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# Intravenous Erythromycin Dramatically Accelerates Gastric Emptying in Gastroparesis Diabeticorum and Normals and Abolishes the Emptying Discrimination Between Solids and Liquids

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Erythromycin, a macrolide antibiotic, has recently been shown to have a motilin like effect on gastrointestinal muscle strips. In this study, we have evaluated the effect of erythromycin on patients with delayed gastric emptying and healthy subjects using the dual radionuclide technique. Twelve patients with gastroparesis diabeticorum and ten healthy age- and sex-matched controls were studied. Gastric emptying of solids and liquids was determined using  $^{99m}\text{Tc}$ -SC scrambled egg and  $^{111}\text{In}$ -DTPA in water. Following a baseline study and on a separate day, each patient and control received a 15-min i.v. perfusion of erythromycin starting at meal ingestion. Eleven out of the 12 patients were restudied after a 3-wk oral administration. In patients and controls, i.v. erythromycin dramatically accelerated gastric emptying of both solids and liquids which were emptied at the same rate. After chronic oral administration, solid and liquid emptying remained significantly accelerated. Erythromycin appears to be a very powerful gastrokinetic drug. Derived compounds with the gastrokinetic effect and without the antibiotic activity could be useful in dyspeptic patients with delayed gastric emptying.

**J Nucl Med 1990; 31:1490-1493**

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**I**t has been shown that, after feeding, the motility pattern of the human distal stomach is characterized by submaximal contractions similar to the fasting Phase II contractions of the interdigestive migrating motor complex (MMC) (1-2). This fed pattern motor activity determines the kinetic of gastric emptying of both liquids and solids, and one can expect that modifications of gastric motor activity change the character of gastric emptying.

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Received Dec. 7, 1989; revision accepted Mar. 19, 1990.  
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Recent in vivo and in vitro observations have demonstrated that erythromycin, the well-known macrolide antibiotic, mimics the effect of the hormone motilin on the gastrointestinal tract in the fasting state and like motilin induces in the stomach a contraction pattern identical to the the strong contractile Phase III of the interdigestive MMC (3-8). The aim of this study was to investigate and characterize the effect of oral and intravenous erythromycin in patients with severely impaired gastric emptying and in healthy subjects.

## MATERIALS AND METHODS

In this study, we have evaluated twelve diabetics (mean age  $47 \pm 12$ , 10 females and 2 males) with severe gastroparesis symptoms and delayed gastric emptying and 10 healthy age- and sex-matched controls. All patients had type I diabetes. None of the patients or controls were consuming drugs likely to interfere with gastrointestinal motility, nor had they a history of gastrointestinal surgery. Diabetics' mean glycosylated hemoglobin (HbA1C) value was  $8\% \pm 2\%$  (normal range 3.6%-6.4%).

A baseline study was first performed in each patient and control followed by a second test after a 15-min i.v. perfusion of 200 mg of erythromycin starting at meal ingestion. Eleven out of the 12 patients were restudied on a third occasion after a 3-wk oral administration of 500 mg of erythromycin t.i.d. All patients and controls underwent the scintigraphic test procedure after an overnight fast and ate the same standardized test meal consisting of one scrambled egg labeled with 500  $\mu\text{Ci}$  of technetium-99m-sulfur colloid ( $^{99m}\text{Tc}$ -SC), 2 slices of white bread, and 150 ml of water containing 100  $\mu\text{Ci}$  of indium-111-DTPA ( $^{111}\text{In}$ -DTPA). Patients' blood sugar level was kept between 5.5 and 8.3 mmol/l during the test using both insulin and glucose infusion.

Immediately following ingestion of the solid phase of the meal, each volunteer sat between the two heads of a dual-headed gamma camera fitted with medium-energy collimators and interfaced to a nuclear medicine computer system. One-minute simultaneous anterior and posterior images were ac-

quired in the  $^{99m}\text{Tc}$  window ( $140 \text{ keV} \pm 10\%$ ) to determine the maximum counts for the solid phase of the meal; the  $247 \text{ keV} \pm 20\%$  indium energy window was then set up and, immediately after ingestion of the water, images were taken to determine the liquid phase zero value.

Images of the stomach were subsequently acquired in both windows for 1 min every 10 min during the first hour and every 15 min during the second hour. Images were stored on a computer and corrected for indium downscatter and technetium decay. Regions of interest were manually drawn around the stomach in order to determine gastric counts for the anterior and posterior images of both solid and liquid meal at all imaging times. The gastric geometric mean counts, that is the square root of the product of the anterior and posterior counts, were then calculated for both meals. The results were expressed as the percentage of solids and liquids retained in the stomach at each time interval following meal conclusion.

