Twenty four hour intragastric acidity and plasma gastrin concentration in healthy volunteers taking nizatidine 150 mg, nizatidine 300 mg, ranitidine 300 mg, or placebo at 21 00 h

S LANZON-MILLER, R E POUNDER, N A F CHRONOS, F RAYMOND, M R HAMILTON, AND D DALGLEISH

From the Academic Department of Medicine, Royal Free Hospital School of Medicine, London

SUMMARY Nine healthy volunteers were studied on the seventh day of dosing at 21 00 h with nizatidine 150 mg (N 150), nizatidine 300 mg (N 300), ranitidine 300 mg (R 300), or placebo, given in a predetermined random order. The double-blind 24 hour studies, using the Royal Free Hospital standard protocol, simultaneously measured intragastric acidity and plasma gastrin concentration. Compared with placebo, subjects responded to dosing with each H₂-antagonist by a significant decrease of 24 hour intragastric acidity (N 150 - 45%; N 300 - 49% R 300 - 56%; $p < 0.01$) and a significant rise of plasma gastrin concentration (N 150 + 20%; N 300 + 27%; R 300 + 58%; $p < 0.01$). All three drug regimens caused similar significant decreases of nocturnal acidity (N 150 - 72%; N 300 - 79%; R 300 - 85%; $p < 0.01$) and increases of nocturnal plasma gastrin concentration (N 150 + 41%; N 300 + 52%; R 300 + 80%; $p < 0.01$). Dosing with ranitidine 300 mg at 21 00 h also caused a simultaneous significant decrease of morning acidity (-32%; $p < 0.05$) with a significant increase of plasma gastrin concentration (+36%; $p < 0.05$), but the antisecretory effects of nizatidine 150 or 300 mg at 21 00 h were only observed during the night, with no effect during the morning. No drug regimen had any effect on acidity or plasma gastrin in the afternoon or early evening.

Nizatidine (Eli Lilly and Company) is a newly-developed histamine H₂-receptor antagonist,¹ which inhibits human gastric acid secretion stimulated by sham feeding, pentagastrin, or peptone meal.^{2,3} The oral bioavailability of nizatidine in man exceeds 90% and the drug has a half-life in plasma of 1.6 hours.² Nizatidine does not interfere with drug metabolism by binding with cytochrome P-450,⁴ nor does it influence male hormone function or fertility.⁵

The purpose of the present double blind placebo controlled study was to compare the effects at a steady state of oral doses of either nizatidine (150 or 300 mg) or ranitidine 300 mg - taken during the

evening - on 24 hour intragastric acidity in healthy subjects.

In view of the recent interest in the rise of plasma gastrin concentration and human gastric carcinoids,⁶⁻⁸ and the development of enterochromaffin-like cell hyperplasia in some rats treated with high doses of antisecretory drugs,^{9,10} 24 hour intragastric acidity was correlated in this study with simultaneous measurement of 24 hour plasma gastrin concentration.^{11,12}

Methods

SUBJECTS

Nine healthy male volunteers took part in the study: they had a median age of 23 years (range 21-24 years), a median height of 1.80 m (range 1.70-1.88 m), and median weight of 73 kg (range 60-94 kg).

Address for correspondence: Dr R E Pounder, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG.

Received for publication 5 May 1988.

24 HOUR INTRAGASTRIC ACIDITY AND PLASMA GASTRIN

The subjects were studied under identical conditions for four 24 hour periods, using the Royal Free Hospital protocol for 24 hour studies.¹¹ During this series of experiments we observed the effect of dosing with drug or placebo at 21 00 h, hence the 24 hour studies started at 19 00 h and finished at 18 00 h on the following evening. In order to synchronise feeding and subsequent intragastric acidity before the start of each 24 hour study, the subjects ate a standard lunch at 13 15 h and were then admitted to the research ward at 17 00 h.

A 10 French gauge salem sump nasogastric tube (Argyle Medical) was positioned in the stomach, and from 19 00 h aliquots (5–10 ml) of intragastric contents were aspirated hourly throughout the study. 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 (Radiometer, Copenhagen). The electrode was calibrated with standard buffers (pH 7, 4.01, and 1.09; Radiometer, Copenhagen) before and halfway through each batch of nine samples.

