Sufotidine 600 mg bd virtually eliminates 24 hour intragastric acidity in duodenal ulcer subjects

J T L Smith, R E Pounder

Abstract
In a double blind study, 24 hour intragastric acidity and 24 hour plasma gastrin concentrations were measured simultaneously in seven duodenal ulcer subjects on the fifth day of receiving either sufotidine 600 mg bd or placebo. Compared with placebo, during treatment with sufotidine 600 mg bd the median integrated 24 hour intragastric acidity was decreased by 95% (range 74% to 99%) from 1000 to 51 mmol/l, whilst the median integrated 24 hour plasma gastrin concentration increased from 416 to 927 pmol/l.

First generation histamine H₂-receptor blockers cause a short lived pulse of decreased intragastric acidity. Meta-analysis of the results of published studies has suggested that the more profound the drug induced decrease of nocturnal intragastric acidity by a particular regimen, the greater the percentage of duodenal ulcers which are healed after four weeks of treatment with that regimen. A new meta-analysis has suggested that the four week duodenal ulcer healing rate can be predicted most accurately by a drug’s ability to maintain 24 hour intragastric pH above 3 (H+ activity below 1 mmol/l), suggesting that control of daytime acidity may also be important. This finding is supported by the fact that the highest four week duodenal ulcer healing rates have been reported during treatment with 30 to 40 mg/day of cimetidine,1 which inhibits nocturnal and daytime acidity. Omeprazole has also had particular success in the management of difficult duodenal ulceration, the more severe grades of oesophagitis, and the Zollinger Ellison syndrome, because of the profound antisecretory effect of this drug.

Sufotidine is a new competitive, long acting histamine H₂-blocker. Earlier healthy volunteer studies, using single day dosing with sufotidine, suggested that sufotidine 600 mg bd taken before breakfast and at bed time could induce a sustained 24 hour decrease of acidity (J T L Smith and R E Pounder; H Merki; unpublished data). The objectives of the present study were to observe the effects of repeat dosing with sufotidine 600 mg bd on 24 hour intragastric acidity and plasma gastrin concentration in subjects with a history of duodenal ulceration.

Methods

Patients
Seven male subjects with a history of endoscopically confirmed duodenal ulceration completed the study; their median age was 53 years (range 26 to 63 years), their median weight was 76 kg (68 to 99.9 kg), their median height was 178 cm (164 to 189 cm), and two of the seven subjects smoked cigarettes (10 to 20 cigarettes per day). Two other subjects withdrew from the study, but both had been dosed only with placebo. The subjects were in symptomatic remission, and not taking antisecretory therapy. The study was double blind, and dosing was given in a predetermined random order.

The subjects were studied twice, on the fifth day of dosing with either sufotidine 600 mg bd or placebo. There was a nine day washout period between the studies, when the subjects received no treatment. Dosing was in the form of six identical tablets taken twice a day – at 0935 and 1935 hours. Compliance with the dosing regimen before the study day was encouraged by the use of a long range paging system (British Telecom); each subject was paged at the recommended time of every dose to remind him to take the tablets.

The study was approved by the Ethics Committee of the Royal Free Hospital and written consent was obtained from each patient. Routine safety studies were performed before and after treatment with both drugs.

The subjects were studied using the Royal Free Hospital standard protocol for 24 hour studies. They were admitted for each study to a research ward after an overnight fast. A 10 French gauge salem sump nasogastric tube (Argyle Medical) was positioned in the stomach. Aliquots (5–10 ml) of intragastric contents were aspirated hourly throughout the study (except at 1000 and 2000 hours), and the pH of each aliquot measured immediately to the nearest 0.01 pH unit by means of a glass electrode and digital pH meter (Radiometer, Copenhagen). The electrode was calibrated with standard buffers (pH 7.00, 4.01, and 1.09: Radiometer, Copenhagen) before and halfway through each hourly batch of samples.

Every hour from 0900 to 2400 hours, and two hourly thereafter, blood was taken through a venous cannula for assay of plasma gastrin concentration. The blood was collected in lithium heparin tubes which contained 0.2 ml aprotinin (Trasylol, Bayer). The tubes were centrifuged immediately, 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 antibody GAS 179 in Professor Bloom’s laboratory at the Hammersmith Hospital, London.

During the study the subjects were fully ambulant around the ward. The food and environmental conditions for both studies were identical to those used in earlier experiments at the Royal Free Hospital. The following meals were served: breakfast, coffee, lunch, tea, dinner...
and a bedtime snack at 0915, 1115, 1315, 1615, 1915, and 2215 hours, respectively.

