication were taken at 2305 hours; the morninging dose of ranitidine 150 mg was taken by one group at 0830 hours.

**STATISTICAL ANALYSES**

Profiles of intragastric acidity and plasma gastrin concentration and were obtained for each subject. The area under the curve for each profile was calculated by the trapezoid rule, with integrated acidity expressed as mmol.l/l and plasma gastrin concentration as pmol.l/l. Values of integrated acidity and plasma gastrin concentration were calculated for the night time (0000 to 0800 hours), and daytime (0900 to 2300 hours). The significance of observed differences between groups was assessed using the Wilcoxon matched paired signed rank test. All statistical calculations were made using the Oxstat program (Wallingford Computing Services, Wallingford).

**ETHICAL AND SAFETY ISSUES**

The studies were approved by the Ethics Committee of the Royal Free Hospital, and written consent was obtained from each subject. Routine laboratory safety studies were performed before and after each study.

**Results**

Forty six subjects tolerated all the experiments...
Figure 6: Changes in integrated nocturnal acidity compared with changes in integrated nocturnal plasma gastrin concentration (2400-0800 hours) in 46 healthy subjects dosed with an \( \mathrm{H}_2 \) antagonist for 35 days. The acidity or plasma gastrin concentration after dosing is expressed as a percentage of the value before dosing (cimetidine 800 mg at night=□; ranitidine 150 mg twice daily=●; ranitidine 300 mg at night=○; nizatidine 300 mg at night=△; famotidine 40 mg at night=■).

Figure 7: Changes in integrated daytime acidity compared with changes in integrated nocturnal plasma gastrin concentration (0900-2300 hours) in 46 healthy subjects dosed with an \( \mathrm{H}_2 \) antagonist for 35 days. The acidity or plasma gastrin concentration after dosing is expressed as a percentage of the value before dosing (cimetidine 800 mg at night=□; ranitidine 150 mg twice daily=●; ranitidine 300 mg at night=○; nizatidine 300 mg at night=△; famotidine 40 mg at night=■).

without any adverse event, but two subjects allocated to receive ranitidine 150 mg twice daily were withdrawn from the study (one had tonsillitis and the other family commitments which precluded continuation in the study). Biochemical and haematological profiles were normal before and after the experiments. Full compliance was reported by all the subjects.

24 HOUR INTRAGASTRIC ACIDITY
Figures 1 to 5 show the profiles of 24 hour median hourly intragastric acidity for the five different regimens of \( \mathrm{H}_2 \) blockade before, during, and immediately after abrupt withdrawal of the antisecretory drugs. Compared with values before dosing, each of the five \( \mathrm{H}_2 \) blocker regimens was associated with a significant decrease in median daytime acidity during dosing, and four of the five regimens were followed by a significant rise in median integrated nocturnal intragastric acidity after dosing (Table I). Analysis of variance could detect no significant difference in the change in nocturnal intragastric acidity (expressed as a percentage of pretreatment acidity) between the five \( \mathrm{H}_2 \) antagonist regimens. Two of the five regimens were associated with a significant rise in median integrated intragastric acidity during the daytime 34 to 48 hours after the last dose of an \( \mathrm{H}_2 \) antagonist (Table II), but analysis of variance detected no significant difference between the groups.

PLASMA GASTRIN CONCENTRATION
Compared with values before dosing, the 24 hour profiles of plasma gastrin concentration were raised during dosing with all of the antisecretory drug regimens,\(^12\) but there was no significant change in the median integrated plasma gastrin concentration during the 24 hours after stopping the drugs.

The individual data points for all 46 subjects, correlating changes in either nocturnal or daytime integrated intragastric acid with integrated plasma gastrin concentration after withdrawal of \( \mathrm{H}_2 \) blockade, are shown in Figures 6 and 7. Figure 6 shows that, compared with before dosing, the rise (median +36%, 95% CI +19, +55%) in nocturnal intragastric acidity, observed in 42 of the 46 subjects after withdrawal of dosing with an \( \mathrm{H}_2 \) blocker regimen, was not associated with a significant change in the plasma gastrin concentration (median +1%; 95% CI −12, +13%). Figure 7 shows that daytime acidity was increased in 33 of the 46 subjects (median +15%; 95% CI +4, +34%), but that the integrated plasma gastrin concentration was unchanged (median +5%; 95% CI −2, +12%).

