Inhibition of food stimulated acid secretion by misoprostol, an orally active synthetic E₁ analogue prostaglandin

J. K. RAMAGE, A. DENTON & J. G. WILLIAMS

Royal Naval Hospital, Plymouth, UK

1 The effect of 200 µg misoprostol (a synthetic prostaglandin E₁ analogue) on food stimulated intragastric acidity has been monitored over a 9 h period in 16 normal volunteers.

2 Misoprostol caused a significant inhibition of intragastric acidity for 2 h post-dosing, but no significant effect was seen thereafter on either basal or food stimulated acidity.

Keywords misoprostol gastric acid secretion prostaglandin E₁ analogue

Introduction

Misoprostol (SC-29333, Figure 1) is a synthetic prostaglandin E₁ analogue that has been shown to be a potent inhibitor of gastric acid secretion in animals (Dajani *et al.*, 1976). It has also been established in animals that doses which do not significantly inhibit acid output may have an ulcer protective effect (Colton *et al.*, 1979, Larsen *et al.*, 1981). In man misoprostol has been shown to reduce nocturnal histamine (Akdamar *et al.*, 1982) and food stimulated secretion (Dajani & Polk, 1981) in doses up to 200 µg given orally. The duration of action of the drug has not been established and we have therefore investigated the effect of misoprostol 200 µg on repeated food stimulated acid secretion in normal volunteers, over a 9 h period.

Methods

Food stimulated gastric acid secretion was measured by monitoring the intragastric acidity

Figure 1 Chemical formula of misoprostol.

in response to an homogenous liquid meal instilled down a nasogastric tube. This meal consisted of one 375 ml can of Clinifed 500 (Roussel Ltd) to which a single oxo cube was added. This was warmed to 37°C and diluted to 550 ml with water. The composition of the meal was protein 42 g, carbohydrate 79 g, fat 12 g and osmolality 510 mmol/l. The pH of the meal was adjusted to 5.5 with a few drops of concentrated HCl (AnalaR) immediately before instillation into the stomach.

The subjects were normal fit male volunteers with no past history of significant gastrointestinal or other disease. No concurrent medication was allowed and no subjects were permitted to smoke or drink ethanol, coffee or tea during the study days or the preceding 24 h. The volunteers attended on 2 separate study days at least 1 week apart. After an overnight fast a 14 FR gauge nasogastric tube (Salem, Sump, Sherwood Medical Industries Inc) was passed and positioned under X-ray control to the most dependent part of the stomach. At 09.00 h the test tablets were administered by mouth with 200 ml of water. At 09.30 h the test meal was instilled down the nasogastric tube. For the next 90 min mixing was continuous by repeated aspiration and reinstallation of the gastric contents through a 50 ml syringe and by turning the subjects from the resting left decubitus position over to the right and back

Correspondence: Surgeon Commander J. G. Williams, Professor of Naval Medicine, Royal Naval Hospital, Haslar, Gosport, Hampshire PO12 2AA, UK.

again every 10 min. Every 5 min a 5 ml sample of gastric contents was aspirated and the pH measured to the nearest 0.01 pH unit using a combined glass electrode and digital pH meter (pHM72, Radiometer Copenhagen, Denmark). After measurement the samples were returned to the stomach. The electrode was kept to 37°C in buffers of pH 4 and pH 7 and its calibration was checked before each reading.

At 90 min the stomach was emptied. pH measurements were made at 30 min intervals until 13.00 h when the test meal procedure was repeated exactly as before. At 14.30 h the stomach was again emptied and pH measurements made at 30 min intervals until 17.00 h when the test meal was again repeated. This sequence of events is summarised in Figure 2.

The subjects were studied on two occasions at least 1 week apart, receiving either misoprostol 200 µg or identical placebo according to a predetermined random order. The studies were conducted double-blind.

Before and 24 h after each study blood and urine were taken for assessment of routine haematology and biochemistry.

For comparison of the effects of misoprostol vs placebo the pH response to the meal was compared by three way analysis of variance with subject, treatment and treatment period as factors. The data were analysed as pH, and not converted to mmol/l H^+ since pH is more normally distributed and is hence more suitable for analysis of variance (Lucas, 1977).

Results

Sixteen normal subjects (all male, mean age 28 years, s.e. mean 1.13, range 20–35, mean weight 73.5 kg, s.e. mean 3.4, range 54–107) were studied. All sixteen subjects completed

the study uneventfully except one who vomited during his final meal. He has been excluded from analysis of the data for the third meal. At the end of the first meal (2 h post dose) the pH of the gastric contents was markedly less with placebo (3.42 ± 0.19 s.e. mean) than with misoprostol (4.38 ± 0.18 s.e. mean). Mean pH for the duration of this meal was 4.97 following misoprostol and 4.51 following placebo ($P < 0.001$). At the end of the second meal the difference was smaller and at the end of the third meal there was very little difference between the two treatments (3.30 for misoprostol, 3.34 for placebo). For the second and third meals, mean pH on misoprostol was not significantly different from placebo; second meal 4.43 ± 0.11 vs 4.33 ± 0.11 , third meal 4.38 ± 0.12 vs 4.39 ± 0.11 , respectively.

