Effects of transdermal scopolamine, alone or in combination with cimetidine, on total 24 hour gastric acid secretion in patients with duodenal ulcer

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SUMMARY Transdermal scopolamine is an antimuscarinic preparation approved for use in the United States for prevention of motion sickness. A recent study using this drug (0.5 mg/patch) suggested that enough scopolamine was absorbed through the skin to reduce basal gastric acid secretion in patients with duodenal ulcer. We have compared the effect of transdermal scopolamine and oral cimetidine (400 mg twice daily) in seven men with chronic duodenal ulcer, both alone and in combination, on acid secretion throughout an entire 24 hour period in a placebo-controlled, randomised, double blinded cross over study. The effect of these drugs on basal, interprandial, and nocturnal gastric juice volume and hydrogen ion concentration also was measured. Transdermal scopolamine had no significant effect on mean 24 hour acid secretion (placebo, 409.4 mmol/day; scopolamine, 364.0 mmol/day) nor did it have a significant effect on gastric juice volume or hydrogen ion concentration. The combination of transdermal scopolamine plus cimetidine was not more effective than cimetidine alone in reducing total 24 hour acid secretion (mean, 231.8 versus 235.3 mmol/day) nor in reducing gastric juice volume or hydrogen ion concentration.

Transderm-Scop (TDS, Ciba-Geigy Corp, Summit, NJ,) is a sustained release formulation of the antimuscarinic drug, scopolamine (1-hyosmine), designed to allow continuous absorption of this belladonna alkaloid from a patch applied to the skin. After delivering a local, skin saturating loading dose, the transdermal system delivers about 0.5 mg of scopolamine at a constant rate over three days (at a rate of about 7 μg/h or 0.1 μg/kg/h). Transderm scopolamine is approved by the Food and Drug Administration in the United States for prevention of nausea and vomiting associated with motion sickness. Two recent studies have suggested that the amount of scopolamine absorbed through the skin is sufficient to inhibit basal and nocturnal gastric acid secretion in patients with duodenal ulcer, suggesting that this product could be useful and convenient as a gastric antisecretory agent.

We evaluated in a placebo controlled, randomised study the effect of transdermal scopolamine on acid secretion in duodenal ulcer patients studied over an entire 24 hour period, during which breakfast, lunch, and dinner were given. The effect of transdermal scopolamine on 24 hour acid secretion was compared with the effect of cimetidine taken in a dose of 400 mg twice daily, a dose which accelerates healing of duodenal ulcers. Because some antimuscarinic drugs enhance the inhibitory effect of histamine H2-receptor antagonists on gastric acid secretion, another purpose of these studies was to determine whether the combination of transdermal scopolamine and oral cimetidine was more effective than cimetidine alone in reducing 24 hour gastric acid secretion in duodenal ulcer patients. Basal, interprandial and nocturnal gastric juice volume and hydrogen ion concentration were also compared.

Methods

PATIENTS AND SUBJECTS

Seven men with chronic, asymptomatic duodenal ulcer, previously diagnosed by barium study and/or endoscopy, participated in these experiments. Their ages ranged from 31–62 years (mean, 50 years).

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Basal and peak acid output (6 μg/kg pentagastrin subcutaneously), determined in preliminary studies, averaged 10.5±3.4 and 49.5±4.6 mmol/h, respectively. Antisecretory medication was discontinued at least three days before each experiment. Studies were approved by a Human Studies Subcommittee on 5 March, 1984 and informed, written consent was obtained from each patient and subject.

STUDY PROTOCOL
Duodenal ulcer patients participated in a double blind, randomised, 4 limb crossover study. Individual experiments were always separated by at least seven days. At 8 pm on the evening before the experiment, patients applied a single patch (transdermal scopolamine or placebo) behind their ear and this patch was left in place for the next 36 hours. At 7:30 am the next morning, an Anderson nasogastric tube (AN10, HW Anderson Products, Inc, Oyster Bay, NY) was positioned in the antrum of the stomach using fluoroscopic guidance. The 24 hour acid secretory study began at 8 am, 12 hours after placement of the transdermal scopolamine or placebo patch. A 600 ml liquidised meal (142 g ground sirloin steak, a piece of toast, 1.6 g butter, and water, adjusted to pH 5-0 with 0.1 N HCl) was infused into the stomach through the nasogastric tube at 9 am (breakfast), 2 pm (lunch) and 7 pm (dinner). Cimetidine tablets (400 mg, Smith Kline Corporation, Philadelphia, PA) or identical looking placebo tablets were taken by mouth with 50 ml water at 9 am and 7 pm. Each patient participated in all four studies: placebo patch – placebo tablets; transdermal scopolamine patch – placebo tablets; placebo patch – cimetidine tablets; and transdermal scopolamine patch – cimetidine tablets, all of which were provided by Ciba-Geigy Corp.

