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The effect of trimebutine maleate on gastric emptying in patients with non-ulcer dyspepsia

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The study was designed to investigate the effect of trimebutine maleate, a drug used in both hyperkinetic and hypokinetic motility disorders, on gastric emptying in patients with non-ulcer dyspepsia having prolonged gastric emptying rates and to compare the parameters used for the determination of the lag period observed during the emptying of solid foods from the stomach. Gastric emptying was measured by the radionuclide technique. Twenty normal volunteers and 43 patients with non-ulcer dyspepsia participated in the study. Radionuclide imaging was performed by using a solid meal labeled with ^{99m}Tc-tin colloid. Of the patients with non-ulcer dyspepsia, 20 had prolonged gastric emptying. They were given three weeks of oral treatment with trimebutine maleate and had their radionuclide gastric emptying study repeated. Treatment with trimebutine maleate resulted in reduction in duration of the lag period and less retention of food at 100 minutes ($p < 0.0005$). After treatment with trimebutine maleate, no significant difference has been observed in the mean symptom score of patients with prolonged gastric emptying. Among the parameters used for the determination of the lag period, lag period determined by a mathematical equation (TLAG) has been found to be longer than the lag period determined by visual inspection of the images (VLAG) and there was correlation between the two parameters when the lag time was short.

Key words: trimebutine maleate, gastric emptying, non-ulcer dyspepsia, lag phase, radionuclide imaging

INTRODUCTION

NON-ULCER DYSPEPSIA (NUD) is a common clinical entity characterized by chronic or recurrent upper gastrointestinal symptoms in which basic laboratory tests, endoscopic and clinical evaluation fail to show an obvious cause for the symptoms. Its pathogenesis is unclear. Delayed gastric emptying has been reported in these patients,[1,2] but many patients with NUD have normal gastric emptying and there may be no association between dyspeptic symptoms and gastric emptying,[3] so that the relation between dyspeptic symptoms and motility is still unclear. Compared with other techniques, scintigraphy is a safe, non-invasive and reliable procedure for the measurement of gastric emptying.

Trimebutine maleate (2-dimethylamino-2 phenyl butyl 3,4,5-trimethoxybenzoate hydrogen maleate) is an enkephalin agonist clinically effective for the treatment of both hyperkinetic and hypokinetic motility disorders.[4–6] Enkephalins are known as endogenous opioid substances. Although exogenous opiates are known to inhibit gastric emptying,[7] there are contradictory results in the literature about the role of endogenous opiates in gastric motility. In studies with healthy volunteers, trimebutine maleate (Trimebutine) has been shown to accelerate,[8] slow down gastric emptying[9] and to cause reduction in duration of the lag period.[10]

Emptying of solids from the stomach is biphasic. There is a period of time before the onset of constant gastric emptying which is known as the lag period. In previous

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studies with normal volunteers performed with radionuclides, different parameters used for the determination of the lag period have been compared.[11] But these parameters are not compared in the evaluation of the response to therapeutic interventions.

The aim of this study was to determine the effect of oral trimebutine in patients with NUD having prolonged gastric emptying rates and to compare the parameters used for the determination of the lag period.

MATERIAL AND METHODS

Study Population

Twenty healthy volunteers (10 male, 10 female; age range: 20–50 years, with a mean age of 41) and 43 patients (24 female, 19 male; age range: 21–49 years, with a mean age of 40) with NUD participated in the study after giving informed consent. Patients with systemic diseases, previous major abdominal surgery and irritable bowel syndrome which is defined as abdominal pain associated with predominant symptoms of constipation or diarrhea were excluded from the study. NUD was diagnosed on the basis of the presence of two or more dyspeptic symptoms such as nausea, vomiting, abdominal pain, heartburn, early satiety and bloating lasting for more than 2 months over at least 2 years in whom clinical examination and upper gastrointestinal endoscopy showed no evidence of focal lesions. Symptoms were scored as follows: 0 = absent, 1 = mild (awareness of signs and symptoms, but easily tolerated), 2 = moderate (interference with normal activities), 3 = severe (incapacitating). Patients with non-ulcer dyspepsia were also assigned to one of five categories on the basis of predominant symptoms: Dysmotility-like dyspepsia (symptoms of abdominal pain or discomfort which starts after eating a meal and is associated with a feeling of bloating, distention, early satiety and nausea); reflux-like dyspepsia (symptoms of epigastric or retrosternal heartburn and regurgitation of acid or food); ulcer-like dyspepsia (epigastric pain which is relieved after eating or taking antacids); aerophagia (abdominal air swallowing with symptoms of repetitive belching, bloating and frequent dry swallowing); essential dyspepsia (symptoms which do not fit into any of the categories described above and have no specific features on history or clinical examination). All other medications that could mask the effect of the study drug were stopped 72 hours prior to the study. Smoking, intake of alcohol and coffee were not allowed 24 h prior to the test.