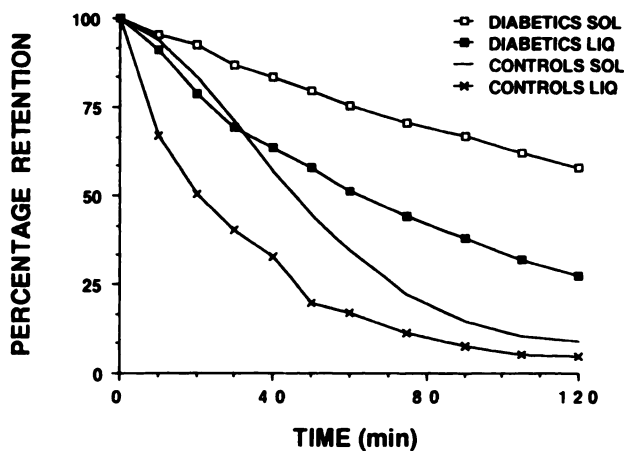
Total and differential leukocyte counts, serum blood level of transaminases, g-glutamyltransferase, alkaline phosphatase, and total and conjugated bilirubin were measured in each patient before the baseline test and every week during the oral administration of erythromycin.

All statistical analyses were performed using the Student's t-test. Results were considered to be statistically significant when  $p \leq 0.05$ .

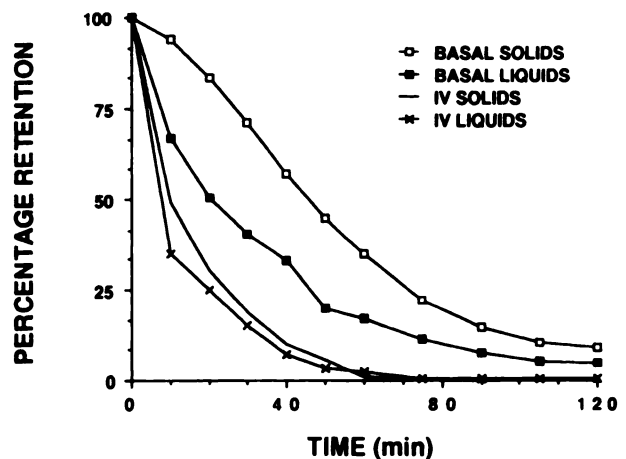
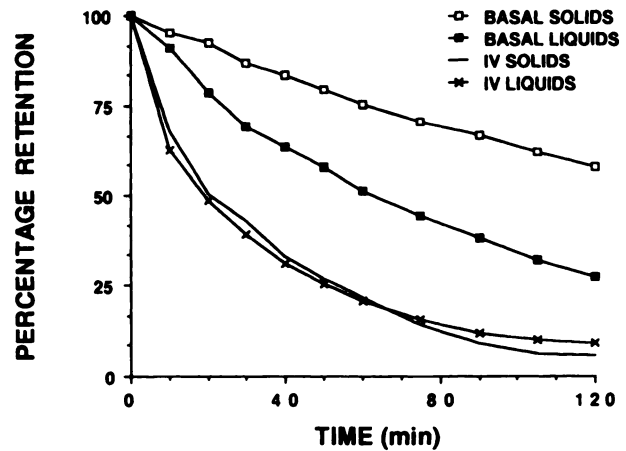
## RESULTS

Compared to controls, baseline gastric emptying of both solid and liquid phase was significantly delayed in diabetic patients (Fig. 1). In controls and patients, the liquid emptying curve followed a single exponential kinetic. In contrast, the solid emptying had a different pattern: in controls the time emptying course was sigmoid in shape, while in diabetics the emptying curve was linear. In both controls and patients, a clear distinction existed between solid and liquid curves.

After i.v. erythromycin, gastric emptying of both solids and liquids was dramatically increased in dia-



**FIGURE 1**  
Gastric emptying of solids and liquids in diabetics with gastroparesis and controls. Compared to controls, gastric emptying of both solids and liquids is significantly delayed.



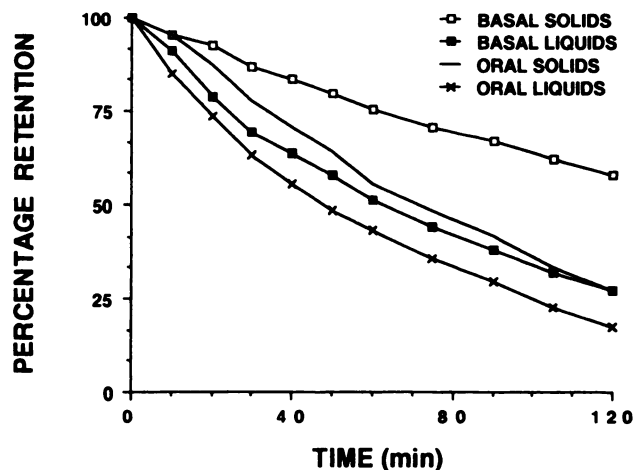
**FIGURE 2**  
Effect of i.v. erythromycin on gastric emptying in diabetics with gastroparesis (A) and in controls (B). Gastric emptying of both solids and liquids is dramatically increased and in both groups the emptying curves follow the same emptying kinetic.

betics (Fig. 2A) and in controls (Fig. 2B). In both groups, we observed a complete abolition of the baseline difference between the solid and liquid emptying curves: both curves followed the same single exponential kinetic.

After chronic oral administration of erythromycin in diabetics (Fig. 3), solid and liquid emptying remained accelerated but the effect was less striking than after the i.v. perfusion and the distinction between solid and liquid curves persisted.

