Dose response inhibition in man of meal-stimulated gastric acid secretion by 15(R)-15-methyl prostaglandin E₂, given orally

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SUMMARY 15(R)-15-methyl prostaglandin E₂ was given orally to healthy male volunteers. Thirty minutes later a 10% peptone meal was introduced into the stomach, and the acid response was measured by continuous intragastric titration with 0.5 N NaOH for the next two hours. The prostaglandin inhibited acid output in a dose dependent manner; the ED₅₀ (dose inhibiting acid output by 50%) was as little as 10 μg per subject (or approximately 140 ng/kg). This compound is the most potent orally active inhibitor of gastric acid secretion in man that is known. It is likely that the antisecretory and cytoprotective properties shared by 15(R)-15-methyl prostaglandin E₂ would be beneficial in the treatment of peptic ulcer and in preventing recurrences.

Several natural prostaglandins such as PGE₁, PGE₂, PGA₁, and PGA₂ were found to inhibit gastric acid secretion in animals¹ ² ³ and humans⁴ ⁵ when administered parenterally, although they are inactive or very weak when given orally.⁶ ⁷ Certain methyl analogues of PGE₂ are also antisecretory but differ from PGE₂ in that they are active orally, are long-acting, and are many times more potent than the parent compound.⁸ ⁹ Such an analogue is 15(R)-15-methyl prostaglandin E₂ (M-PGE₂, arbaprostil) which was previously shown to inhibit acid secretion in humans.¹⁰ ¹¹ We report here the effect of various doses of M-PGE₂, given orally, on gastric acid output stimulated by a meal. The purpose was to establish a dose response curve. The results show that M-PGE₂ is one of the most potent antisecretory agents in humans when given by the oral route.

Methods

Twenty-five healthy male volunteers between 18 and 27 years old were studied (Table 1). Informed consent was provided by each subject. They were without gastrointestinal symptoms and had normal values for blood chemistry, haematology, and urinalysis. A physical examination and an electrocardiogram were normal. After an overnight fast (10.00 pm), an 18-gauge French double-lumen Salem tube was introduced into the stomach. The subjects were semi-reclined in a lounge chair for the rest of the study. The gastric contents were

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Age (yr)</th>
<th>Weight (lb)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(μg)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>20.8 ± 1.9 (19-24)</td>
<td>164.3 ± 16.4 (151-191)</td>
</tr>
<tr>
<td>25</td>
<td>27.4 ± 3.8 (22-30)</td>
<td>176.5 ± 14.1 (157-196)</td>
</tr>
<tr>
<td>50</td>
<td>25.2 ± 6.6 (21-37)</td>
<td>162.4 ± 5.1 (156-168)</td>
</tr>
<tr>
<td>100</td>
<td>26.8 ± 5.7 (19-33)</td>
<td>174.8 ± 25.8 (154-217)</td>
</tr>
<tr>
<td>150</td>
<td>26.4 ± 5.2 (18-32)</td>
<td>173.8 ± 24.1 (137-203)</td>
</tr>
</tbody>
</table>

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emptied by gravity and gentle suction. Either drug or placebo was then administered in 15 ml of an aqueous solution through the nasogastric tube, which was then clamped for 30 minutes. After that time, 600 ml of a 10% peptone meal (Bacto-Peptone, Difco Laboratories, Detroit, Michigan) adjusted to pH 5.5 with HCl was introduced into the stomach through the nasogastric tube. Acid output was measured by an intragastric titration method previously described. briefly, 32 ml of the gastric contents were aspirated and returned to the stomach eight times per minute with the use of an automatic pipetting machine (Brewer, Model 60453, Scientific Equipment Products, Baltimore, Maryland). The pH of the gastric contents was detected by a pH electrode (Standard pH meter, Model DHM-62, Radiometer, Copenhagen) located between the nasogastric tube and the automatic pipette. When the pH fell below 5.5 as a result of acid secretion by the stomach, 0.5 N sodium hydroxide was delivered by an automatic titrator (Radiometer, Model TTT60) directly into the stomach via the smaller lumen of the nasogastric tube. The titration was continued for two hours. The amount of NaOH administered to keep the gastric pH constant at 5.5 was recorded on graph paper and the total amount thus delivered per 15 minute intervals was used for calculation. These values were analysed by a two-way analysis of variance, the differences among the five dose levels were analysed by the Kruskal-Wallis test, and the pairwise comparisons obtained by the Wilcoxon test.

The subjects were divided into five groups, each group receiving a different dose of M-PGE₂. These doses were 10, 25, 50, 100, and 150 μg subject. Each subject participated twice during the study, one day receiving placebo and the other day one of the doses of M-PGE₂. The two studies were separated by one week. The treatments were randomised and administered in a double-blind manner. M-PGE₂ was supplied as a solution of 250 μg/ml dissolved in triacetin, and diluted on the morning of each study with water to a volume of 15 ml.

Results

M-PGE₂ inhibited food-induced acid output, and the effect was dose-dependent. Table 2 gives the mean acid output, in mmol/15 min, for each time interval and at each dose level. Since the response to the meal alone (meal plus placebo) varied between individuals, the results were also expressed for each dose level as percent of the placebo response (Fig. 1). This Figure shows that doses of 100 and 150 μg produced near total inhibition of acid secretion.