Blood was taken through a venous cannula at hourly intervals between 19 00 h and 18 00 h the next day, except during the night when sampling was omitted at 01 00, 03 00, 05 00, and 07 00 h. Additional samples were taken at 45 and 75 minutes after the start of dinner, breakfast, and lunch. The blood was collected in lithium-heparin glass tubes which contained 0.2 ml aprotinin (Trasyol, Bayer). The tubes were centrifuged immediately, the plasma transferred to plastic tubes and frozen immediately 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.¹³ This antibody cross-reacts equally with G17 and G34, but does not react with cholecystokinin.

During the study the subjects were fully ambulant around the research ward. The food and environmental conditions for all four studies were identical to those used in earlier studies at the Royal Free Hospital.¹¹ The following meals were served: dinner, a bedtime snack, breakfast, coffee, lunch, and afternoon tea at 19 15, 22 15, 09 15, 11 15, 13 15, and 16 15 h respectively.

DOSING

The study was carried out double blind, the dosing being given in a predetermined random order. The subjects were studied on the seventh day of dosing with either placebo, nizatidine 150 mg, nizatidine 300 mg, or ranitidine (Zantac, Glaxo, Greenford UK)

Fig. 1 Twenty four hour median hourly intragastric acidity on the seventh day of dosing at 21 00 h with either placebo (●), nizatidine 150 mg (◆), nizatidine 300 mg (▲), or ranitidine 300 mg (■) in nine healthy subjects. B, breakfast; C, coffee; L, lunch; T, tea; D, dinner; N, night snack.

300 mg. An earlier human volunteer study had established that the ranitidine 150 mg capsule had the same oral bioavailability as a Zantac 150 mg tablet (Dr P Keohane, personal communication). Each dose of treatment was given as two capsules: two placebo capsules, nizatidine 150 mg capsule and one placebo capsule, two nizatidine 150 mg capsules, or two ranitidine 150 mg capsules, respectively.

ETHICAL APPROVAL AND STATISTICAL ANALYSIS

The study was approved by the Ethical Committee of the Royal Free Hospital and written consent was obtained from each subject before entry to the study. Routine safety studies were performed before and after each of the four seven day courses of treatment.

A 24 hour profile of intragastric acidity and plasma gastrin concentration was obtained for each subject. The integrated area under the curve (AUC) for each profile was calculated by the trapezoid rule to provide the integrated 24 hour value, with acidity expressed as mmol/h/l and plasma gastrin as pmol/h/l. Comparisons between 24 hour periods were made using the Wilcoxon's matched pairs signed-rank test.

The results of plasma gastrin and acidity were also divided into four meal related intervals (22 00–08 00, 09 00–13 00, 13 00–19 00, 19 00–22 00 h). The integrated AUC was calculated for each of these intervals. These results were compared using the Kruskal Wallis non-parametric one-way analysis of variance. In the text 'significant' relates to any difference where $p < 0.05$.

Results

The experiments were well tolerated. No adverse

Fig. 2 Twenty four hour median plasma gastrin concentration on the seventh day of dosing at 21 00 h with either placebo (●), nizatidine 150 mg (◆), nizatidine 300 mg (▲), or ranitidine 300 mg (■) in nine healthy subjects. B, breakfast; C, coffee; L, lunch; T, tea; D, dinner; N, night snack.

event was reported, and no clinically significant abnormality was detected in routine haematology and biochemistry profiles before and after treatment with each drug regimen.

INTRAGASTRIC ACIDITY

Figure 1 shows the median hourly intragastric acidity for the three treatment groups, compared with placebo. Each H_2 -blocker regimen caused a similar decrease of nocturnal acidity with recovery during the following day.

Figure 2 shows that all subjects responded to treatment with an antisecretory drug by a decrease of

Fig. 3 Integrated 24 hour intragastric acidity on the seventh day of dosing with placebo, nizatidine 150 mg, nizatidine 300 mg, or ranitidine 300 mg at 21 00 h in nine healthy subjects. The open circle indicates the median value for each group.

integrated 24 hour intragastric acidity. Median 24 hour integrated intragastric acidity was 805 mmol/h/l on placebo, 445 and 408 mmol/h/l (−45 and −49%) on nizatidine 150 and 300 mg respectively, and 356 mmol/h/l (−56%) on ranitidine 300 mg. The decreases of 24 hour acidity were all significant ($p < 0.01$).

