Nocturnal Intragastric Acidity During and After a Period of Dosing With Either Ranitidine or Omeprazole

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The magnitude and duration of changes in nocturnal intragastric acidity caused by 25 days of dosing with the antisecretory drugs ranitidine and omeprazole were investigated in a double-blind study of 22 healthy subjects. Nocturnal intragastric acidity was studied before (twice), during (on day 25), and after (every 3 days for 21 days) dosing with either 300 mg ranitidine at night or 40 mg omeprazole every morning. Three and six days after withdrawal of dosing with ranitidine, median integrated nocturnal intragastric acidity was increased significantly (17% and 14%, P = 0.01 and P = 0.05, respectively) compared with before dosing. Three days after withdrawal of dosing with omeprazole, median integrated nocturnal intragastric acidity was decreased significantly (-23%, P = 0.003). Compared with before dosing, no significant differences were seen in the ranitidine group between days 9 and 21 or the omeprazole group between days 6 and 21 after cessation of dosing. Fasting plasma gastrin concentration was measured on the morning of each study; compared with before treatment, the only significant elevations occurred on the last day of dosing with omeprazole (before, 4 pmol/L; during, 7 pmol/L). It is concluded that rebound intragastric hyperacidity after dosing with 300 mg ranitidine at night or sustained hypoacidity after dosing with 40 mg omeprazole every morning reflect transient disturbances of gastric function that are unlikely to be of clinical importance.

Recent studies have demonstrated an increase of nocturnal gastric acid secretion [1], or increased nocturnal intragastric acidity [2], after a short course of treatment with a histamine H₂-receptor antagonist. Conversely, gastric acid secretion takes several days to return to normal after treatment with omeprazole [3,4].

The purpose of the present double-blind study was to compare nocturnal intragastric acidity before, during, and after dosing with either 300 mg ranitidine at night or 40 mg omeprazole every morning. Nocturnal gastric function was assessed every 3 days for 21 days in the recovery phase after dosing to detect the extent and duration of rebound hyperacidity after H₂-blockade or sustained hypoacidity after omeprazole.

Materials and Methods

Subjects and Dosage Regimens

Twenty-four healthy men took part in the study with median age 21 years (range, 19–29 years), median weight 76 kg (60–97 kg), and median height 1.83 m (1.61–1.98 m). Seven of the subjects smoked cigarettes. All were normal on physical examination and all had normal hematologic and biochemical laboratory profiles.

The subjects were randomly selected to receive 25 days of double-blind, double-dummy dosing with either 300 mg ranitidine at night (identical active and placebo tablets supplied by Glaxo Group Research Ltd., Greenford, Middlesex, England) or 40 mg omeprazole every morning (identical gelatin capsules filled individually by the Pharmacy Department of the Royal Free Hospital (London, England) with either maize starch British Pharmacopoeia or enteric coated granules of omeprazole [Losec; Astra Pharmaceuticals Ltd., King's Langley, Hertfordshire, England]). Compliance was encouraged by the use of a digital alarm wrist watch (Casio WR 50M, London, England), which alerted each subject twice daily when dosing was due. On the final day of dosing (day 25), the morning capsule and evening tablet were administered by an investigator at 8 AM and 11 PM, respectively.

Nocturnal Acidity Studies

The subjects were studied twice, 3 nights apart, before the commencement of dosing. The third study was conducted...
performed on the final (25th) day of dosing. Thereafter, a study was performed every third night for 21 days after cessation of dosing—a total of 10 studies on each subject.

On the study days, the subjects were observed eating the same lunchtime (1 PM) and evening (6 PM) meals, which were provided by the investigators. A 10F gauge Salem Sump nosegastric tube (Argyle Medical, Crawley, West Sussex, England) was positioned in the stomach at 8 PM. A standard bedtime snack was served at 10:45 PM and the subjects retired to bed at midnight.

Aliquots of intragastric contents (5 mL) were aspirated hourly from 9 PM to 7 AM. The pH of each aliquot was measured immediately to the nearest 0.01 pH unit using a glass electrode and digital pH meter (Radiometer, Copenhagen, Denmark). The electrode was calibrated with standard buffers (pH 7.00, 4.01, and 1.09; Radiometer) before each hourly batch of 12 samples. The aspirated aliquots were not returned to the stomach.

