Effect of enprostil, a synthetic prostaglandin E₂ on 24 hour intragastric acidity, nocturnal acid and pepsin secretion

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SUMMARY We have studied the effect of a prostaglandin E₂ analogue (enprostil), on intragastric acidity, gastric acid and pepsin outputs during a 24 hour period in nine patients with duodenal ulcer in remission. Enprostil 35 µg bd dose inhibited 24 hour intragastric acidity by 38% and a 70 µg nocturnal dose by 33%. Decrease in nocturnal pepsin secretion was both volume and concentration related.

Prostaglandin E₂ is known to inhibit gastric secretion although the mechanism is not fully understood.¹ This together with a postulated cytoprotective action² makes prostaglandin E₂ analogues attractive for trial in the treatment of peptic ulceration. Enprostil is a synthetic dehydroprostaglandin E₂ currently undergoing clinical trial in the treatment of gastroduodenal ulceration in doses of 35 and 70 µg twice daily. A dose of 70 µg nocte is planned for further trials. This dose will reduce food stimulated acid secretion by 89% in normal volunteers.³ We have studied the effect of enprostil 35 µg bd and 70 µg nocte on 24 hour intragastric acidity, nocturnal acid, and pepsin outputs in duodenal ulcer patients.

Methods

SUBJECTS

Nine male volunteers with endoscopically diagnosed duodenal ulcer disease in symptomatic remission took part in the study. The age range of the group was 26–54 years (mean 39 years) and length of history 18 months–22 years.

The subjects were studied during three 24 hour periods not less than one week apart. They were admitted to the ward at 0700 h, and a sump type nasogastric tube passed. Identical standard meals comprising 375 ml Clinifed 500 (Roussel) and one

Oxo cube dissolved in 200 ml hot water were taken by mouth at 0800, 1300, and 1800 h. Timing of tea and cigarettes were kept as constant features for each individual on all study days. Samples (5 ml) were aspirated for pH recording (pHm82 Radiometer, Copenhagen) at 15 minute intervals for three hours after the meals and then half hourly until the next meal. Overnight from 0030 the stomach was kept empty by continuous aspiration (pump – Ameda, Switzerland) and specimens collected in hourly aliquots. A 5 ml specimen was titrated to pH 7 to estimate hydrogen ion concentration and a further sample stored at +4°C for the measurement of peptic activity within 24 hours by the method of Gray and Billings.⁴

The study was double blind, the subjects receiving placebo, enprostil 35 µg bd or 70 µg nocte in random order. The capsules were given at 2300 on the night before study and at 0730 and 2300 h on the study day.

For comparison between different treatment periods the pH data were converted to hydrogen ion activity. Median values for the 24 hour, morning, afternoon, evening and night time periods were calculated from the hourly and half hourly values. Data have been presented graphically as the median with 25th and 75th percentiles for descriptive purposes. Statistical analysis was by a two sided Wilcoxon's paired comparison test on individual differences between each of the doses.

Ocular tonometry, routine haematology, and biochemistry were undertaken before and after the study period. The study was approved by the

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Results

INTRAGASTRIC ACIDITY

The median hydrogen ion activity curve over 24 hours for each of the treatment regimens and placebo is shown in Figure 1. The median hydrogen ion activities for the 24 hour, morning, afternoon, evening, and night time periods are shown in Figure 2.

Compared with placebo the median hourly hydrogen ion activity for the 24 hour period was lowered by 38% by enprostil 35 μ g bd and 33% by enprostil 70 μ g nocte ($p < 0.05$ for both treatments vs placebo). In the morning 35 μ g bd produced a significant inhibition compared with both placebo ($p < 0.01$) and 70 μ g nocte ($p < 0.01$). The nocturnal dose did not significantly affect acidity the following morning. Overnight the inhibition achieved by the two doses was 87% for enprostil 35 μ g bd and 80% for 70 μ g nocte. There was no significant difference between the effect of the two doses.

Fig. 1 Median 24-hour hydrogen ion activity curves ($n=9$) with 25th and 75th percentiles for placebo (+—+), enprostil 35 μ g bd (O— —O), and enprostil 70 μ g nocte (x.....x). Data points are hourly readings from 0830.