Table 1 shows the acidity data analysed according to 'meal-related intervals' and that all three drugs caused a significant decrease of nocturnal intragastric acidity, but there was no significant difference between either dose of nizatidine, nor between nizatidine and ranitidine. Neither dose of nizatidine had any effect on daytime acidity, however, whilst ranitidine 300 mg given at 21 00 h not only decreased nocturnal acidity, but it also caused a significant decrease of morning intragastric acidity. During treatment with ranitidine 300 mg at 21 00 h, intragastric acidity was not significantly different from placebo during the afternoon and early evening.

Table 1 Meal related integrated intragastric acidity (mmol/h/l, with 95% confidence limits) in nine healthy volunteers on the seventh day of dosing with either placebo, nizatidine 150 mg, nizatidine 300 mg, or ranitidine 300 mg at 21 00 h

Interval	Evening 19 00–22 00 h	Night 22 00–08 00 h	Morning 09 00–13 00 h	Afternoon 13 00–19 00 h
Placebo	25 15–34	414 377–632	98 64–113	219 152–238
Nizatidine 150 mg	35† 14–36	118* 74–241	95† 71–146	217† 181–240
Nizatidine 300 mg	25† 22–36	87* 42–106	112† 64–139	195† 168–295
Ranitidine 300 mg	33† 12–38	60* 22–90	67‡ 39–91	211† 124–249

* $p < 0.01$, compared with placebo; †NS, compared with placebo; ‡ $p < 0.05$, compared with placebo, and nizatidine 150 or 300 mg.

PLASMA GASTRIN CONCENTRATION

Figure 3 shows the median plasma gastrin concentra-

Table 2 Meal related integrated plasma gastrin concentration (pmol/h/l, with 95% confidence limits) in nine healthy volunteers on the seventh day of dosing with either placebo, nizatidine 150 mg, nizatidine 300 mg, or ranitidine 300 mg at 21 00 h

Interval	Evening 19 00–22 00 h	Night 22 00–08 00 h	Morning 09 00–13 00 h	Afternoon 13 00–19 00 h
Placebo	39 25–48	117 80–139	55 34–63	84 61–94
Nizatidine 150 mg	34† 28–60	165* 129–215	51† 41–69	92† 74–102
Nizatidine 300 mg	41† 28–45	178* 149–225	51† 44–70	82† 68–123
Ranitidine 300 mg	42† 36–53	211* 162–254	75‡ 66–95	102† 75–122

* $p < 0.01$, compared with placebo; †NS, compared with placebo;

‡ $p < 0.05$, compared with placebo, and nizatidine 150 or 300 mg.

tion throughout the 24 hours and Figure 4 the integrated 24 hour plasma gastrin concentration for each subject. The subjects responded to dosing with an H₂-antagonist by a rise of integrated 24 hour plasma gastrin concentration: median 24 hour integrated plasma gastrin concentration was 291 pmol/h/l on placebo, 349 and 370 pmol/h/l (+20 and +27%) on nizatidine 150 mg and 300 mg respectively, and 461 pmol/h/l (+58%) on ranitidine 300 mg – these increases of 24 hour plasma gastrin concentration were all significant ($p < 0.01$).

Table 2 records integrated plasma gastrin concentration according to 'meal related intervals'. All three drugs caused a significant rise of nocturnal plasma gastrin concentration compared with placebo treat-

Fig. 4 Integrated 24 hour plasma gastrin concentration on the seventh day of dosing with placebo, nizatidine 150 mg, nizatidine 300 mg, or ranitidine 300 mg at 21 00 h in nine healthy subjects. The open circle indicates the median value for each group.

ment. During the morning, plasma gastrin concentration during dosing with ranitidine was significantly higher than during dosing with either regimen of nizatidine or placebo. During the afternoon and early evening no difference was observed in the plasma gastrin concentration during dosing with any of the H₂-antagonists, compared with placebo.

