Enhancement of Gastric Emptying of Solids by Erythromycin in Patients With Roux-en-Y Gastrojejunostomy

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Background: Roux-en-Y reconstruction is sometimes associated with symptoms that suggest food stasis, as a result of dysmotility of either the gastric remnant and/or the efferent jejunal limb.

Objective: To study the possible effect of intravenous erythromycin lactobionate on gastric emptying of solids in patients who have undergone a Roux-en-Y procedure.

Patients: Twenty-four patients with a Roux-en-Y procedure participated in the study. Ten of them had undergone truncal vagotomy with pyloroplasty; the remaining 14 had undergone a Billroth II subtotal gastrectomy as the initial antiulcer procedure. Sixteen healthy subjects served as controls.

Methods: All healthy subjects and patients underwent assessment of gastric emptying of a standard radiolabeled solid meal after administration of placebo or 200 mg of erythromycin lactobionate intravenously. Scanning was done with a gamma camera, and emptying curves were constructed. From these curves the half-time of gastric emptying was calculated.

Results: Patients with severe symptoms of gastric stasis had a significantly longer half-time than did patients with mild or no symptoms (P = .002). Patients with a Billroth II subtotal gastrectomy as the initial antiulcer procedure had a significantly worse grade of symptoms (P = .01) and a significantly prolonged half-time (P = .02) compared with patients with a truncal vagotomy with pyloroplasty as the initial antiulcer procedure. Erythromycin significantly reduced the half-time in the controls (P<.001) and all patients after Roux-en-Y procedure (P<.001).

Conclusion: Erythromycin could be a useful prokinetic drug in patients with Roux stasis syndrome.

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Roux-en-Y gastrojejunostomy may cause the so-called Roux stasis syndrome as a result of delayed gastric emptying of both solids and liquids. The clinical manifestation of the syndrome is of varying severity, and it may appear either immediately or late postoperatively. The syndrome includes epigastric fullness, epigastric pain, nausea, and food vomiting. In the more severe form of the disorder, weight loss and gastric bezoars may develop. The prevalence of the syndrome ranges from 10% to 50%. In a series of 202 patients with Roux-en-Y gastrectomy reported by Gustavsson et al, symptoms of gastric stasis were present in 30% of cases. Both atony of the vagotomized gastric remnant and dismotility of the efferent jejunal limb have been implicated in the development of functional obstruction and the pathogenesis of the syndrome.

Exclusion of organic obstruction and scintigraphic studies of gastric emptying that show retention of solid food in the gastric remnant and/or the efferent jejunal limb confirm the diagnosis of the Roux stasis syndrome. In the majority of patients, symptoms subside with time. In the more severe form of the syndrome, prokinetics, such as bethanechol chloride and metoclopramide hydrochloride, are of limited value, whereas surgical reduction of the gastric remnant and shortening of the efferent limb may offer symptomatic improvement. Pacing of the efferent limb has also been tentatively applied.

It has been recently shown that macrolide antibiotics have prokinetic properties. In particular, erythromycin lactobionate acts as a motilin agonist, by occupying its receptors on the smooth muscle of the upper gastrointestinal tract. Low doses of erythromycin induce phase III–like activity of the migrating motor complex in the stomach of both humans and dogs. Administration of 200 mg of erythromycin lactobionate accelerates gastric emptying in...
PATIENTS AND METHODS

Twenty-four patients participated in the study. Nineteen of them were men; 5, women. Their age ranged from 32 to 68 years (mean ± SD age, 52.8 ± 10.7 years). They had all undergone a Roux-en-Y subtotal gastrectomy with gastrojejunostomy as the remedial operation for post–gastric surgery alkaline reflux gastritis syndrome, dumping syndrome, recurrent ulceration, or a combination of the above gastric motor disorders. The initial antulcer operation had been a Billroth II gastrectomy in 14 of them (11 men and 3 women, with a mean age of 37.6 ± 9.4 years), performed 31 to 45 years earlier, and a TVP in the remaining 10 (8 men and 2 women, with a mean age of 46.8 ± 9.2 years), performed 3 to 28 years earlier.

