INHIBITION OF FOOD STIMULATED ACID SECRETION BY FENOCTIMINE, A NEW ANTI-SECRETORY AGENT

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1 The effect of fenoctimine, a new anti-secretory agent, has been studied on food stimulated acid secretion in six normal volunteers.

2 When tested between 2 and 4 h after dosing, and compared with placebo, fenoctimine 50 mg inhibited acid secretion by a mean of 29%, 150 mg by 43% and 250 mg by 47%.

Introduction

Fenoctimine (4-diphenylmethyl)-1-((octylimino) methyl) piperidine sulphate (1:1 hemihydrate) (Figure 1) is a novel anti-secretory agent which has been shown in animals to inhibit acid secretion, both basal and when stimulated by histamine, gastrin or bethanechol (Jacoby *et al.*, 1982). In animals the compound does not appear to have specific anticholinergic or H_2 -receptor antagonist activity, and has a long duration of action, anti-secretory activity being detected as long as 48 h after dosing.

We have used *in vivo* intragastric titration to study the effect of fenoctimine on food stimulated gastric acid secretion in normal subjects.

Methods

Food stimulated gastric acid secretion was measured using a modified form of the technique described by Fordtran & Walsh in 1973 and already described by us (Pounder *et al.*, 1976), and further modified by the substitution of a homogeneous liquid meal (Mills *et al.*, 1982). This consisted of one 375 ml can of Clinifeed 500 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 mosmol/l. The pH of the meal was adjusted to 5.5 with a few drops of concentrated hydrochloric acid (AnalaR) immediately before installation into the stomach. The subjects were normal, fit male volunteers with no past history of significant gastrointestinal disease. No medication was allowed for the 7 days before the study. No alcohol was allowed for 24 h and no smoking for 12 h before and during each study. The subjects fasted overnight. At 08.00 h they were given the test capsules with 200 ml water, after blood and urine had been taken for toxicology profile and an ECG had been performed. Ninety minutes later a double lumen 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 110 min after the capsules had been given the stomach was emptied before the test meal was instilled through the larger lumen of the tube, over a period of 5 min.

Throughout the experiment the gastric contents were mixed by continuous aspiration and re-instillation of the contents with a 50 ml syringe attached to the larger lumen of the nasogastric tube. In addition,

Figure 1 Formula of fenoctimine sulphate.

every 10 min the subjects were turned from the resting left decubitus position over to the right and back again. The pH of the gastric contents was measured to the nearest 0.01 pH unit using a combined glass electrode and digital pH meter (pHM 62, Radiometer, Copenhagen) every 2 min throughout the experiment. This pH was measured on 5 ml aspirates which were returned to the stomach after each measurement. The electrode was kept at 37°C in buffers of pH 4 and pH 7, and its calibration was checked before each reading.

The intragastric pH was maintained at 5.5 by adjusting the rate of a sodium bicarbonate infusion using a variable speed pump (Watson Marlow Flow Inducer coupled to a Delta pump). The bicarbonate was infused through the smaller lumen of the nasogastric tube at a concentration of 333 mmol/l for the fenoctimine studies and 666 mmol/l for the placebo studies. The volume of bicarbonate added to the stomach every 2 min was read off a burette reservoir connected to the pump. The rate of gastric acid secretion was deemed to be equivalent to the mmols of sodium bicarbonate required to keep the pH of the gastric contents at 5.5.

The experiments continued for 2 h following the instillation of the meal. The volume of meal remaining in the stomach at this time was aspirated and measured.

The subjects were studied on four occasions to assess the effect of fenoctimine 50 mg, 150 mg and 250 mg as compared with placebo. At least 2 weeks was allowed to elapse between each study and the whole series of experiments were conducted double-blind. The test medication capsules were identical in presentation and the different concentrations of

bicarbonate for infusion were made up in the laboratory. The four experiments on each individual were conducted according to a predetermined random order.

One subject received placebo on two occasions in addition to the three test medication doses, to assess the reproducibility of the technique. The studies were double-blind until his final placebo run.

Immediately after each experiment the subjects were examined. Blood and urine were taken for assessment of laboratory parameters at 24 and 72 h.

For comparison of the effects of the different doses of fenoctimine on food stimulated gastric acid output, Friedman's test for non-parametric data was employed. For analysis of the differences between starting infused and residual volumes, Student's *t*-test was used.

All subjects gave their informed consent to the procedures which were approved by the appropriate ethical committees.

