Gastric Emptying in Patients with Gastric Ulcers
— Effects of Oral and Intramuscular Administration of Anticholinergic Drug

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In our previous report on gastric emptying, we noted that delayed gastric emptying might be one of the etiological factors of gastric ulcers. Gastric emptying was measured using the acetaminophen method. The gastric emptying value was indicated as "μg/ml", the acetaminophen concentration 45 min after test meal ingestion.

In this study, the effects of an anticholinergic drug on gastric emptying were investigated in gastric ulcer patients. Oral and intramuscular administrations of butropium bromide (BB) were studied.

The following results were obtained:
1. Oral administration of 10 and 15 mg of BB accelerated gastric emptying to a statistically significant degree (p < 0.05), compared with the placebo in delayed gastric emptying cases in a dose-dependent manner (r = 0.978).
2. Intramuscular administration of small doses of BB (0.25 and 0.5 mg) also accelerated gastric emptying in delayed gastric emptying cases, but in general, intramuscular administration of BB (0.25 - 2.0 mg/person) inhibited gastric emptying in a dose-dependent manner (r = -0.999).
3. Intramuscular administration of BB (0.25 - 2.0 mg/person) inhibited gastric emptying in a dose-dependent manner in rapid gastric emptying cases (r = -0.977).

(Key Words: Gastric Ulcer, Gastric Emptying, Anticholinergic Drug, Acetaminophen Method)

INTRODUCTION

Alterations in gastric motility or in gastric emptying (an expression of motility) have been seen repeatedly in patients with gastric and duodenal ulcers. In both of these ulcer diseases, it is unclear whether altered motility is caused by the ulcers or whether these defects in motility are independent expressions of some underlying pathophysiologic process.

Patients with gastric ulcers have hypotonic pyloric sphincters. Pressures in the area of the pylorus are subnormal during fasting (6, 25), and the pylorus in patients with gastric ulcers does not contract as much as in normal persons in response to acid or nutrients in the lumen of the proximal small intestine (6, 20, 21). As a result, duodenal contents reflux into the stomachs of patients with gastric ulcers to a much greater degree than in normal subjects. Therefore it is thought that postprandial gastric emptying in patients with gastric ulcers is slower than in normal subjects (5, 11, 20).

Results of many studies on gastric emptying have shown that patients...
with duodenal ulcers have more rapid gastric emptying of food than normal subjects (10, 11, 16, 18).

In this paper, we attempted to measure gastric emptying using the acetaminophen method (11, 14), and we investigated the effect of oral and intramuscular administration of an anticholinergic drug, including differences between the oral and intramuscular routes.

MATERIALS

Sixty five gastric ulcer patients in the active ulcer stage (23) consisting of 55 males and 10 females, mean age: 48.5 years, were studied. All patients were inpatients and showed no evidence of complicated duodenal ulcers, severe hepatic disease, renal disease or cardiovascular disease.

METHODS

Gastric emptying was measured by the acetaminophen method (11, 14). As an indicator of the gastric emptying rate, plasma acetaminophen concentration was measured by the dye method (19, 22) (diphenylpicrylhydrazyl dye), as μg/ml, 45 min after ingestion of a high calory pasty test meal together with 1.5g of acetaminophen. The test meal was made by Horinouchi-Kanzume Co. Ltd, and marketed by the Okuno Co. The trade mark is OKUNOS-A and 200ml of test meal contains 4.8% protein, 2.3% fat and 15.0% carbohydrate.

High plasma concentrations of acetaminophen mean rapid gastric emptying, while low concentrations mean slow (delayed) gastric emptying.

RESULTS

1. Investigations concerning the acetaminophen method

1) Comparative study between the acetaminophen method and isotope method

Ten cases were studied at the same time by the acetaminophen method and isotope method (T99m Tc-DTPA 3 mCi). Fig. 1 shows the statistical correlation between plasma acetaminophen concentration 45 min after test meal ingestion and the half-time (t 1/2) of isotope activity measured by a gamma camera (r = -0.853, p < 0.005).

The gastric emptying test using the acetaminophen method was found to be as objective as the test using the isotope method.

2) Reproducibility of the acetaminophen method

Reproducibility of the present method was studied in 10 normal female subjects. Examinations were repeated three times successively at intervals of 3 days. Results of the three examinations are shown in Table 1. There was no significant difference among the three results in each person. Consequently, the differences between these results may be taken as the variability of the technique and the condition of the subjects. It is evident that this method is reasonably reproducible at different times in the same subjects.

As the anticholinergic drug, butropium bromide (BB, butoxybenzyl hyoscyamine bromide) made by Eisai Co. was used in this study.

The results of treatment with the placebo and BB were compared and statistically evaluated by means of paired "t" test. Differences in the p value of less than 0.05 were considered to be significant.
Effect of Anticholinergic Drug on Gastric Emptying

Fig. 1 Comparison between acetaminophen method and isotope method
There is statistical relation between plasma acetaminophen concentration 45 min after test meal ingestion and half time (t1/2) of isotope activity.