Roux-en-Y gastrojejunostomy involved an efferent jejunal limb 50 cm long in all patients. Truncal vagotomy was added in patients who had undergone Billroth II gastrectomy as the initial antulcer procedure. Upper gastrointestinal tract symptoms were recorded according to a standard questionnaire by a physician unaware of the surgical status of the patients and were classified as follows: grade 0, no complaints; grade 1, very mild symptoms of gastric stasis requiring minor adjustments of meal; grade 2, moderate symptoms of gastric stasis requiring small meals and intermittent prokinetic drug intake; and grade 3, severe symptoms of gastric stasis requiring reduction of the daily amount of food consumption, weight loss, daily intake of prokinetic drugs, and abstention from normal daily activities.

Gastric emptying of a standard solid meal was studied in all patients on 2 occasions, 7 days apart, after they were given either 40 mL of isotonic sodium chloride solution intravenously (placebo) or 200 mg of erythromycin lactobionate diluted in 40 mL of water for intravenous injection, in a double-blind manner. All medications that might affect gastrointestinal motility or secretion were discontinued at least 3 days before each study. Each study started at 9 AM after an overnight fast. The meal consisted of a hamburger and 140 g of fresh tomato. The hamburger was made of 100 g of minced beef, 20 g of toasted bread, 10 g of olive oil, and half an egg that was labeled with 300 µCi of technetium Tc 99m sulfur colloid. The meal contained 1646 kJ (32% protein, 52% fat, and 16% carbohydrates). The meal was consumed within 10 minutes, and infusion of either placebo or erythromycin lasted for another 10 minutes. With the subjects seated in front of a gamma camera, scans of the abdominal field were acquired for 60 seconds, every 5 minutes, for a total of 150 minutes. The radioactivity over the gastric area, which was defined with the use of a light pen, was counted and then corrected for isotope physical decay. The results were expressed as a percentage over the initial value (first scan at the completion of the meal) and plotted against time to obtain the emptying curves. From these curves, the half-time of gastric emptying (T1/2; the time elapsed from completion of the meal to the point at which half of the meal had left the stomach) was calculated.

Another 16 sex-matched healthy subjects (12 men and 4 women, with a mean age of 36.2 ± 6.3 years) without any gastrointestinal tract symptoms participated in the study as controls. All subjects and patients gave informed consent, and the protocol of the study was approved by the Ethical Committee of the Medical School of the University of Crete, Crete, Greece.

Unless otherwise stated, all values are expressed as mean ± SD. Statistical analysis was performed by applying either the Mann-Whitney U test, the Wilcoxon rank sum test, or the Fisher exact test as appropriate, for paired and unpaired values. Regression analysis was used to identify any possible correlation between different variables in the same group. P < .05 were considered statistically significant.

RESULTS

The time elapsed from the Roux-en-Y procedure to the study of gastric emptying was similar between the patients who had undergone TVP (20.9 ± 12.8 months) and those who had undergone Billroth II subtotal gastrectomy (17.9 ± 12.6 months) as the antulcer operation. Symptoms were classified as grade 0 in 7 patients, grade 1 in 9, grade 2 in 5, and grade 3 in 3. Patients with severe manifestation of the Roux stasis syndrome showed a significantly increased T1/2 of gastric emptying (142 ± 9.2 minutes) in comparison with those complaining of moderate (103.4 ± 12.3 minutes; P < .002), minor (87.6 ± 25.4 minutes; P < .001), or no (79.7 ± 41.3 minutes; P = .002) symptoms of gastric stasis (Figure 1).

Patients who had undergone a Billroth II gastrectomy as the antulcer operation had an overall significantly worse grading of Roux stasis syndrome than did patients who had undergone a TVP (P = .01). Seven of the 14 patients who had undergone a Billroth II procedure were classified as grade 2 or 3, as opposed to 1 of the 10 patients who had undergone a TVP procedure who reported symptoms of gastric stasis after the Roux-en-Y procedure and was classified as grade 2. In addition, T1/2 of gastric emptying was significantly greater (P < .02) in patients who had undergone a Billroth II gastrectomy (105.4 ± 33.6 minutes) than in patients who had undergone a TVP (75.9 ± 29.4 minutes) as the initial antulcer operation. In fact, the latter subset of patients showed a T1/2 of gastric emptying similar to that of the controls (Table). This is in accordance with the fact that only 1 patient who had undergone an initial TVP experienced symptoms of gastric stasis after the Roux-en-Y procedure. In patients who had undergone a Billroth II gastrectomy as the initial antulcer surgery, T1/2 of gastric emptying was significantly inversely related to the time...
interval between the Roux-en-Y procedure and the study of gastric emptying \((r = -0.95, P < .001)\). In other words, the shorter the interval, the greater the delay of gastric emptying (Figure 2).