CORRELATION OF INTRAGASTRIC ACIDITY AND PLASMA GASTRIN CONCENTRATION

Figure 5 shows that there is a significant inverse correlation between the integrated 24 hour intragastric acidity and integrated 24 hour plasma gastrin concentration in these subjects (Spearman rank -0.49 ; $p = 0.02$).

Discussion

The results of this study show that, at steady state, nizatidine 150 or 300 mg in the evening causes a significant decrease in nocturnal intragastric acidity, but has no effect on daytime acidity during the following day. Earlier experiments have shown that nizatidine 150–300 mg inhibits nocturnal acid secretion as assessed by continuous aspiration^{3,14} (rather than the hourly sampling of acidity used in the present study). The present study could detect no significant difference between nizatidine 150 and 300 mg, suggesting that these doses must be towards the top of the dose response curve for this drug. In a double blind multicentre trial in the United States, the four week duodenal ulcer healing rates for nizatidine 25 mg bd, 150 mg bd, 300 mg nocte and placebo were 50, 68, and 67%, respectively.¹⁵

In the present study ranitidine 300 mg during the evening caused a similar decrease of nocturnal acidity to either dose of nizatidine. If it is true that control of nocturnal acidity relates closely to duodenal ulcer healing at four weeks,¹⁶ it could be anticipated that nizatidine 300 mg nocte will be similar (in terms of ulcer healing) to ranitidine 300 mg nocte. The only published controlled study in 777 patients reported four week duodenal ulcer healing rates of 81 and 80%, and eight week healing rates of 92 and 93%, for nizatidine 300 mg and ranitidine 300 mg nocte, respectively.¹⁷

There are three potential disadvantages of decreasing intragastric acidity in man: allowing pathogens access to the small and large intestine,¹⁸ allowing bacterial proliferation in the stomach,¹⁹ and inducing a rise in plasma gastrin concentration.¹² The advantage of the evening or nocturnal administration of a relatively short acting antisecretory drug is that there is a pulse of inhibition of gastric acid secretion overnight. Thus, in terms of the present experiments, either nizatidine 150–300 mg or ranitidine 300 mg in

Fig. 5 Integrated 24 hour intragastric acidity correlated with integrated 24 hour plasma gastrin concentration in nine healthy subjects on the seventh day of dosing with either placebo (●), nizatidine 150 mg (◆), nizatidine 300 mg (▲), or ranitidine 300 mg (■) at 21 00 h. The regression has a Spearman rank correlation coefficient of -0.49 ($p < 0.05$).

the evening can control nocturnal acidity, with essentially normal daytime acidity. The normal intragastric acid present during the daytime should ensure not only the 'sterilisation' of pathogens in the main meals of the day, but it should eliminate any chance of bacterial colonisation in the stomach.

Every subject responded in this study to dosing with either nizatidine or ranitidine by a decrease of integrated 24 hour intragastric acidity (Fig. 2) and by a rise of integrated 24 hour plasma gastrin concentration (Fig. 4). There was a significant inverse correlation between intragastric acidity and plasma gastrin concentration (Fig. 5). Similar results have been observed during treatment with ranitidine 150 mg bid, omeprazole 20 mg om,¹² and famotidine 40 mg nocte.²⁰ Although all these antisecretory drugs cause a significant rise of plasma gastrin concentration, the degree of elevation is mild compared with that observed in patients with pernicious anaemia.¹¹ Of these drug regimens, nizatidine 150 and 300 mg at 21 00 h have the shortest duration of antisecretory activity and they cause the least rise in 24 hour plasma gastrin concentration. Cimetidine 800 mg or 400 mg nocte are also short acting antisecretory regimens, but neither has been tested under the conditions of the Royal Free Hospital standard protocol for 24 hour intragastric acidity and plasma gastrin concentration.

In conclusion, evening administration of nizatidine

150 or 300 mg, or ranitidine 300 mg, cause similar decreases of nocturnal acidity, with associated nocturnal elevation of plasma gastrin concentration. Ranitidine 300 mg has a longer duration of action than the other dosing regimens, causing changes of acidity and plasma gastrin not only in the night but also the morning.

Capsules containing placebo, nizatidine and ranitidine were supplied by Drs P Keohane and Dr R John of Eli Lilly and Company, who also provided financial support for the study. The manuscript was processed by Mrs Julia Young. Technical support was provided by Nurse Judy Sercombe and Mr David Smart.