During the 24 hour period, patients were confined to a study bed and permitted to read, watch television, or sleep according to their wishes. Smoking was prohibited. Urine was voided into a plastic urinal.

MEASUREMENT OF GASTRIC ACID SECRETION
GASTRIC JUICE VOLUME AND pH
Two methods were used alternately to measure gastric acid secretion: gastric aspiration and in vivo intragastric titration. From 8 am to 9 am, basal acid secretion was measured by gastric aspiration, as previously described. Volume of gastric juice was measured in 15 minute increments and pH of each sample was determined using a pH meter (Radiometer, Copenhagen, Denmark). In each gastric juice sample pH was converted to hydrogen ion concentration by the method of Moore and Scarlata. Acid secretion during the basal, interprandial and nocturnal periods (see below) was calculated by multiplying the volume times hydrogen ion concentration of each gastric juice sample.

From 9 am to 11 am, acid secretion in response to the liquidised breakfast meal was measured by in vivo intragastric titration to pH 5·0 with 0·3 N sodium bicarbonate. At 11 am, the stomach contents were emptied and gastric aspiration resumed until 2 pm. Acid secretion in response to lunch was measured by in vivo titration from 2 pm until 4 pm. The stomach was emptied again at 4 pm and aspiration resumed until 7 pm. Acid secretion in response to dinner was measured by titration from 7 pm until 9 pm. Then, after the stomach was emptied, nocturnal acid secretion was measured by aspiration from 9 pm until 8 am the next morning. To prevent volume depletion as a result of prolonged aspiration of gastric juice, isotonic saline was infused intravenously at a rate of 75 ml/h (from 8 am to 9 pm) or 100 ml/h (from 9 pm to 8 am).

STATISTICAL ANALYSIS
Results are expressed as mean±one standard error. Differences in acid secretion with the various medication regimens were compared for significance by analysis of variance. p values less than 0·05 were considered significant.

Results
ACID SECRETION
As shown in Table 1, 24 hour gastric acid secretion

Table 1 24 hour acid secretion with different medication regimens in seven patients with duodenal ulcer

<table>
<thead>
<tr>
<th>Acid secretion (mmol/24 hr)</th>
<th>Placebo</th>
<th>TDS*</th>
<th>Cimetidine†</th>
<th>TDS plus cimetidine‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>320-1</td>
<td>286-9</td>
<td>122-8</td>
<td>139-9</td>
</tr>
<tr>
<td>2</td>
<td>178-6</td>
<td>160-4</td>
<td>79-6</td>
<td>100-9</td>
</tr>
<tr>
<td>3</td>
<td>317-4</td>
<td>301-1</td>
<td>126-7</td>
<td>129-6</td>
</tr>
<tr>
<td>4</td>
<td>293-9</td>
<td>345-6</td>
<td>132-7</td>
<td>188-2</td>
</tr>
<tr>
<td>5</td>
<td>670-5</td>
<td>603-2</td>
<td>420-4</td>
<td>426-9</td>
</tr>
<tr>
<td>6</td>
<td>658-7</td>
<td>521-4</td>
<td>443-3</td>
<td>319-9</td>
</tr>
<tr>
<td>7</td>
<td>426-9</td>
<td>320-3</td>
<td>321-3</td>
<td>317-3</td>
</tr>
<tr>
<td>Mean</td>
<td>409-4</td>
<td>364-0</td>
<td>235-3†</td>
<td>231-8‡</td>
</tr>
<tr>
<td>±SEM</td>
<td>±71-3</td>
<td>±56-7</td>
<td>±58-6</td>
<td>±46-6</td>
</tr>
</tbody>
</table>

*0·5 mg transdermal scopolamine patch applied behind the ear at 8 pm the evening prior to the 24 hour study.
†400 mg cimetidine by mouth at 9 am and 7 pm.
‡p<0.05 vs placebo and also vs TDS.