Study Protocol

In all subjects, after at least a 6-hour fast, the radionuclide gastric emptying study was performed in the upright position starting immediately after the completion of a solid meal consisting of an egg sandwich. Images were acquired by using a single headed gamma camera (Siemens-Diacam) with a low energy all purpose collimator which was interfaced to a computer (Power Macintosh 8100-110) by using a 256 × 256 matrix. The egg sandwich was prepared by injecting 37 MBq of ^{99m}Tc-tin colloid into two beaten raw eggs. The eggs were then cooked until firm. Patients were then given one glass of water. The mean time taken to eat the sandwich was 7 minutes with a range of 5–10 min. The meal had a caloric content of 250 calories (23% protein, 40% fat, 37% carbohydrate). After eating the meal, sequential anterior and posterior images of one minute duration were collected every 5 min for 30 minutes and every 10 minutes during the rest of the study. Each study continued for 100 minutes. In the intervals between image acquisition, the patients were allowed to walk around or to sit down.

Data Analysis

After completion of data acquisition, regions of interest (ROIs) were placed over the entire stomach on both anterior and posterior projections and the geometric mean of the anterior and posterior counts were calculated after decay correction. Gastric emptying data were analyzed by using a modified power exponential curve-fitting according to the function; $y(t) = 1 - (1 - e^{-kt})^{\beta}$.[12,13]

The following parameters were computed:

1. TLAG: Lag phase calculated from the curve-fitting representing the time required for trituration of the major portion of the meal.[14,15]
2. VLAG: The time at which radioactivity first appeared in the duodenum as determined by visual inspection.
3. R_{100}: % retention of food at 100 min (Maximum counts obtained during the lag period were used to calculate R_{100}).
4. k: The emptying rate in $min^{(-1)}$
5. β: Initial shape of the emptying curve.

All parameters were calculated in controls and in patients before and after treatment. Patients having a R_{100} value which was more than 2 SD above the normal value were given 3 weeks of oral treatment with trimebutine maleate (one 100 mg tablet 30 min before three daily meals with the last dose taken 1–2 hours before the study) and then underwent a repeat radionuclide gastric emptying study.

Parameters obtained before treatment were compared with measurements obtained after treatment by using Student's t test for paired studies. A p-value of < 0.05 was taken as significant.

RESULTS

On the basis of predominant symptoms, patients with NUD were assigned to the following categories: Patients with normal gastric emptying (n = 23): dysmotility-like dyspepsia (n = 10), essential dyspepsia (n = 6), aerophagia (n = 3), ulcer-like dyspepsia (n = 2), reflux-like dyspepsia (n = 2). Patients with prolonged gastric emptying (n = 20):

Table 1 Gastric emptying parameters for controls and for patients both before and after treatment

	Controls	Non-ulcer dyspepsia		
		Normal gastric emptying	Abnormal gastric emptying	
			pretreatment	posttreatment
VLAG (min)	15.7 ± 8.7	17.2 ± 6.4	28.7 ± 12.4	15.3 ± 7
TLAG (min)	45.1 ± 16.1	47.3 ± 17.1	67.2 ± 18.6	40.6 ± 19.5
k	0.016 ± 0.005	0.018 ± 0.004	0.009 ± 0.003	0.018 ± 0.031
β	2.22 ± 0.67	2.28 ± 0.65	2.04 ± 0.66	1.71 ± 0.39
R_{100} (%)	37.5 ± 8.4	41.4 ± 9.6	63.7 ± 9.5	46.5 ± 7.8

Mean ± SD values are used

VLAG: Lag period determined by visual inspection, TLAG: Lag period determined by mathematical equation, k: emptying rate in $min^{(-1)}$, β: initial shape of the emptying curve, R_{100} (%): % retention of food at 100 min

dysmotility-like dyspepsia (n = 9), essential dyspepsia (n = 6), aerophagia (n = 2), reflux-like dyspepsia (n = 2), ulcer-like dyspepsia (n = 1). The mean symptom scores of patients with normal gastric emptying and prolonged gastric emptying did not differ significantly and were 8.4 ± 2.4 and 8.9 ± 2.6, respectively. After 3 weeks of treatment with trimebutine maleate, the mean symptom score of patients with prolonged gastric emptying was 8.7 ± 2.7 and the difference was not significant compared to pretreatment values.

In all subjects including controls, the gastric emptying curve was characterized by a lag period, followed by constant emptying. Among 43 patients with NUD, 20 (46%) had prolonged gastric emptying determined on the basis of the R_{100} value. Their lag period was prolonged and they had more retention of food at 100 minutes. These 20 patients with prolonged gastric emptying time underwent a repeat gastric emptying study after treatment with trimebutine maleate. Our results are summarized in Table 1.