References

- 1 Morton DM. Pharmacology and toxicology of nizatidine. *Scand J Gastroenterol* [suppl] 1987; 122: 1-8.
- 2 Callaghan JT, Bergstrom RF, Rubin A, *et al*. A pharmacokinetic profile of nizatidine in man. *Scand J Gastroenterol* [suppl] 1987; 122: 9-17.
- 3 Kovacs TOG, van Deventer GM, Maxwell V, Sytnik B, Walsh JH. The effect of an oral evening dose of nizatidine on nocturnal and peptone-stimulated gastric acid and gastrin secretion. *Scand J Gastroenterol* [suppl] 1987; 122: 41-6.
- 4 Klotz U. Lack of effect of nizatidine on drug metabolism. *Scand J Gastroenterol* [suppl] 1987; 122: 18-23.
- 5 Van Thiel DH, Gavalier JS, Heyl A, Susen B. An

- evaluation of the anti-androgen effects associated with H₂-antagonist therapy. *Scand J Gastroenterol* [suppl] 1987; **122**: 24–8.
- 6 Borch K, Renvall H, Liedberg G. Gastric endocrine cell hyperplasia and carcinoid tumors in pernicious anaemia. *Gastroenterology* 1985; **88**: 638–48.
- 7 Harvey RF, Bradshaw MJ, Davidson CM, Wilkinsin SP, Davies PS. Multifocal gastrin carcinoid tumours, achlorhydria, and hypergastrinaemia. *Lancet* 1985; **i**: 951–3.
- 8 Borch K, Renvall H, Liedberg G, Andersen BN. Relations between circulating gastrin and endocrine cell proliferation in the atrophic gastric fundic mucosa. *Scand J Gastroenterol* 1986; **21**: 357–63.
- 9 Ekman L, Hansson E, Havu N, Carlsson E, Mattsson H, *et al*. Toxicological studies on omeprazole. In: Borg KO, Olbe L, eds. Omeprazole Book One. *Scand J Gastroenterol* [suppl 108] 1985; **20**: 53–69.
- 10 Larsson H, Carlsson E, Mattsson H, *et al*. Plasma gastrin and gastrin enterochromaffin-like cell activation and proliferation. *Gastroenterology* 1986; **90**: 391–9.
- 11 Lanzon-Miller S, Pounder RE, Hamilton MR, *et al*. 24 hour intragastric acidity and plasma gastrin concentration in healthy subjects and patients with duodenal or gastric ulcer, or pernicious anaemia. *Aliment Pharmacol Ther* 1987; **1**: 228–38.
- 12 Lanzon-Miller S, Pounder RE, Hamilton MR, *et al*. 24 hour intragastric acidity and plasma gastrin concentration before and during treatment with either ranitidine or omeprazole. *Aliment Pharmacol Ther* 1987; **1**: 239–52.
- 13 Bryant MG, Adrian TE. Gastrin. In: Bloom SR, Long RG, eds. *Radioimmunoassay of gut regulatory peptides*. London: Saunders, 1982: 51–9.
- 14 Dammann HG, Gottlieb WR, Walter TA, *et al*. Nocturnal acid suppression with a new H₂-receptor antagonist – nizatidine. *Hepatogastroenterology* 1986; **33**: 217–20.
- 15 Dyck WP, Cloud ML, Offen WW, Matsumoto C, Chernish SM. Treatment of duodenal ulceration in the United States. *Scand J Gastroenterol* [suppl] 1987; **122**: 47–55.
- 16 Hunt RH, Howden CW, Jones DB, Burget DW, Kerr GD. The correlation between acid suppression and duodenal ulcer healing. *Scand J Gastroenterol* [suppl] 1986; **21**: 22–8.
- 17 Dammann HG, Gottlieb WR, Walter TA, Muller P, Simon B, Keohane P. The 24-hour acid suppression profile of nizatidine. *Scand J Gastroenterol* [suppl] 1986; **21**: 61–70.
- 18 Howden CW, Hunt RH. Relationship between gastric secretion and infection. *Gut* 1987; **28**: 96–107.
- 19 Sharma BK, Santana IA, Wood EC, *et al*. Intragastric bacterial activity and nitrosation before, during and after treatment with omeprazole. *Br Med J* 1984; **289**: 717–9.
- 20 Lanzon-Miller S, Pounder RE, Ball SG, Dagleish DJ, Coward J, Jackson AO. The effect of famotidine 40 mg nocte on 24 hour intragastric acidity and plasma gastrin concentration in healthy subjects. *Scand J Gastroenterol*. 1988; **23**: 244–50.