**STATISTICAL ANALYSIS**

Twenty-four-hour profiles of intragastric acidity and plasma gastrin concentration were obtained for every subject in each study period. No gastric aspirates were taken at 1000 or 2000 hours to avoid aspirating drug hence, to calculate the 24-hour integrated acidity profiles, intragastric acidity values of 1-30 and 0-13 mmol/l were used at these times, respectively. The 1-30 and 0-13 mmol/l values represent the median intragastric acidity at 1000 and 2000 hours in 46 healthy subjects, studied under identical conditions when receiving placebo at the Royal Free Hospital. The area under the time-concentration curve for each profile was calculated by the trapezoidal rule, with integrated acidity expressed as mmol/l and integrated plasma gastrin as pmol/l. To make these values comparable with single point measurements of either acidity or gastrin, each value should be divided by 23.

The significance of the difference between the integrated 24-hour values were assessed using Wilcoxon’s matched-pair signed rank test. The correlation between integrated 24-hour acidity and plasma gastrin concentration was tested using Spearman rank correlation. Differences occurring with a probability of 5% or less were considered significant.

**Results**

Two subjects withdrew from the study, but both were found to be taking placebo. The remaining seven subjects completed each part of the study, and no clinically significant abnormality was observed in any of the routine haematology or biochemistry profiles, before or after dosing with either placebo or sufotidine.

**INTRAGASTRIC ACIDITY**

Figure 1 shows the hourly median intragastric acidity on the fifth day of dosing with either placebo or sufotidine 600 mg bd. It shows that during dosing with sufotidine 600 mg bd there was a consistent and profound decrease of acidity throughout the 24 hours.

Figure 2 shows that the median integrated 24-hour intragastric acidity for the seven duodenal ulcer subjects with a history of duodenal ulceration during dosing with placebo was 1000 mmol/h/l (range 618–1449 mmol/h/l). On the fifth day of dosing with sufotidine 600 mg bd, integrated 24 hour intragastric acidity was decreased in every subject to a median value of 51 mmol/h/l (range 5–158 mmol/h/l; 95%; p 0.001). For the seven subjects the decreases of 24 hour intragastric acidity ranged from 74% to 99%.

The median intragastric acidity was above pH 3 for 17% of the study, with an inter-subject range of 8–33%.

**PLASMA GASTRIN CONCENTRATION**

The 24-hour profiles of median plasma gastrin concentration on the fifth day of dosing with either placebo or sufotidine 600 mg bd are shown in Figure 3, which shows a consistent rise of median plasma gastrin concentration throughout the 24 hours during dosing with sufotidine.

Figure 4 shows that the median integrated 24-hour plasma gastrin concentration for the seven subjects during dosing with placebo was 416 pmol/l/h (range 208–947 pmol/l/h); the concentrations on the fifth day of dosing with sufotidine 600 mg bd had risen in every subject to a median of 927 pmol/l/h (range 629–1951 pmol/l/h; p 0.001).

**RELATIONSHIPS BETWEEN INTRAGASTRIC ACIDITY AND PLASMA GASTRIN CONCENTRATIONS**

Figure 5 shows a non-significant inverse correlation between integrated 24-hour intragastric acidity and integrated 24-hour plasma gastrin concentration in the 14 paired data sets from this study ($r_s=0.4418$; $p=0.114$).

**Discussion**

This study shows that a twice daily regimen using an H₂-blocker is capable of produc-
ing virtual elimination of intragastric acidity throughout the day and night in subjects with a history of duodenal ulceration. Hitherto, studies using twice daily regimens of H2-blockers have failed to control day time acidity, particularly in the late afternoon.\textsuperscript{1,2}

The subjects in this study responded to dosing with sufotidine with a median 95\% decrease of 24 hour acidity, ranging from 74\% to 99\%. When 12 duodenal ulcer patients were dosed with omeprazole 20 mg daily for a month under identical conditions at the Royal Free Hospital, they showed a median 97\% decrease of 24 hour acidity, but their individual responses ranged from 30\% to 100\%.\textsuperscript{3} When higher doses of omeprazole are given (30 mg/day, or more), all patients respond with a consistency similar to that seen with sufotidine 600 mg bd.\textsuperscript{3}

Five days of dosing with sufotidine 600 mg bd were tolerated without any adverse reaction by the seven subjects. The present regimen and lower dose regimens are suitable for testing by clinical trial for their use in the treatment of resistant peptic ulceration, and severe oesophagitis.

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