After 3 weeks of treatment with oral trimebutine, gastric emptying rates were increased with reduction in the duration of the lag period and less retention of food at 100 min ($p < 0.0005$). Compared to pretreatment values, out of 20 patients, 17 had accelerated gastric emptying, 2 had no change and one patient had slower gastric emptying. The mean lag period determined after treatment with trimebutine was slightly shorter than the lag period of controls. But the difference was statistically insignificant ($p > 0.05$).

In controls and in patients (both before and after treatment) TLAG was significantly longer than VLAG ($p < 0.0005$). The difference between the two values was 38.6 ± 15.2 min before the treatment and 25.3 ± 13.5 min after the treatment. When the two values were compared in each individual group itself, two values have been found to be correlated in normals and in patients after treatment ($r = 0.63$, and $r = 0.81$, respectively). But no correlation was present in patients before the treatment ($r = 0.33$); so the two values were correlated when the lag period was relatively short.

Although k values increased after treatment compared to pre-treatment values, the difference was statistically insignificant ($p > 0.05$).

DISCUSSION

Exogenous opioid substances such as morphine are known to inhibit gastric emptying.[8,16] The demonstration of specific opiate receptors in the brains of some species suggested the possibility of the existence of endogenous morphine-like compounds such as enkephalins. Later enkephalins were demonstrated in the myenteric plexus of the gastrointestinal tract, with particularly high concentrations in the stomach and small bowel.[17] There are several opiate receptors known. Different classes may have different effects on gastric motor activity.

The role of enkephalinergic substances as a neurotransmitter in the control of gastrointestinal motility have been studied extensively in animal models. Trimebutine was demonstrated to have an inhibitory effect on the gastric smooth muscle of some species. Studies with animals have revealed that trimebutine inhibited gastric contractile amplitude, antroduodenal co-ordination and the responses mediated by cholinergic postganglionic nerves.[18,19] Sullivan et al. reported that an enkephalin analogue administered parenterally delayed gastric emptying in normal volunteers. It is also known that the pylorus has an especially rich enkephalinergic innervation. So they stated that the stimulatory effect of this agent on the pylorus could be responsible for the delay in gastric emptying. Other possibilities were inhibition via the central nervous system and indirectly via the inhibition of acetylcholine release from the vagus.[9]

In some studies enkephalins have been shown to have a contractile action. The inhibition of neuropeptidases such as enkephalinase have been shown to potentiate enkephalin stimulated contraction of gastric muscle cells.[20] Studies with healthy volunteers have shown that trimebutine accelerates gastric emptying[8] and shortens the lag period.[10]

The action of trimebutine on the stomach has been shown to vary depending on its route of administration. Gue et al. have shown that k-opioid agonists given orally

increased the gastric emptying of solids in dogs, and this effect was not produced by parenteral administration. They stated that this effect, observed only for oral administration, may be due to a selective stimulation of mucosal or submucosal k-receptors of the gastroduodenal area affecting motor activities of the fundus and pylorus.[21]

The lag phase observed during the emptying of solid foods from the stomach represents the time period before the subsequent equilibrium emptying phase. It includes the movement of food from the proximal to distal part of the stomach and trituration of food into small particles before passing into the pylorus. It may be determined by visual analysis (VLAG), obtained from curve-fitting (TLAG).[12] In this study, in order to obtain the geometric mean, we used an intermittent imaging technique. Compared with continuous data acquisition, its temporal resolution is poor. This may lead to a few minutes of misinterpretation in the determination of VLAG.

Our results suggest that trimebutine shortens the lag time in starting the emptying of a solid meal from the stomach and accelerates gastric emptying, since % retention at 100 min was also significantly lower than the pretreatment values. The stimulatory effect of this agent may be explained by its predominant action on the circular muscle of the antrum and/or by its influence on the secretion of certain gut hormones.[10,22] If its predominant action would be on the pylorus, it would be expected to cause the prolongation of both the lag period and the subsequent emptying phase.

In this study, we excluded patients who had NUD in whom gastric emptying rates turned out to be normal. These constituted 54% of patients with NUD. NUD is a heterogeneous syndrome and, apart from gastric dysmotility, infection with *Helicobacter pylori* and chronic gastritis may be responsible for the symptoms.

In conclusion, our results have shown that;

a) 46% of patients with NUD had prolonged gastric emptying.

b) Three weeks of treatment with oral trimebutine appeared to increase solid emptying rates with a reduction in the duration of the lag period and less retention of solid at 100 minutes.

c) Although intermittent imaging would lead to a few minutes of misinterpretation in detecting VLAG, since VLAG is easier to interpret and does not need any mathematical function for its determination, we recommend the use of VLAG value in routine gastric emptying studies with solids.

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