Figure 2 shows that the antisecretory effect was dose-dependent when the dose is plotted on a logarithmic scale. The ED₅₀—that is, the dose inhibiting acid output by 50%—was 10 μg/
Table 2 Mean acid secretion (mmol/15 min) during placebo treatment and drug treatment

<table>
<thead>
<tr>
<th>Time period (min after introduction of treatment)</th>
<th>10 µg</th>
<th>25 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Drug</td>
<td>% of Placebo</td>
</tr>
<tr>
<td>Placebo</td>
<td>Drug</td>
<td>% of Placebo</td>
</tr>
<tr>
<td>35–50</td>
<td>1.45±0.64*</td>
<td>0.68±0.35</td>
</tr>
<tr>
<td>50–65</td>
<td>3.16±1.00</td>
<td>0.88±0.44</td>
</tr>
<tr>
<td>65–80</td>
<td>3.02±1.04</td>
<td>1.72±0.76</td>
</tr>
<tr>
<td>80–95</td>
<td>3.68±1.01</td>
<td>2.60±1.12</td>
</tr>
<tr>
<td>95–110</td>
<td>4.28±1.42</td>
<td>2.66±1.11</td>
</tr>
<tr>
<td>110–125</td>
<td>5.22±1.11</td>
<td>2.88±1.19</td>
</tr>
<tr>
<td>125–140</td>
<td>8.94±5.34</td>
<td>3.22±1.17</td>
</tr>
<tr>
<td>140–155</td>
<td>2.70±0.63</td>
<td>2.22±0.78</td>
</tr>
<tr>
<td>Total</td>
<td>32.35±9.01</td>
<td>10.86±5.94</td>
</tr>
<tr>
<td>50 µg</td>
<td>3.86±1.54</td>
<td>0.64±0.20</td>
</tr>
<tr>
<td>50–65</td>
<td>5.82±1.50</td>
<td>1.38±0.45</td>
</tr>
<tr>
<td>65–80</td>
<td>5.54±1.13</td>
<td>0.60±0.29</td>
</tr>
<tr>
<td>80–95</td>
<td>5.40±0.80</td>
<td>0.54±0.17</td>
</tr>
<tr>
<td>95–110</td>
<td>5.90±1.11</td>
<td>0.84±0.29</td>
</tr>
<tr>
<td>110–125</td>
<td>5.74±0.88</td>
<td>0.96±0.38</td>
</tr>
<tr>
<td>125–140</td>
<td>5.68±1.15</td>
<td>0.86±0.43</td>
</tr>
<tr>
<td>140–155</td>
<td>5.86±0.99</td>
<td>0.78±0.44</td>
</tr>
<tr>
<td>150 µg</td>
<td>41.60±9.05</td>
<td>6.54±2.25</td>
</tr>
<tr>
<td>150 µg</td>
<td>41.60±9.05</td>
<td>6.54±2.25</td>
</tr>
</tbody>
</table>

*SEM.
†Significantly lower than mean acid secretion during placebo treatment *p < 0.01.
‡p < 0.05.

The mean mmol of acid secreted per 15 minute time intervals for each group during two hours of meal stimulated intragastric titration. Acid secretion was measured by mmol of base (0.5 N NaOH) titrated to maintain intragastric pH constant at 5.5.

Discussion

This study shows that M-PGE₂ inhibits food-induced gastric secretion at extremely low doses. The compound is the most potent orally active antisecretory agent in man ever described. In view of this activity, and as methyl analogues of PGE₂ have been shown to inhibit formation of gastric and duodenal ulcers in animals,²⁻⁹ M-PGE₂ would be expected to accelerate the healing rate of peptic ulcer in humans, and also to prevent ulcer recurrence.

Two studies have shown that M-PGE₂, or its methyl ester, given three to four times a day for two weeks, accelerated the healing rate of gastric¹⁴ and duodenal¹⁵ ulcers. In a multicentre study, M-PGE₂ given at a dose of 100 µg contained in a soft elastic capsule, four times a day for four weeks, markedly accelerated the healing of duodenal ulcers, and the effect was already apparent

subject, or approximately 140 ng/kg. Although the total duration of action was not determined, as illustrated in Fig. 1, it is clear that the antisecretory effect was near maximal, for each dose, for the 2½ hours after administration of the prostaglandin, at which time the study was terminated.

As an indirect measure of gastric emptying, the amount of peptone meal that had to be administered to the volunteers to continue the intragastric titration was quantified. The nasogastric tube was placed in a dependent area of the stomach in all the volunteers. There was no statistical difference (p>0.05) in the amount of peptone meal that was added between the placebo and M-PGE₂ treated days, or between the different treatment groups.

No side-effects were observed except at the highest dose of 150 µg; at that dose, three out of five subjects experienced loose stools later on the same day.
after 14 days of treatment. The present results suggest that still lower doses may promote healing and prevent relapses.

The anti-ulcer property of methyl analogues of PGE<sub>2</sub> is likely to be due not only to inhibition of acid secretion but also to gastric cytoprotection produced by these agents. This dual mode of action should be particularly beneficial in the treatment of peptic ulcer.

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References