Gastric emptying of the controls showed a biphasic pattern, with a lag period of practically no emptying that lasted for 38.6 ± 15.1 minutes and a postlag period of actual emptying that fit a linear model. Erythromycin significantly decreased the T½ of gastric emptying in the controls \((P < .001)\) (Table and Figure 3). In contrast, the gastric emptying of the patients after Roux-en-Y procedure did not exhibit a lag phase, and the emptying curve fit an exponential model (Figure 4). Erythromycin significantly accelerated the gastric emptying in all patients by reducing the T½ (Figure 4). This was evident in both those who had undergone a Billroth II gastrectomy and those who had undergone a TVP as the initial antiulcer procedure and the TVP as the initial antiulcer procedure (Figure 5) (Table). The posterythromycin curve of gastric emptying fit an exponential model (Figure 5). The extent of acceleration of gastric emptying after erythromycin administration was significantly greater in patients than in controls \((P = .04)\).

**COMMENT**

Myoelectrical disturbances have been implicated in the pathogenesis of the Roux stasis syndrome. Lack of coordination between the vagotomized gastric remnant and the malfunctioning efferent jejunal limb, which has been dissociated from its natural pacemaker at the proximal duodenum, may account for the abnormally delayed emptying.\(^\text{21}\) The motor abnormalities of the efferent jejunal limb, which have been manometrically detected in symptomatic patients,\(^\text{6,8}\) include absence or abnormal periodicity and often disruption of the migrating motor complex. During the fasting state, high-amplitude contractions may also be observed. In addition, and most importantly, the efferent jejunal limb fails to convert its motility to the fed pattern.

Vantrappen et al\(^\text{23}\) demonstrated a variety of electromyographic abnormalities of the Roux limb in symptomatic patients. These abnormalities include an inversion of the slow-wave frequency gradient, absence of single and repetitive propagated spike bursts during phase II of the migrating motor complex, and increased frequency of ectopic and abortive phase III activity. The aforementioned authors speculated that these abnormalities may explain the delayed emptying of the jejunal limb. Supportive of this speculation are the observations that experimentally achieved inversion of the slow-wave frequency gradient at the duodenum and jejunal area results in an oral propagation of contractions and symptomatic delayed emptying.\(^\text{24-26}\)

Although Vantrappen et al\(^\text{23}\) found that Roux-en-Y reconstruction results in an inversion of the slow-wave frequency at the efferent jejunal limb of the symptomatic patients, thus speculating oral propagation of contractions as the cause of stasis, they failed to show any association between symptoms of Roux stasis and the rate of gastric emptying. On the contrary, we found that patients with severe symptoms of gastric stasis showed a significantly increased T½ of gastric emptying. This discrepancy might be the result of a smaller number of patients involved in the former study.

In the present study, patients who had undergone an initial Billroth II gastrectomy exhibited a significantly worse symptomatic score and more delayed gastric emptying after Roux-en-Y procedure than did patients who had undergone an initial TVP as the antiulcer procedure and a Roux-en-Y procedure as the subsequent remedial one. Although, according to some reports, vagotomy does not seem to affect slow-wave frequency and coupling,\(^\text{27}\) a possible explanation of this difference might be the addition of vagotomy during Roux-en-Y reconstruction in the former group of patients. In patients who undergo a TVP, after an initial myoelectrical derangement because of the vagotomy, the gastro-duodenal area readjusts its motility patterns as the months pass after the operation.\(^\text{28}\) Hence, any possible myoelectrical abnormality after Roux-en-Y reconstruction in these patients is expected to be the result of dissociation of the

<table>
<thead>
<tr>
<th>Grade</th>
<th>T½ of Gastric Emptying, min</th>
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<tbody>
<tr>
<td>0</td>
<td>60 ± 40</td>
</tr>
<tr>
<td>1</td>
<td>90 ± 60</td>
</tr>
<tr>
<td>2</td>
<td>120 ± 80</td>
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<tr>
<td>3</td>
<td>150 ± 100</td>
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\(n=7\), \(n=9\), \(n=5\), \(n=3\).

**Figure 1.** Half-time (T½) of gastric emptying according to severity of symptoms. Patients with severe symptoms of Roux stasis syndrome had a significantly longer T½ than did patients with moderate, mild, or no symptoms. The grades are explained in the “Patients and Methods” section.