Figure Responses of jejunal biopsies from control (○) and CF (●) children to 5 mM BaCl₂. The SCC for each tissue is shown before the addition of BaCl₂ and at the peak of the response. The mean (1 SE of the mean) was 12.5 (3.6) (6) μA/cm² for control biopsies and 10.5 (3.1) (4) μA/cm² for CF biopsies ($p > 0.05$).

ted by jejunal biopsies from CF children (Figure), an effect that was not significantly different from the response obtained in biopsies from a control group.

It therefore appears that the increased SCC across CF jejunum induced by A23187 is unlikely to result from the opening of basolateral K⁺ channels alone, but could represent a Cl⁻ secretory response brought about by the elevation of intracellular Ca²⁺. Patch clamp analysis of the luminal membranes of enterocytes affected by CF would provide a more definitive answer to this problem.

J. HARDCASTLE, P. T. HARDCASTLE, J. GOLDHILL,
C. J. TAYLOR, AND P. S. BAXTER

Department of Biomedical Science,
The University,
Sheffield S10 2TN, and
Department of Paediatrics,
Children's Hospital,
Sheffield S10 2TH.

References

- Giraldez F, Sepúlveda FV, Sheppard DN. An outward rectifying Cl⁻-selective channel in isolated Necturus enterocytes. *J Physiol* 1988 (In press).

- Welsh MJ, Liedtke CM. Chloride and potassium channels in cystic fibrosis airway epithelia. *Nature* 1986; **322**: 467–70.
- Frizzell RA, Rechkemmer G, Shoemaker RL. Altered regulation of airway epithelial cell chloride channels in cystic fibrosis. *Science* 1986; **233**: 558–60.
- Boucher RC, Cotton CU, Gatzky JT, Knowles MR, Yankaskas JR. Evidence for reduced Cl⁻ and increased Na⁺ permeability in cystic fibrosis human primary cell cultures. *J Physiol* 1988; **405**: 77–103.
- Hardcastle J, Hardcastle PT. The involvement of basolateral potassium channels in the intestinal response to secretagogues in the rat. *J Physiol* 1986; **379**: 331–45.
- Taylor CJ, Baxter PS, Hardcastle J, Hardcastle PT. Failure to induce secretion in jejunal biopsies from children with cystic fibrosis. *Gut* 1988; **29**: 957–62.
- Hardcastle J, Hardcastle PT, Noble JM. The effect of barium chloride on intestinal secretion in the rat. *J Physiol* 1983; **344**: 69–80.
- Hardcastle J, Hardcastle PT, Noble JM. The secretory action of barium chloride in rat colon. *J Physiol* 1985; **361**: 19–33.

News

International Bilirubin Workshop

This workshop will be held in Trieste, Italy, 6–8 April, 1989. For inquiries and registration forms contact either of the Directors: Claudio Tiribelli, MD, Istituto Patologia Medica, University of Trieste, 34100 Trieste, Italy. Tel: (40)-776-4525, Fax: (40)-910-690; or J. Donald Ostrow, MD, V.A. Lakeside Medical Center, 333 East Huron Street, Chicago, IL 60611, USA. Tel: (312)-943-6600, Ext 358, Fax: (312)-908-0365.

31st International Congress of Physiological Sciences

Will be held in Helsinki, Finland, on 7–14 July, 1989. Information from The Congress Secretariat, PO Box 722, SF-00101 Helsinki, Finland. (Telefax: 358–0–611 188).

Correction

24 h Intragastric acidity and plasma gastrin concentration . . . Lanzon-Miller *et al.* October 1988 issue pp 1364–9. The fourth column in Figures 3 and 4 should be correctly labelled ranitidine 300 mg.