Discussion
The results of these studies confirm and extend Fullarton and colleagues' original report of rebound nocturnal hyperacidity\(^10\): increased nocturnal intragastric acidity does occur after
Rebound intragastric hyperacidity after abrupt withdrawal of histamine H₂ receptor blockade

Abruptly stopping short acting histamine H₂ receptor antagonists.

In retrospect, why was it generally thought that H₂ blockers do not induce hypersecretion of acid? Some experiments were performed before the expected complete plasma elimination of the H₂ antagonist, and others were completed some weeks after withdrawal of treatment, almost all the original experiments examined maximal acid secretion, stimulated by either histamine or pentagastrin. It is now clear that measurement of nocturnal intragastric acidity represents the prolonged observation of spontaneous gastric function, unaffected by meals or outside stimuli. Reliable studies of basal gastric acid secretion are exceptionally difficult, but remarkable reproducibility can be achieved in studies of nocturnal intragastric acidity. This sensitivity has allowed the detection of rebound hyperacidity, and similarly the detection of nocturnal tolerance to H₂ blockade.

The mechanism of nocturnal rebound hyperacidity remains unclear. A drug induced decrease in intragastric acidity induces a rise in the plasma gastrin concentration, and it is possible that continued H₂ blockade could induce proliferation of G cells or sustained hypergastrinaemia. The present studies show that when the phenomenon of rebound hyperacidity is occurring, plasma gastrin concentrations have returned to the values before dosing. Hence, rebound hyperacidity is not the result of hypergastrinaemia — but it could be argued that the concentration of gastrin remains 'inappropriately' high, as it is not decreased at a time when intragastric acidity is increased. It is possible therefore that part of the phenomenon of rebound acid hypersecretion results from a persisting drug induced change in gastric release.

The original experiments, using pentagastrin or histamine tests to measure maximal acid output, showed that there is no increase in parietal cell mass after short-term treatment with an H₂ blocker. It remains a possibility that prolonged pharmacological control of gastric acid secretion results in an overactivity of, or increased sensitivity to, vagal drive. It will be very difficult to devise experiments in man that can either prove or disprove whether rebound hypersecretion is due to vagal drive.

An alternative mechanism to explain the rebound hypersecretion of acid after withdrawal of an H₂ antagonist is that H₂ receptors become more sensitive, or 'up regulated' during treatment. Aadland and Berstad showed that the mean acid output in response to a low dose of intravenous histamine increased from 6.7 to 10.1 mmol/hour, when measured before and 60–84 hours after stopping four weeks of treatment with cimetidine 1 g/day. The acid output measured one to four weeks later had returned to pretreatment values. This response is consistent with augmented parietal cell sensitivity to histamine stimulation. Jones et al assessed the sensitivity of the H₂ receptor using impromidine, a specific H₂ agonist, before and after a three month course of ranitidine 150 mg at night. Six duodenal ulcer patients were studied 10 hours after the last dose of ranitidine: basal acid output increased from 1.2 to 2.8 mmol/hour, and acid output during maximal impromidine infusion increased from 36.9 to 44.2 mmol/hour. The antiserotonin effect of intravenous ranitidine given after impromidine was also enhanced at the end of treatment. Thus, the hypersecretory response could be a result of 'up regulation,' whether by increased number, affinity, or activity (in coupling to adenylate cyclase) of the H₂ receptors.

Fullarton et al suggested that rebound hyperacidity could be one explanation for recurrent peptic ulceration after withdrawal of H₂ blockade. Recent experiments at the Royal Free Hospital have shown that the phenomenon of nocturnal hyperacidity exists for only six days after 25 days of dosing with ranitidine 300 mg at night — from days 9–21 after dosing there is no significant change in intragastric acidity, compared with values before dosing.

Miss Doris Elliott prepared this manuscript. The study was supported by grants from Glaxo Group Research Limited. Enthusiastic technical assistance was provided by Nurse J Sercombe and the following clinical medical students: P Peyer, J Tuckey, J Greening, A Emmanuel, A Muir, J Abbert, L Pullis, H Reid, H Seymour.