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ranaged from 178.6–670.5 mmol/day on the placebo
day (mean, 409.4 mmol/day). Transdermal scopol-
amine had a relatively small and statistically insignif-
ificant effect on mean 24 hour acid secretion (mean,
364.0 mmol/day, Table 1). On the other hand, cimeti-
dine reduced acid secretion significantly, with a
mean rate of 235.3 mmol/day (Table 1, p<0.05 vs
placebo and also vs transdermal scopolamine).
The combination of transdermal scopolamine plus cimeti-
dine was not more effective than cimetidine alone
in reducing acid secretion (Table 1, p>0.05 vs cimeti-
dine alone). Mean acid secretion rates for each hour
from 8 am one day until 8 am the next day are shown in
the Figure.

Acid secretion rates during the seven time inter-
vals of the day are compared in Table 2. Basal acid
output (8 am–9 am) averaged 12.5 and 9.2 mmol/h
on the two study days in which the placebo patch
was applied 12 h earlier, compared with 10.7 and
13.7 mmol/h on the two study days in which the
transdermal scopolamine patch was applied
(p>0.05). Transdermal scopolamine had no signif-
icant effect on acid secretion during any time period.
The 9 am dose of cimetidine with breakfast inhibited
acid secretion in response to breakfast by 47%,
between breakfast and lunch by 89%, in response to
lunch by 34%, and between lunch and dinner by
25%, indicating that the inhibitory effect of cimeti-
dine was declining gradually. The 7 pm dose of
Cimetidine with dinner inhibited acid secretion in
response to dinner by 43% and inhibited nocturnal
acid secretion by 38%. Per cent inhibition of acid
secretion at different time periods with transdermal
scopolamine plus cimetidine was similar to the
inhibition produced by cimetidine alone.

GASTRIC JUICE VOLUME
The mean volumes of gastric juice secreted during

the basal, interprandial and nocturnal periods are
shown in Table 3. Cimetidine and the combination
of cimetidine plus transdermal scopolamine reduced

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**Table 2. Mean (±SE) acid secretion (mmol) during seven periods of the day in seven duodenal ulcer patients**

<table>
<thead>
<tr>
<th></th>
<th>Basal 8–9 am</th>
<th>Breakfast 9–11 am</th>
<th>Interprandial 11 am–2 pm</th>
<th>Lunch 2–4 pm</th>
<th>Interprandial 4–7 pm</th>
<th>Dinner 7–9 pm</th>
<th>Nocturnal 9 pm–8 am am</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>12.5±4.0</td>
<td>20.5±3.2</td>
<td>15.1±2.8</td>
<td>31.3±3.9</td>
<td>18.5±4.8</td>
<td>27.4±2.6</td>
<td>10.7±2.9</td>
</tr>
<tr>
<td>TDS$^+$</td>
<td>10.7±4.8</td>
<td>10.3±3.4</td>
<td>14.9±4.3</td>
<td>27.1±2.1</td>
<td>14.2±3.8</td>
<td>26.9±2.7</td>
<td>8.9±1.9</td>
</tr>
<tr>
<td>Cimetidine$^+$</td>
<td>9.2±3.4</td>
<td>16.1±3.2</td>
<td>1.7±0.9</td>
<td>21.3±2.5</td>
<td>13.8±5.2</td>
<td>15.5±2.9</td>
<td>6.7±2.5</td>
</tr>
<tr>
<td>TDS$^+$ plus</td>
<td>13.7±3.9</td>
<td>20.0±2.7</td>
<td>0.8±0.4</td>
<td>20.3±4.0</td>
<td>10.7±2.3</td>
<td>18.4±3.6</td>
<td>6.0±2.1</td>
</tr>
</tbody>
</table>

$^*$ Acid secretion measured by gastric aspiration.

$^+$ Acid secretion measured by in vivo intragastric titration to pH 5.0.

$^+$ 5 mg transdermal scopolamine (TDS) patch applied behind ear at 8 pm the evening before the study.

$^+$ 400 mg cimetidine by mouth at 9 am and at 7 pm.

$^+$ p<0.05 vs placebo.
gastric juice volume significantly (p<0.05) during the period between breakfast and lunch (11 am–2 pm) but neither regimen reduced gastric juice volume significantly during the period between lunch and dinner (4 pm–7 pm). Only the combination of cimetidine plus transdermal scopolamine significantly reduced total gastric juice volume during the night.

HYDROGEN ION CONCENTRATION
Transdermal scopolamine alone had no significant effect on hydrogen ion concentration (Table 4).