Table 1 Reproducibility of the acetaminophen method
There is good reproducibility at different times in the same subjects.

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>First Ex.</th>
<th>Second Ex.</th>
<th>Third Ex.</th>
<th>Mean ± SD</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>32</td>
<td>F</td>
<td>10.8</td>
<td>9.4</td>
<td>11.5</td>
<td>10.6 ± 0.9</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>F</td>
<td>12.9</td>
<td>12.3</td>
<td>12.7</td>
<td>12.6 ± 0.3</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>F</td>
<td>10.8</td>
<td>11.8</td>
<td>11.8</td>
<td>11.5 ± 0.5</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>F</td>
<td>8.5</td>
<td>9.6</td>
<td>11.0</td>
<td>9.7 ± 1.0</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>F</td>
<td>11.2</td>
<td>13.5</td>
<td>15.7</td>
<td>13.5 ± 1.8</td>
</tr>
<tr>
<td>6</td>
<td>26</td>
<td>F</td>
<td>12.9</td>
<td>14.6</td>
<td>11.3</td>
<td>12.9 ± 1.3</td>
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<tr>
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<td>22</td>
<td>F</td>
<td>10.0</td>
<td>8.7</td>
<td>6.6</td>
<td>8.4 ± 1.4</td>
</tr>
<tr>
<td>8</td>
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<td>F</td>
<td>8.5</td>
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</tr>
<tr>
<td>9</td>
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<td>F</td>
<td>8.4</td>
<td>9.7</td>
<td>9.7</td>
<td>9.5 ± 0.6</td>
</tr>
<tr>
<td>10</td>
<td>24</td>
<td>F</td>
<td>4.3</td>
<td>9.3</td>
<td>3.3</td>
<td>5.3 ± 2.6</td>
</tr>
</tbody>
</table>

Mean ± SD 9.8 ± 2.4 10.8 ± 2.0 10.1 ± 3.3

2 Effects of the anticholinergic drug on gastric emptying in gastric ulcer patients with delayed gastric emptying compared with the placebo

Fig. 2 shows the results of oral and intramuscular administration of BB in gastric ulcer patients with delayed gastric emptying compared with the placebo.

The left side of Fig. 2 shows the results of oral administration of 5 mg, 10 mg and 15 mg of BB compared with the placebo. In these patients, the mean values were low, from 6.1 ± 2.6 to 7.3 ± 3.2 μg/ml when given the
placebo, but they had higher values after BB administration indicating that 10mg and 15mg of BB administered orally accelerated gastric emptying to a statistically significant degree (p<0.05). The dose response curve of oral BB administration for gastric emptying indicated a statistically significant accelerating tendency (y = 0.32x + 5.5, r = 0.978).

The right side of Fig. 2 shows the results of intramuscular administration of 0.25mg, 0.5mg, 1.0mg and 2.0mg of BB per person compared with the placebo. The mean values after intramuscular injection of 0.25 and 0.5mg, of BB per person were significantly higher than those with the placebo (p<0.05).

However, after intramuscular injection of 1.0mg of BB, gastric emptying showed no change compared with the placebo.

In contrast, the mean value after intramuscular injection of 2.0mg of BB was significantly lower, 4.3 ± 2.3μg/ml, than that with the placebo. The dose-response curve for intramuscular BB administration indicated a significant inhibitory effect on gastric emptying (y = -0.3837x + 11.8, r = 0.999)

Fig. 2  Effects of anticholinergic drug on gastric emptying in gastric ulcer patients with delayed gastric emptying.
Left side shows the results of oral administration of BB (butropium bromide) on gastric emptying compared with the placebo.
Right side shows the results of intramuscular administration of BB.
3 Effects of the anticholinergic drug on gastric emptying in gastric ulcer patients with rapid gastric emptying

Fig. 3 shows the results of intramuscular administration of BB compared with the placebo. With the placebo, the mean values were high, from 15.3 ± 3.5 to 13.4 ± 1.9 µg/ml in patients with so-called rapid gastric emptying. The mean values after intramuscular injection of 0.5, 1.0 and 2.0 mg of BB per person were significantly lower, 11.1 ± 3.9 µg/ml, 10.4 ± 5.0 µg/ml and 7.1 ± 4.3 µg/ml, than those with the placebo. (p < 0.005).