Fig. 2 Histogram of hydrogen ion activity (median with 25th and 75th percentiles, $n=9$) for different time periods on placebo, enprostil 35 μ g bd and enprostil 70 μ g nocte.

Table Nocturnal volume of gastric secretion, hourly acid and pepsin output, and pepsin concentration between the hours 0030 and 0730. $n=9$, median (25th–75th percentiles)

	Volume output (ml/h)	Acid output (mmol/h)	Pepsin output (IU/h)	Pepsin concentration (IU/l)
Placebo	57.7 (23–62.3)	3.4 (1.6–4.1)	4.1 (1.7–5)	80 (43–89)
Enprostil 35 µg bd	42.7* (29–47.7)	0.67† (0.4–0.8)	0.6† (0.4–1.5)	36† (11–40)
Enprostil 70 µg nocte	26.7* (22–26.9)	0.7† (0.4–0.8)	1.5* (0.3–1.6)	58* (4–62)

* $p<0.05$. † $p<0.01$ vs placebo.

NOCTURNAL SECRETION

Median values with 25th and 75th percentiles for nocturnal acid and pepsin output are shown in the Table.

During the overnight period total acid output was decreased by 80% by enprostil 35 µg bd and 79% by enprostil 70 µg nocte ($p<0.01$ for both doses vs placebo). There was no significant difference between the 35 µg bd and 70 µg nocte dose regimens.

Nocturnal pepsin output was decreased by 85% ($p<0.01$) and 63% ($p<0.05$) by enprostil 35 µg bd and 70 µg nocte respectively. Both doses lowered pepsin concentration compared with placebo ($p<0.01$), and significantly lowered volume output ($p<0.05$). The decrease in volume was more marked after the 70 µg nocte dose, but this was not statistically significant compared to 35 µg bd.

UNWANTED EFFECTS AND SAFETY PROFILE

Nausea was experienced by no patient on placebo, three of nine on enprostil 35 µg bd and one of nine on enprostil 70 µg nocte. Diarrhoea was noted by one patient after enprostil 35 µg bd and one subject with nausea vomited the day after the study (35 µg bd). No changes were observed outside the normal range on ocular tonometry, haematology, and biochemistry.

Discussion

These data show that enprostil is an effective inhibitor of gastric acid and pepsin secretion. The percentage decrease in 24 hour intragastric acidity is similar to that reported for cimetidine 400 mg bd (30–42%).^{5,6} Very little difference between the 35 µg bd and 70 µg nocte dose is seen overnight. This supports previous work that suggests that the two doses under trial are at the top of the dose response curve.⁷

Experience with H₂ antagonists suggests that 24-hour control of intragastric acidity is not required to heal ulcers, nocturnal control being sufficient.⁸ The decrease in nocturnal secretion we have shown with enprostil 70 µg nocte is less than we have shown after cimetidine 800 mg nocte but enprostil 35 µg bd is equivalent to cimetidine 400 mg bd in identical studies with the same group of subjects.⁹

The decrease in nocturnal pepsin secretion is both volume and concentration related. While the percentage decrease in nocturnal acid output is comparable with that seen after cimetidine 400 mg¹⁰ the pattern of reduction of pepsin secretion is different. In a previous study⁹ we found the concentration of pepsin remained the same or increased after cimetidine 400 mg bd, whereas the fall in pepsin output was mainly volume related. There are a number of possible explanations for the differing pattern of pepsin secretion after enprostil. Pepsin is inactivated above pH 5 but significant denaturation (and loss of detection) does not occur unless the pH of the specimen is above 6.¹¹ In this study the overnight pH profile was similar to that seen after cimetidine 400 mg and we believe this explanation unlikely. It is possible that enprostil has a direct action on the chief cell but there is no published evidence for this. Such an effect could be mediated *via* changes in gastrointestinal hormones: enprostil has been shown to lower serum gastrin, in the presence of rising intragastric pH,⁷ but data are not yet available on other hormones. Gastrin,¹² motilin¹³ and secretin¹⁴ have all been shown to increase pepsin secretion in man. Finally there is some evidence that prostaglandins stimulate bicarbonate secretion which would lessen any decrease in volume related to inhibition of acid secretion, and therefore lower pepsin concentration.¹⁵

Reduction in pepsin concentration and a cytoprotective effect may prove to be important in healing. Because the healing rate of duodenal ulcers

is related to the dose of H2 receptor antagonist,¹⁶ however, and by implication to the degree of suppression of intragastric acidity,¹⁷ enprostil 35 µg bd is likely to produce similar healing figures to cimetidine 400 mg bd on the basis of acid suppression alone. Conversely a single nocturnal dose of enprostil 35 or 70 µg is unlikely to achieve healing rates equivalent to currently recommended doses of H2 receptor antagonists.