At 7 AM, a single blood sample was taken for assay of plasma gastrin concentration. The blood was collected in lithium heparin tubes that contained 0.2 mL aprotinin (Trasylol; Bayer UK, Ltd., Newbury, England). The tubes were centrifuged immediately, and the plasma was transferred to plastic tubes and frozen to -20°C. A radioimmunoassay for gastrin using antibody GAS179 was performed in Professor Bloom's laboratory at the Royal Postgraduate Medical School, London, England (5).

**Ethical Approval**

The study was approved by the Ethics Committee of the Royal Free Hospital and written consent was obtained from each subject.

**Statistical Analysis**

Nocturnal profiles of intragastric acidity were obtained for each subject. The area under the time-concentration curve for each profile was calculated by the trapezoid rule, with integrated nocturnal acidity (10 PM to 7 AM) expressed as mmol * h/L. The significance of differences between the integrated nocturnal acidity values and the fasting plasma gastrin values was assessed using the Wilcoxon matched-pair signed rank test using the Oxstat program (Microsoft Corporation, Wallingford Computing Services Ltd., Wallingford, England).

**Results**

Two subjects failed to complete the studies: one because of an intercurrent influenza-like illness (dosed with ranitidine) and one for personal reasons (dosed with omeprazole). Their incomplete results were excluded from the final analysis. Otherwise, the medications and studies were well-tolerated. The excellent reproducibility of the technique was demonstrated in the two predosing studies; the median integrated nocturnal intragastric acidity for the 22 subjects was 627 mmol * h/L (95% CI 485–708 mmol * h/L) for study 1, and 582 mmol * h/L (95% CI 492–718 mmol * h/L) for study 2. The difference is not significant ($P = 0.465$).

Integrated nocturnal intragastric acidity (10 PM to 7 AM) for the eleven subjects before, during, and after dosing with 300 mg ranitidine at night is shown in Figure 1. On the 25th day of dosing, 300 mg ranitidine administered at night produced a significant decrease of median nocturnal integrated acidity from 593 to 187 mmol * h/L (−68% compared with predosing). Three and six days after abrupt cessation of dosing, median integrated nocturnal acidity increased to 693 and 677 mmol * h/L acidity; these differences are statistically significant at $P = 0.01$ and $P = 0.05$, respectively. The median acidity was 662 mmol * h/L on day 9 after cessation of dosing, but this 12% increase is not statistically significant ($P = 0.328$). From 12 to 21 days after cessation of dosing with ranitidine, no significant change was observed in nocturnal intragastric acidity compared with before dosing.

Figure 2 shows the integrated nocturnal acidity for each subject before, during, and after dosing with 40 mg omeprazole every morning. Omeprazole produced a significant decrease of median integrated nocturnal acidity from 641 to 81 mmol * h/L (−87%) on day 25 of dosing compared with predosing. Three days after the abrupt cessation of dosing, the median integrated nocturnal acidity was still significantly decreased at 495 mmol * h/L (−23%; $P = 0.003$). Although median nocturnal acidity remained low on day 6 after dosing (516 mmol * h/L; −19%), the difference compared with predosing is not statistically significant ($P = 0.476$). No significant change was observed in nocturnal intragastric acidity from 6 to 21 days after cessation of dosing with omeprazole compared with predosing.

Figure 3 superimposes the median nocturnal intragastric acidity from 10 PM to 7 AM for study 1, and 582 mmol * h/L (95% CI 492–718 mmol * h/L) for study 2. The difference is not significant ($P = 0.465$).
gastric acidity (±95% CI) for the two groups; it demonstrates the extent of the difference between the two groups during the first 6 days postdosing and the similarity of the two groups at the beginning and end of the series of experiments.

The fasting plasma gastrin concentrations for each study day (7 AM) are shown in Figures 4 and 5. Compared with before dosing, the only statistically significant change in median fasting plasma gastrin concentration occurred on the last day of dosing with omeprazole, when the median plasma gastrin concentration was 7 pmol/L compared with 4 pmol/L before dosing (P = 0.004).

The subject who demonstrated a sustained increase in fasting plasma gastrin concentration from days 6 to 21 postdosing (in the omeprazole group) had the greatest suppression of intragastric acidity of all the subjects. He felt perfectly well throughout the study and has not been investigated further.