It is evident from this figure that the dose-response curve of intramuscular BB administration for gastric emptying in rapid cases indicated a significant inhibitory effect ($y = -3.193x + 13.4, r = -0.977$).
DISCUSSION

This report concerns an investigation of gastric emptying as an etiological factor in peptic ulcers and the effect of an anticholinergic drug on gastric emptying in peptic ulcer patients. Gastric emptying was studied using the acetaminophen method as an indicator of the gastric emptying rate. The plasma concentration was measured by the dye method (19, 22) (diphenylpicrylhydrazyl dye), as µg/ml, 45 minutes after ingestion of a high calory pasty test meal (200ml) together with 1.5g of acetaminophen. There was a statistically significant correlation (p<0.005) between the acetaminophen method and the isotope method (using^{99m}Tc-DTPA).

In our previous study (11, 12) in normal subjects who had no proven GI-tract disease, the gastric emptying value was 9.4 ± 2.6µg/ml. In gastric ulcer patients, it was 7.7 ± 3.3µg/ml which was significantly slower than in normal subjects or duodenal ulcer patients. In duodenal ulcer patients, it was 11.3 ± 3.4µg/ml, which was significantly more rapid than in normal subjects or gastric ulcer patients.

At the present time, tests for measuring gastric emptying have little application in the diagnosis and prognosis of gastrointestinal disease. Their use is essentially experimental in understanding physiological and clinical problems. One such problem is the effect of peptic ulceration and various types of vagotomy on the rate and pattern of gastric emptying.

Evidence is conflicting and highlights some of the difficulties in interpretation of results among institutions as well as exposing deficiencies in understanding the pathophysiology of these conditions. Patients with duodenal ulcers have shown an increase in the overall rate of gastric emptying (7, 10, 16, 18), but others present no change (4, 9, 17). The most striking difference between these conflicting reports is methodology. In patients with gastric ulcers, the change in gastric emptying also seems to depend on the type of meal chosen. The picture is further complicated by the position of the gastric ulcer (12) and possible presence of associated duodenal ulceration (13).

With liquid test meals a delay in gastric emptying was found (3, 11, 8), lending support to the theory that gastric stasis produces gastric ulceration. Even after excluding patients with pyloro-duodenal pathology, George (8) showed delayed gastric emptying in the presence of a simple lesser curve ulcer.

Anticholinergics decrease basal and stimulated gastric acid and pepsin secretion. However, Sun and Shay (24) reported the effects of different doses of an anticholinergic drug on the same patients. They noted that suppression of gastric acidity to pH 4.5 or more did not occur at any dose without accompanying dryness of the mouth but that the dose producing dryness of the mouth did not necessarily bring about such pH values of acidity. Are anticholinergic drug effective against ulcers?

They may be effective in reducing nocturnal pain, but this has been carefully studied under optimal experimental conditions. Baume, Hunt and Pipper (1) reported that an anticholinergic plus an antacid increased healing rates in gastric ulcer patients more than antacids alone. They also claimed that recurrent rates were lower in the anticholinergic group. This study
needs further confirmation.

Butropium bromide (BB: butoxybenzyl hyoscyamine bromide) relaxes smooth muscle and relieves intestinal, biliary and renal colic. Wakabayashi (26) attributed this action largely to ganglion-blocking activity, which in his experiments was more prominent that the atropine-like properties of the drug.

Herxheimer (15) reported different effects after subcutaneous injection and oral administration of hyoscine butylbromide (HBB “Buscopan”) which is an anticholinergic drug resembling BB. His report indicated that after subcutaneous injection of the drug, its ganglion-blocking actions such as paralysis of accommodation are particularly prominent but orally, doses of up to 600mg of HBB are inactive in man. Observations of human urine suggested that very little of this drug is absorbed when administered orally.

Brodie (2) investigated the effects of an anticholinergic drug on gastric secretion, gastric emptying and pupil diameters in the rat. Gastric acid output was depressed after oral administration of propantheline at one-fifth the doses that inhibited gastric emptying and one-third the dose required to dilate the pupils.

A comparison of oral and subcutaneous profiles of propantheline suggests that part of the action of this drug may be due to a direct effect on the gastric parietal cells, since it required a higher dose for inhibitory action than the other parameters when it was given subcutaneously.

In our results, oral administration of an anticholinergic drug (10 and 15mg of BB) accelerated gastric emptying in gastric ulcer patients with delayed gastric emptying with dose-response. Intramuscular administration of this drug inhibited gastric emptying in all gastric ulcer patients with a high dose-response curve, but in delayed gastric emptying cases, small doses by intramuscular administration (0.25 and 0.5mg of BB) accelerated gastric emptying compared with the placebo. However, the mechanism of accelerating action of this drug on delayed gastric emptying is still obscure and further fundamental studies are necessary. Delayed gastric emptying may be considered to the result of gastric stasis due to excessive pyloric dysfunction, increasing duodenogastric reflux (20, 21) and disturbances in gastroduodenal muscle contractions (27).

Small doses of anticholinergic drug have a normalizing action on delayed gastric emptying, which is different from the pharmacological action of anticholinergics. Therefore, treatment with an anticholinergic may be necessary and reliable from the standpoint of the pathophysiology of gastric ulcers.

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