Antisecretory activity of pirenzepine versus cimetidine in man: a controlled study

F PROCACCIANTE, G CITONE, C MONTESANI, AND G RIBOTTA

From the Department of Surgery, School of Medicine, University of Roma, Italy

SUMMARY Antisecretory effect of single oral therapeutic doses of pirenzepine (25 mg and 50 mg) and cimetidine (200 mg and 400 mg) was studied in 12 patients with duodenal ulcer. Gastric secretion was studied in basal condition and after stimulation with pentagastrin. Basal, maximum and peak acid output, basal and maximum acidity, and basal and maximum volume were calculated after computerised correction for pyloric loss and duodenal reflux. Both drugs showed dose-related inhibition of all facets of gastric secretion. Cimetidine (200 mg) had a greater inhibitory effect on gastric basal secretion, but a similar effect on pentagastrin stimulated secretion as with pirenzepine (50 mg). Cimetidine (400 mg) showed about twice the inhibitory activity of pirenzepine (50 mg) both on basal and stimulated secretion.

The inhibitory effect of pirenzepine on gastric secretion in man has been shown both in basal conditions and on secretion stimulated by pentagastrin.1–4

As almost all previous studies on pirenzepine were performed with uncorrected data on gastric secretion the extent of the inhibition reported by different authors varies from 14%2 to 97%1 for basal output and from 22%3 to 56%1 for the output stimulated by pentagastrin. The difference in these results is attributed to the difference in: (1) dosage used; (2) routes of administration; (3) techniques of study of the gastric secretion; and (4) the sample on which the study has been carried out.

In order to obtain univocal data on the inhibitory capacity of pirenzepine on gastric secretion, we studied the effects of single doses of pirenzepine on basal and pentagastrin stimulated gastric secretion, calculated with computerised correction for pyloric loss and duodenal reflux, and compared these with single doses of cimetidine, the histamine H2 receptor antagonist already used in other studies as the substance for reference purposes.6,7 The study was carried out double blind and drugs administered orally, in the dosage suggested for therapy – that is, 25–50 mg pirenzepine and 200–400 mg cimetidine.

Methods

Patients

Twelve patients were studied, 11 men and one woman; of these, 11 were suffering from duodenal ulcers and one from erosive duodenitis, all ascertained by endoscopy. The minimum secretory values accepted for entry to the trial were: BAO >2–5 mmol/h, MAO >18 mmol/h. The mean age was 38 years (range 21–60 years) with an eight year mean duration of the illness (range one to 30 years). Nine patients were smokers (19 cigarettes a day on average) and 11 patients drank alcohol (five occasional, five moderate, and one heavy). Five patients had already used cimetidine in the past and none had used pirenzepine.

In each patient gastric secretion was studied three times, at intervals of not less than 48 hours. The first secretion study provided control values and the subsequent ones carried out in the same manner as the first, but were started 60 minutes after the administration of the drugs. This interval was chosen on the basis of the pharmacokinetics of the two drugs,8,9 to obtain maximum plasma concentration and absence of residue in the stomach during the test.

Study of the Gastric Secretion

After positioning of the nasogastric tube (Anderson AN 10, a modified three way model) in the fasted patient the gastric secretion was collected by pump with intermittent aspiration (Hico Gastrovac) for

Address for correspondence: Dr Fabio Procaccianti, Patologia Chirurgica VII, c/o 2 Clinica Chirurgica, Policlinico Umberto I, 00161 Roma, Italy.

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fractions of 10 minutes each, during the whole period of 120 minutes.

At the beginning of the second and third test, a check was made to confirm that there was no residue of drug in the gastric juice. After the first basal 30 minutes, pentagastrin (Gastrodiagnost, Merck) 6 µg/kg/h was infused (Perfusor V, Braun) for a period of 90 minutes. Volume, pH, and titratable acidity (to pH 7) of each sample were measured (autotitrator Radiometer).

Pyloric loss was estimated by the colorimetric method using an intragastric infusion of phenol red while duodenal reflux was measured on the basis of sodium concentration in the gastric aspirate according to Hobsley’s formula.

Basal, maximum and peak acid output, basal and maximum acidity, basal and maximum volume were calculated with computerised correction for pyloric loss and duodenal reflux.10,11

TREATMENT
The single doses compared with each other were 25 and 50 mg pirenzepine and 200 and 400 mg cimetidine, administered in the form of powder contained in identical wafers.

EXPERIMENTAL DESIGN
The study was designed as a double-blind balanced incomplete block cross-over trial with randomised sequences. Each patient was subjected, in random order, to two of four possible treatments at intervals of at least 48 hours one from the other.

The characteristics of the experimental design were: K=4 treatments — that is, two doses of pirenzepine and two of cimetidine; n=6 replications, each dose being replicated in six patients; b=12 blocks — that is, 12 patients; u=2 block units — that is, treatments per patient; λ=2 pair replications; with an efficiency (E) of 67% with respect to the complete randomised blocks design.

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E = \frac{K (-1)}{u (K-1)}
\]

STATISTICAL ANALYSIS
The results obtained after each treatment, expressed as percentage of inhibition, were compared with the control values by Student’s t test. The Wilcoxon’s signed rank test for matched pairs was used to compare the median of treatments with respective controls.