**Half-time of Gastric Emptying After Administration of Placebo or Erythromycin Lactobionate**

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD Half-time, min *</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Normal Subjects</td>
</tr>
<tr>
<td>Placebo</td>
<td>85.7 ± 14.6</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>37.6 ± 14.9</td>
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</tbody>
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* TVP indicates truncal vagotomy with pyloroplasty; Bill II, Billroth II gastroenterostomy. For all groups, \(P < .001\).
efferent jejunal limb from its natural pacesetter at the proximal duodenum. On the other hand, in patients who undergo Billroth II gastrectomy, addition of truncal vagotomy to Roux-en-Y reconstruction is expected to cause further gastrojejunal dysmotility that is manifested by worse symptoms suggesting Roux stasis syndrome, at least during the first postoperative period. This hypothesis is supported by our finding that, in patients who had undergone a Billroth II gastrectomy, the $T_{1/2}$ of gastric emptying after Roux-en-Y procedure plus truncal vagotomy was inversely related to the time interval between the operation and the gastric emptying study. Therefore, Roux stasis syndrome is expected to subside eventually.

The findings of the present study confirmed previous reports, according to which intravenous erythromycin accelerates gastric emptying of solids in healthy subjects by almost abolishing the lag phase and by reducing the overall $T_{1/2}$ of gastric emptying. Considering that the lag phase of gastric emptying of solids is inversely related to the antral pressure activity and that erythromycin increases antral but not jejunal pressure wave activity, it can be assumed that enhancement of gastric emptying after giving erythromycin is the result of the increased peristaltic activity of the antrum.

Roux-en-Y gastrojejunostomy is associated with a pattern of gastric emptying of solids that lacks a lag phase. This can easily be explained by the fact that this operation includes excision of the antral mill, the activity of which is responsible for the presence and duration of the lag phase. The findings of the present study showed that administration of erythromycin to patients who had un-
deregone a Roux-en-Y reconstruction invariably enhanced the gastric emptying of solids, and that the post-erythromycin T1/2 of gastric emptying was unrelated to the preerythromycin levels. It is tempting to speculate that, in patients who have undergone a Roux-en-Y operation, erythromycin enhances the gastric emptying of solids by inducing strong contractions of the gastric remnant, similar to those the drug induces in the antrum of normal humans.29 Furthermore, after erythromycin administration, the gastric emptying of solids was faster and the T1/2 shorter in the Roux-en-Y group than in the controls. This is possibly because of the absence of the antrum and pylorus, and a lower resistance of flow across the gastrojejunosotmy, in patients who had undergone a Roux-en-Y operation.

The mechanism of action of erythromycin on gastrointestinal tract motility is still under research. It has been suggested that erythromycin exerts its action by occupying motilin receptors mainly on the smooth muscle.31 However, erythromycin may also act on preganglionic-cholinergic neurons, whereas atropine pretreatment partially blocks the stimulatory effect of erythromycin on antral motility.32,33 In addition, motilin receptors have also been identified in the central nervous system.34 Erythromycin possibly occupies these receptors and increases gastric motility through vagally mediated pathways. Supportive of this hypothesis is that vagal cooling produces a significant inhibition of the erythromycin-induced enhanced gastric emptying in pigs.35

Under the above concepts, erythromycin must have accelerated gastric emptying in patients who had undergone a Roux-en-Y reconstruction by occupying motilin receptors on the smooth muscle and/or presynaptic neurons, thus increasing the contractile activity of the gastric remnant. As all patients had undergone a truncal vagotomy, a central action of erythromycin should be excluded. In the present study, the question of a possible effect of erythromycin on the motility of the efferent jejunal limb was not addressed. According to reports by some authors,30,31 the increased contractile activity after erythromycin is confined only to the antrum and, in very low doses, to the proximal duodenum. The drug does not seem to affect the more distal parts of the intestine. It is therefore unlikely that erythromycin might have increased the motility of the efferent jejunal limb in patients who had undergone a Roux-en-Y reconstruction, although simultaneous manometry of the Roux limb should provide the answer.

In conclusion, erythromycin accelerates gastric emptying in patients who have undergone a Roux-en-Y operation, and the drug might prove useful as a gastrokinetic agent in Roux stasis syndrome. Of course, further studies are required to establish the clinical effectiveness of the drug when given continuously either intravenously or orally.

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REFERENCES