Discussion

The results of these experiments show clear differences of intragastric acidity following the withdrawal of dosing with either an H₂-antagonist (ranitidine) or a blocker of H⁺,K⁺-ATPase (omeprazole). The former is associated with transient intragastric hyperacidity, whereas the latter is followed by sustained intragastric hypoacidity.

When the histamine H₂-receptor antagonists were first introduced for the treatment of peptic ulceration, there was speculation that cessation of treatment would be followed by rebound hypersecretion of gastric acid (6–15). Initial experiments suggested that this phenomenon did not occur, but recent studies have demonstrated conclusively that rebound hypersecretion of gastric acid and increased intragastric hyperacidity do occur in the days immediately after withdrawal of dosing with all the generally available, short-acting histamine H₂-receptor antagonists (1.2). The present study has confirmed that nocturnal hyper-
acidity does occur after cessation of H₂-blockade, and it demonstrates not only the extent of the hyperacidity but also its duration. In this study, a small but significant increase of nocturnal intragastric acidity (+17% and +14%) was observed on days 3 and 6 following 25 days of dosing with 300 mg ranitidine at night. Nocturnal intragastric acidity was not significantly different from predosing values between days 9 and 21 postdosing, indicating that rebound hyperacidity is not a prolonged or permanent phenomenon after 25 days of dosing with an H₂-receptor antagonist.

The first experiments using omeprazole in humans demonstrated that the drug has a prolonged duration of action (16) with the persistence of an antisecretory effect that is not related to the plasma omeprazole concentration. This prolonged activity is thought to be due to the acid-activated omeprazole, in the form of its sulphenamide, being bound to H⁺,K⁺-ATPase in the gastric secretory canaliculus (17). The exact mechanism of clearance of omeprazole from the secretory canaliculus and the recovery of gastric acid secretion following dosing with omeprazole remain uncertain, but it is thought that recovery after dosing with omeprazole is due to generation of new H⁺,K⁺-ATPase by the parietal cell (17). Experiments with omeprazole showed that the recovery of normal gastric acid secretion in peptic ulcer patients occurs approximately 7 days after cessation of dosing, giving an impression that young healthy volunteers may recover more rapidly. Sharma et al. observed a 26% mean decrease of 24-hour intragastric acidity in 8 of 9 duodenal ulcer patients 1 week after cessation of omeprazole, with normal intragastric acidity observed 7 weeks later (3), but the present and earlier studies in healthy volunteers show recovery of normal gastric function in <1 week (4). We observed a marked and sustained increase in fasting gastrin after omeprazole dosing in one subject. Similar unexplained elevations in plasma gastrin have been reported in occasional subjects in the past (4).

The present experiment demonstrates prolonged hypoaclidity following cessation of dosing with 40 mg omeprazole every morning, healthy subjects recovering with predosing values of nocturnal acidity by day 6 postdosing. Examination of the individual subjects' values in Figure 2 indicates that the use of a median value does not obscure either interindividual variation in the return of intragastric acidity or the possibility of transient hyperacidity. Rebound hyperacidity was not detected in the days after recovery of normal gastric acid secretion in the omeprazole-dosed subjects.

Finally, could postdosing changes of intragastric acidity affect the rate of duodenal ulcer relapse? The observed duration of the changes of intragastric acidity are so short that they are extremely unlikely to affect the longer-term management of a peptic ulcer patient. The return of duodenal ulceration after acute ulcer healing with a histamine H₂-receptor antagonist demonstrates a consistent rate of reulceration without a surge of early ulceration (18–20). The available data after ulcer healing with omeprazole suggest that it is associated with neither a more rapid nor a delayed return of ulceration compared with ulcers healed during H₂-blockade (21). One unusual study demonstrated that 16% of duodenal ulcers had recurred within 2 weeks of cessation of a 2-week healing course of omeprazole, indicating that sustained hypoaclidity does not provide short-term protection from ulcer relapse (22).

In conclusion, rebound hyperacidity after H₂-blockade and sustained hypoaclidity after treatment with omeprazole reflect predictable but transient disturbances of gastric function that are unlikely to be relevant in the clinical management of patients with peptic ulceration.

References