<table>
<thead>
<tr>
<th>Interprandial</th>
<th>Nocturnal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal 8-9 am</td>
<td>11 am-2 pm*</td>
</tr>
<tr>
<td>Placebo</td>
<td>158±36</td>
</tr>
<tr>
<td>TDS</td>
<td>135±46</td>
</tr>
<tr>
<td>Cimetidine†</td>
<td>129±39</td>
</tr>
<tr>
<td>TDS‡ plus</td>
<td>149±31</td>
</tr>
</tbody>
</table>

*Interprandial gastric juice volume was calculated as the average of the volume secreted during the three hour periods (11 am–2 pm and 4 pm–7 pm) while nocturnal gastric juice volume was calculated as the average of the volume secreted during the 11 hour period from 9 pm–8 am.
‡0.5 mg transdermal scopolamine (TDS) patch applied behind ear at 8 pm the evening before the study.
§400 mg cimetidine by mouth at 9 am and at 7 pm.
$p<0.05$ versus placebo and TDS alone.

Table 4  Mean (±SE) basal, interprandial and nocturnal hydrogen ion concentration (mmol/l) in seven duodenal ulcer patients

<table>
<thead>
<tr>
<th>Interprandial</th>
<th>Nocturnal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal 8-9 am</td>
<td>11 am-2 pm*</td>
</tr>
<tr>
<td>Placebo</td>
<td>72±10±0</td>
</tr>
<tr>
<td>TDS</td>
<td>61±3±11.5</td>
</tr>
<tr>
<td>Cimetidine†</td>
<td>57±8±11.4</td>
</tr>
<tr>
<td>TDS‡ plus</td>
<td>80±4±2.9±4</td>
</tr>
</tbody>
</table>

*Hydrogen ion concentration during the three hour interprandial periods (11 am–2 pm and 4 pm–7 pm) and the 11-hour nocturnal period (9 am–8 am) is the average hydrogen ion concentration secreted during each of these periods.
‡0.5 mg transdermal scopolamine (TDS) patch applied behind ear at 8 pm the evening before the study.
§400 mg cimetidine by mouth at 9 am and at 7 pm.
$p<0.05$ versus placebo and TDS alone.

Cimetidine and the combination of cimetidine plus transdermal scopolamine reduced hydrogen ion concentration significantly during both interprandial periods and during the night. The drug combination was not more effective than cimetidine alone in decreasing hydrogen ion concentration.

Discussion

By combining the techniques of gastric aspiration and in vivo intragastric titration, we have developed a method for measuring acid secretion throughout a 24 hour period, including acid secretion in response to three meals, the periods after the meals and during the night. We have previously applied this technique for comparison of 24 hour acid secretion in normal subjects and duodenal ulcer patients and to evaluate the effect of cimetidine and partial cell vagotomy on 24 hour acid secretion.

Data from previous studies suggest that antimuscarinic drugs reduce basal and nocturnal acid secretion by about 40–60%. Because two recent reports indicated that transdermal scopolamine reduced basal acid secretion by 65% and nocturnal acid secretion by 75% in duodenal ulcer patients and because the drug is commercially available for the prevention of motion sickness, we felt it was important to study and report the effect of transdermal scopolamine on acid secretion throughout an entire 24 hour period in duodenal ulcer patients. While transdermal scopolamine reduced 24 hour acid secretion slightly in six out of seven patients, we could not confirm a significant inhibitory effect of transdermal scopolamine on basal, interprandial or nocturnal acid secretion nor did we find a significant effect of the compound on gastric juice volume or hydrogen ion concentration (Tables 2–4). Furthermore, transdermal scopolamine reduced total 24 hour acid secretion by only 9±5% (range, -18 to 23%, p<0.05). Transdermal scopolamine also did not enhance the inhibitory effect of cimetidine on acid secretion (Table 1 and Figure) as has been reported with other antimuscarinic drugs.

We are uncertain why our data disagree with other recent reports. Possibilities include differences in patient selection or in study design. For example, placebo and transdermal scopolamine were administered in random order in our study, whereas the placebo (control) experiment had always preceded transdermal scopolamine in one of the previous studies. This was not true in the other study, however, which was carried out in a double blind randomised manner. The 24 hour study design we used would seem to negate any possible effect of the normal diurnal variation in acid secretion which could affect interpretation of results.
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with antisecretory drugs. Our experience with this preparation in patients with duodenal ulcer disease suggests that the amount of scopolamine absorbed through the skin (according to the manufacturer, around 7 μg/h or 0.1 μg/kg/h) is insufficient to cause a significant reduction in gastric acid secretion, gastric juice volume, or hydrogen ion concentration, or to enhance the inhibitory effect of H₂-receptor antagonists.

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