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 cytotoxic 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 nocto 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 Clinifeed 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 500 l sample stored at +4°C for the measurement of pepsic 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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Medical Research Subcommittee of the Royal Naval Medical Research Committee.

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 µg bd and 33% by enprostil 70 µg nocte (p<0.05 for both treatments vs placebo). In the morning 35 µg bd produced a significant inhibition compared with both placebo (p<0.01) and 70 µg 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 µg bd and 80% for 70 µg 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 µg bd (O—O—O), and enprostil 70 µg nocte (X—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 µg bd and enprostil 70 µg 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)

<table>
<thead>
<tr>
<th>Volume output (ml/h)</th>
<th>Acid output (mmol/h)</th>
<th>Pepsin output (IU/h)</th>
<th>Pepsin concentration (IU/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>57-7 (23-62-3)</td>
<td>3-4 (1-6-4-1)</td>
<td>4-1 (1-7-5)</td>
</tr>
<tr>
<td>Enprostil</td>
<td>42-7*</td>
<td>0-67†</td>
<td>0-6† (0-4-1-5)</td>
</tr>
<tr>
<td>35 μg bd</td>
<td>29-47-7</td>
<td>0-4-0-8</td>
<td>1-5* (0-3-1-6)</td>
</tr>
<tr>
<td>Enprostil 70 μg noite</td>
<td>22-26-9</td>
<td>0-4-0-8</td>
<td>8t (1-6-1)</td>
</tr>
</tbody>
</table>

*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 and 79% by enprostil 70 μg noite (p<0-01 for both doses vs placebo). There was no significant difference between the 35 μg bd and 70 μg noite 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 noite 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 noite 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 noite. 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%).

Very little difference between the 35 μg bd and 70 μg noite 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.

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

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 mg bd, the pattern of reduction of pepsin secretion is different. In a previous study 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. 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, but data are not yet available on other hormones. Gastrin, motilin, secretin 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.

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