Results

Six normal subjects (all male—mean age 30.2 years, s.e. mean 2.4, range 24–41, mean weight 72.9 kg, s.e. mean 3.3, range 66.5–88.8) were studied. One subject was studied twice following placebo capsules and Figure 2 shows the results for these two studies plotted against each other. The correlation coefficient was 0.998, equation $y = 0.294 + 1.095x$. The residual volumes and pH were 240 ml, pH 5.5 (study x) and 300 ml pH 5.46 (study y). Figure 3 shows the mean and standard errors of the mean for the cumulative bicarbonate infused for the placebo and three active dose studies in the six volunteers. Mean cumulative acid secretion at 2 h after the meal (4 h after oral dosing) was 82.6 mmol following placebo. This was reduced by 29% to 58.9 mmol after fenoctimine 50 mg ($P < 0.1$), 43% to 46.7 mmol after 150 mg ($P < 0.01$) and 47% to 43.8 mmol after 250 mg ($P < 0.002$). When analysed in 20 min intervals, inhibition significantly better than placebo was apparent with the two higher doses of fenoctimine from the first 20 min period onwards.

There was no statistical difference between the aspirated starting volumes of the experiments nor in the volumes of bicarbonate infused except in the experiments following fenoctimine 50 mg, where a greater volume of infusate was required than in the placebo experiments ($P < 0.01$), (Table 1).

There was no significant difference between the residual volumes of the meal left in the stomach at 2 h although this tended to be higher following the placebo dose, (Table 1). Mean residual pH and pH range is also shown in this table.

A number of subjects complained of dry mouth follow-

Figure 2 Reproducibility: Results (mmol bicarbonate infused) of identical placebo studies in Subject No. 3.

Figure 3 Cumulative bicarbonate infused (mmol) plotted against time. Mean and s.e. mean for six subjects, who each received placebo (■) and three different doses of fenoctimine (● 50 mg, ○ 150 mg, □ 250 mg).

ing the higher doses of fenoctimine. There were no other significant clinical symptoms.

Clinical examination revealed no significant abnormalities and no abnormalities were detected on blood, urine and electrocardiographic screening.

Discussion

We have shown that fenoctimine causes significant inhibition of food stimulated acid secretion. The results suggest that the plateau of the dose response

curve is reached at around 150 mg, with little further inhibition occurring following 250 mg. Our meal of Clinifeed and oxo appears to be a particularly potent stimulus to acid secretion, causing a mean acid output for the six subjects of greater than 40 mmol/h following placebo, which is substantially greater than that produced by peptone in duodenal ulcer subjects (Henn *et al.*, 1975) and a little greater than that produced by steak in normals (Pounder *et al.*, 1976). Comparison with other compounds is difficult due to such differences in experimental method. The degree of inhibition achieved is less than that obtained with cimetidine 200 mg, given orally to normal subjects just before a steak meal (Pounder *et al.*, 1976), but greater than that achieved by cimetidine 200 mg orally in normals, when Clinifeed (without oxo) was used as the meal (Mills *et al.*, 1982). The inhibition is also greater than that achieved in duodenal ulcer patients with optimum doses of an anticholinergic (isopropamide), where again steak was used as the meal and only 35% inhibition was achieved (Richardson *et al.*, 1975). It has not yet been determined what level of inhibition of food stimulated acid secretion is compatible with healing of duodenal ulcers.

To try to minimise differences in infused volume of bicarbonate a more dilute solution was used in all the active drug studies (333 mmol/l) than in the placebo studies (666 mmol/l). This resulted in similar volumes of infusate throughout the experiments except when fenoctimine 50 mg was tested. The increased volume of infusate required in these experiments reflects the relatively poor inhibition obtained at this dosage and it is possible the increased volume may have caused some increase in acid secretion in these studies. The comparatively wide range in pH of the residual volumes reflects the imprecision of control of intragastric pH towards the end of the experiments as gastric volumes fall. However, at such pH values these fluctuations represent a very small range of hydrogen ion activity.

The tablets were given 2 h before testing meal stimulated acid secretion which suggests that there is some prolongation of effect, in agreement with studies on the inhibition of pentagastrin stimulated secretion in normal volunteers, which suggested that

Table 1 Volume (ml) of gastric aspirates and bicarbonate infused. Means and s.e. mean for each dose of fenoctimine and placebo. The mean pH and range of values for the residual aspirates are also shown.

	Test medication			
	250 mg	150 mg	50 mg	Placebo
Initial aspirate	64 ± 6.1	58 ± 11.7	76 ± 16.1	69 ± 12.4
Bicarbonate infused	136 ± 23.5	132 ± 13.6	186 ± 23.3	123 ± 9.8
Residual aspirate	147 ± 27.3	200 ± 36.9	163 ± 38.4	244 ± 42.6
Residual pH Mean	5.55	5.51	5.48	5.56
Range	5.32 – 5.68	5.42 – 5.52	5.41 – 5.72	5.32 – 5.82

significant inhibition will be present for at least 8 h following fenoctimine 250 mg (Williams *et al.*, 1981).

The complaint of dry mouth from a number of patients on the higher dose of fenoctimine suggests that the compound may have an anticholinergic effect although this has not been detected in animals (Jacoby *et al.*, 1982). No other untoward effects were detected and the compound would appear to be safe in the short term but detailed toxicology is clearly required to ensure the safety of long term studies and

treatment. Nevertheless, the possible novel mode of action and the long duration of effect make fenoctimine a compound worthy of further study.

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