References

- 1 Isenberg JI. Prostaglandins: pharmacologic principles. *Adv Ulcer Dis* 1980; **537**: 416–20.
- 2 Navert H, Lamothe F, Lebel L, Tetreault H, Haddad H. Evaluation of the gastrointestinal cytoprotective effects of enprostil following aspirin administration in man. *Gastroenterology* 1984; **86**: 1194.
- 3 Davis GR, Santa Ana CA, Morawski SG, Fordtran JS. Effect of synthetic PGE2 on food-stimulated gastric acid secretion. *Clin Pharmacol Ther* 1982; **31**: 215.
- 4 Gray SP, Billings JA. Kinetic assay of human pepsin with albumen-bromphenol blue as substrate. *Clin Chem* 1983; **29**: 447–51.
- 5 Gledhill T, Howard OM, Buck M, Paul A, Hunt RN. Single nocturnal dose of an H2-receptor antagonist for the treatment of duodenal ulcer. *Gut* 1983; **24**: 904–8.
- 6 Dammann HG, Friedl W, Miller P, Simon B. Comparison of the effects of ranitidine and cimetidine twice daily on the 24 hour intragastric acidity in man. *Ital J Gastroenterol* 1983; **15**: 254–5.
- 7 Davis GR, Fordtran JS, Walsh J, Pennelly LW, Lewis PL, Sevelius H. The effect of enprostil, a synthetic prostaglandin E2, on gastric acid secretion and serum gastrin concentration in normal human subjects. *Dig Dis Sci* (In press).
- 8 Ireland A, Colin-Jones DG, Gear P, *et al.* Ranitidine 150 mg twice daily vs 300 mg nightly in treatment of duodenal ulcers. *Lancet* 1984; **2**: 274–6.
- 9 Deakin M, Ramage JK, Colin-Jones DG, Gray S, Billings J, Williams JG. Does smoking affect the response to cimetidine in duodenal ulcer disease? *Lancet* 1985; **1**: 1049.
- 10 Pounder RE, Hunt RH, Vincent SH, Milton-Thompson GJ, Misiewicz JJ. 24-hour intragastric acidity and nocturnal acid secretion in patients with duodenal ulcer during oral administration of cimetidine and atropine. *Gut* 1977; **18**: 85–90.
- 11 Piper DW, Fenton BH. pH stability and activity curves of pepsin with special reference to their clinical importance. *Gut* 1965; **6**: 506–8.
- 12 Peden NR, Boyd EJS, Callachan A, Shepherd DM, Wormsley KG. The effects of impromidine and pentagastrin on gastric output of histamine, acid and pepsin in man. *Hepato-Gastroenterol* 1982; **29**: 30–4.
- 13 Rupp H, Domschke S, Domschke W, Wunsch E, Jaeger E, Demling L. Effects of 13-Nle-motilin in man-inhibition of gastric evacuation and stimulation of pepsin secretion. *Scand J Gastroenterol* 1975; **10**: 199–202.
- 14 Brooks AM, Isenberg J, Grossman M. The effect of secretion, glucagon and duodenal acidification on pepsin secretion in man. *Gastroenterology* 1969; **57**: 159–202.
- 15 Feldman M. Gastric bicarbonate secretion in humans. Effect of pentagastrin, bethanecol and 11,16,16-trimethyl prostaglandin E2. *J Clin Invest* 1983; **72**: 295–303.
- 16 Howden CW, Jones DB, Hunt RH. Nocturnal doses of H2 receptor antagonists for duodenal ulcer. *Lancet* 1985; **1**: 647–8.
- 17 Jones DB, Howden CW, Burget DW, Kerr GD, Hunt RH. The rational use of H2 receptor antagonists for the treatment of duodenal ulceration. *Am J Gastroenterol* 1985; **80**: 841.