The analysis of variance (anova) for balanced incomplete blocks (BIB) on mean differences between controls and treatments was performed.12

Results
The Table shows mean percentages of inhibition induced by the various treatments as compared with control values. Both pirenzepine (25 mg and 50 mg) and cimetidine (200 mg and 400 mg) caused a significant inhibition (p<0.028 by Wilcoxon’s test) of gastric acid output, related to the dose (Figs 1, 2, and 3).

Cimetidine (200 mg) inhibits basal gastric secretion (BAO, basal volume, basal acidity) more

Table. Mean percentage of inhibition after each treatment. Six replications for each dose. Comparison with the control values was performed with Student’s t test

<table>
<thead>
<tr>
<th></th>
<th>PRZ 25 mg</th>
<th>PRZ 50 mg</th>
<th>CMT 200 mg</th>
<th>CMT 400 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAO</td>
<td>44</td>
<td>59</td>
<td>85*</td>
<td>98*</td>
</tr>
<tr>
<td>MAO</td>
<td>18</td>
<td>35*</td>
<td>36*</td>
<td>59*</td>
</tr>
<tr>
<td>PAO</td>
<td>15</td>
<td>25*</td>
<td>32*</td>
<td>53*</td>
</tr>
<tr>
<td>BAC</td>
<td>30</td>
<td>33*</td>
<td>72*</td>
<td>93*</td>
</tr>
<tr>
<td>MAC</td>
<td>11</td>
<td>12</td>
<td>12</td>
<td>37</td>
</tr>
<tr>
<td>Basal volume</td>
<td>36</td>
<td>20</td>
<td>51*</td>
<td>57*</td>
</tr>
<tr>
<td>Maximum volume</td>
<td>12</td>
<td>24*</td>
<td>31*</td>
<td>40*</td>
</tr>
</tbody>
</table>

*p<0.05  t p<0.01  tp<0.001.
CMT = cimetidine  PRZ = pirenzepine.

Fig. 1  BAO differences after single treatment. Each column is the median of six patients. The inhibition was always significant with p=0.028 by Wilcoxon’s test.
than does pirenzepine (25 mg). Cimetidine (200 mg) and pirenzepine (50 mg) had similar effect on gastric secretion stimulated by pentagastrin (MAO, PAO, maximum volume, maximum acidity). The inhibitory effect of cimetidine (400 mg) was nearly double that of pirenzepine (50 mg) not only on basal but also on stimulated values of gastric secretion. Pirenzepine and cimetidine were compared on the basis of the design for balanced incomplete blocks (anova BIB). There were significant differences in favour of cimetidine for MAO (p<0.05), PAO (p<0.01), basal acidity (p<0.05), maximum acidity (p<0.05), and maximum volume (p<0.05) (Figs 4 and 5).

After pirenzepine (50 mg) two patients noticed a dry mouth and one had intermittent palpitations.

**Discussion**

This study shows the real effect of single oral doses of pirenzepine on gastric secretion vs cimetidine used as a 'means of comparison' because of its well-noted capacity in gastric secretion reduction. The two drugs were tested, in different doses, on the same patient, within a short period of time, therefore the different capacity of inhibition was not due to individual differences.

**Fig. 2** MAO differences after single treatment. Each column is the median of six patients. Inhibition was always significant with \( p=0.028 \) by Wilcoxon's test.

**Fig. 3** PAO differences after single treatment. Each column is the median of six patients. Inhibition was always significant with \( p=0.028 \) by Wilcoxon's test.

**Fig. 4** Decrease effect of different treatments on maximum and peak acid output. Global comparison, performed with mean differences adjusted for block effect (anova BIB), showed significant differences (MAO with \( p<0.05 \) and PAO with \( p<0.01 \)) between four treatments.
On the basis of our results we think that in order to obtain a significant reduction of gastric acid secretion, with no side effects, cimetidine should be the first choice owing to its superior efficacy and absence of remarkable side effects.

This evaluation was made possible because of the experimental design previously used by us in a similar study, which allows the reduction of gastric function tests undergone by the same subject, from five to three, with an experimental efficiency of almost 70%.

Our results confirm the inhibitory effect of pirenzepine on all facets of gastric secretion, related to the dose. As far as stimulated secretion (MAO, PAO, maximum volume, and acidity) was concerned, the effect of pirenzepine at its highest dosage (50 mg) was similar to that of cimetidine at its lowest dosage (200 mg). Therefore if it is necessary to increase the dosage of these drugs in order to obtain a higher inhibition, which could be therapeutically more efficacious, this is possible with cimetidine, used successfully at a dose of 400 mg bid, whereas pirenzepine at higher dosage induces unwanted muscarine effects. In fact three of our patients presented such side effects after a dose of 50 mg.

In this trial we did not study the combination of the two drugs as used by Londong et al. After a single intravenous bolus injection of cimetidine plus pirenzepine, at a ratio of one to 10, they obtained an almost complete inhibition of acid secretion but with unpleasant side effects.

References