The mean pH during both interdigestive periods was higher for misoprostol than placebo (between first and second meal misoprostol 2.48 ± 0.36 , placebo 1.94 ± 0.12 , between second and third meal misoprostol 2.45 ± 0.38 , placebo 2.05 ± 0.11 but the difference was not statistically significant for either period. These results have been displayed graphically in Figure 3.

No subject complained of any untoward effects during or after the studies apart from one volunteer who vomited 30 min after the start of his third meal. This is thought to be due to irritation from his nasogastric tube and he rapidly recovered once this was withdrawn. No subject complained of diarrhoea.

No significant abnormal results were seen on haematological or biochemical screening.

Discussion

These results indicate that misoprostol inhibits food stimulated gastric acidity significantly for

Figure 2 Summary of sequence of events during each study.

Figure 3 Mean pH ($\pm$ s.e. mean) plotted against time for 16 subjects receiving misoprostol 200 μ g (●) or placebo (x).

up to 2 h post-dosing. Acidity in response to the second meal (4 h post dose) also shows some inhibition though without statistical significance. The inhibition of basal gastric acidity seen when measured from 2 h post-dosing is not statistically significant.

The method used is simple, well tolerated and is comparable with previous 24 h studies which have measured intragastric acidity by aspiration of samples (Pounder *et al.*, 1975, 1976). It gives no information concerning volume of secretion and it does not quantify actual acid output but assesses acidity while the stomach responds to the meal in a physiological manner. The meal used is a potent stimulus to acid secretion causing a mean acid output of greater than 40 mmol/h when measured by *in vivo* titration (Williams *et al.*, 1983).

The mean rise in pH during breakfast (to 4.38) in the misoprostol group is greater than that in the control group (to 3.42). This difference is less than that seen with cimetidine 400 mg, using an identical technique (unpublished data). In the light of evidence of cytoprotection in animal studies (Colton *et al.*, 1979; Larsen *et al.*, 1981) it will be of interest to see whether misoprostol, given orally in a single dose of relatively low potency and short duration of action as an antiseecretory agent will be effective in the healing of peptic ulcers.

We are grateful to the Medical Officer-in-Charge, Royal Naval Hospital Plymouth, for permission to perform these studies and to G. D. Searle & Co, High Wycombe, Buckinghamshire, for supplies of misoprostol. We are also grateful to Mrs Jeanette Rawlins for clerical assistance.

References

- Akdamar, K., Agrawal, N. & Ertan, A. (1982). Inhibition of nocturnal gastric secretion in normal human volunteers by misoprostol: a synthetic prostaglandin E_1 methyl ester analog. *Am J. Gastroenterol.*, **77**, 902-904.
- Colton, D. G., Callison, D. A. & Dajani, E. Z. (1979). Effects of prostaglandin E_1 derivative, SC-29333, and aspirin on gastric ionic fluxes and potential difference in dogs. *J. Pharmac. exp. Ther.*, **210**, 283-288.
- Dajani, E. Z., Driskill, D. R., Bianchi, R. G., Collins, P. W. & Pappo, R. (1976). SC-29333: A potent inhibitor of canine gastric secretion. *Digestive Diseases*, **21**, 1049-1057.
- Dajani, E. Z. & Polk, R. C. (1981). G. D. Searle & Co. Investigational Brochure for SC-29333, a gastric antiseecretory agent.
- Larsen, K. R., Jensen, N. F., Davis, E. K., Jensen, J. C. & Moody, F. G. (1981). The cytoprotective effects of ($\pm$)-15-deoxy-16- α , β -hydroxy-16-

- methyl PGE₁, methyl ester (SC-29333) versus aspirin-shock gastric ulcerogenesis in the dog. *Prostaglandins*, **21**, Suppl., 119–24.
- Lucas, M. (1977). pH or hydrogen ion concentrations in statistics. *Lancet*, **ii**, 826.
- Pounder, R. E., Williams, J. G., Milton-Thompson, G. J. & Misiewicz, J. J. (1976). Effect of cimetidine on 24 h intragastric acidity in normal subjects. *Gut*, **17**, 133–138.
- Pounder, R. E., Williams, J. G., Milton-Thompson, G. J. & Misiewicz, J. J. (1975). 24 h control of intragastric acidity by cimetidine in duodenal ulcer patients. *Lancet*, **ii**, 1069–1072.
- Williams, J. G., Robertson, R. J. & Milton-Thompson, G. J. (1983). Inhibition of food stimulated acid secretion by fenotimine, a new anti-secretory agent. *Br. J. clin. Pharmac.*, **15**, 673–676.

(Received January 31, 1984,
accepted September 2, 1984)