Percentages of meal retention in the stomach at 60 and 120 min (mean  $\pm$  1 s.d.) are summarized in Table 1 for each group and study test. The values observed confirm the dramatic acceleration of gastric emptying after i.v. erythromycin and the significant improvement after chronic oral administration of the drug.

No clinical side-effect nor significant changes in laboratory tests were seen in patients during the oral intake period. No significant decrease was observed in HbA1C or daily insulin dose at the end of the oral trial.



**FIGURE 3**  
Effect of oral administration of erythromycin on gastric emptying in gastroparetic patients. Both solid and liquid emptying remained accelerated but the distinction between solids and liquids persists.

### DISCUSSION

The remarkable ability of the stomach to selectively empty solids and liquids at different rates has been popularly designated solid-liquid discrimination. This phenomenon has been explained by the functional sieving action of the contracting terminal antrum and the pylorus, which allows the rapid passage of liquid from the stomach to the duodenum while solids are retained (2). During the fed pattern, the sieving efficiency of the stomach is related to the submaximal non-lumen obliterating peristaltic contractions, which repeatedly propel large solid particles toward the closed pylorus and repropel them into the stomach for fragmentation before they are allowed to pass the pylorus. In the fasting state, Phase III contractions of the interdigestive motor complex occur to empty from the stomach its fasting content and indigestible debris. These contractions are forceful lumen obliterating distal gastric peristaltic

waves which sweep down the gastric content through the opened pylorus (1).

Motilin, a 22-amino-acids peptide hormone secreted by the mucosa of the upper part of the small intestine, has been shown to play an important role in the interdigestive myoelectric motility pattern of the gut, particularly in the induction of the Phase III powerful contractions (3,9-11). Although the mechanism of action of erythromycin on gastrointestinal motility is not yet fully elucidated and no structural relationship between erythromycin and motilin has been demonstrated (12), there is now strong evidence that erythromycin binds to antral and duodenal motilin receptors (8,12-13) and initiates the potent contractile Phase III of the interdigestive motor complex (3-8). The dramatic acceleration of gastric emptying we have observed in this study in diabetics with severe gastroparesis and in controls shows that erythromycin induces a potent post-cibal motor-activity in the stomach. We believe that the complete abolition of solid-liquid discrimination we have observed corresponds to the abolition of the sieving action of the distal stomach and reflects the induction in the stomach of powerful Phase III contractions, which squeeze the distal stomach content into the duodenum through the pylorus. This is supported by our preliminary radiocinematographic observations that i.v. erythromycin induces in the distal stomach very powerful lumen obliterating contractions and by our recent study showing that the solid-liquid discrimination represents the retention of solid food particles in the stomach (14). The resurgence of this discrimination after oral administration of erythromycin suggests that the effect might be related to the drug blood level.

Gastric retention in diabetes contributes to poor control of the disease due to the unpredictable absorption of food, which compromises the effects of exogenous insulin and oral hypoglycemic drugs and adds to the "brittleness" of the diabetes. Various gastrokinetic compounds have been tested in the treatment of severe

**TABLE 1**  
Percentage Meal Retention

	Solids		Liquids	
	60 min	120 min	60 min	120 min
<b>Patients</b>				
Baseline	75 ± 21 <sup>*</sup>	58 ± 24 <sup>*</sup>	51 ± 16 <sup>*</sup>	27 ± 11 <sup>*</sup>
IV Erythromycin	22 ± 15 <sup>†</sup>	6 ± 5 <sup>†</sup>	21 ± 15 <sup>†</sup>	9 ± 10 <sup>†</sup>
Oral Erythromycin	60 ± 19	27 ± 19 <sup>‡</sup>	48 ± 20	20 ± 16 <sup>‡</sup>
<b>Controls</b>				
Baseline	35 ± 5	9 ± 3	17 ± 3	4 ± 1
IV Erythromycin	1 ± 0 <sup>†</sup>	1 ± 2 <sup>†</sup>	2 ± 2 <sup>†</sup>	1 ± 2 <sup>†</sup>

<sup>\*</sup> p < 0.0005 versus controls.

<sup>†</sup> p < 0.0005 versus baseline.

<sup>‡</sup> p < 0.05 versus baseline.

gastroparesis diabeticorum. Unfortunately, none of the compounds presently available have really been proven useful (15-16). In this study, we have shown that the chronic oral administration of a motilin agonist significantly improves gastric emptying in gastroparetic patients. The lack of a significant decrease in HbA1C parallel to the improvement of gastric emptying is not surprising and can be explained by the long period of time required for HbA1C to reflect a new glycemic profile.

In conclusion, i.v. and oral administration of erythromycin significantly accelerate gastric emptying in diabetic patients with gastroparesis diabeticorum. Intravenous erythromycin abolishes the so-called gastric-solid-liquid emptying discrimination phenomenon. Development of compounds with the motilin agonist effect, but without antibiotic activity, should open the door for the hormonal treatment of delayed gastric emptying. The radionuclide technique is a powerful tool to test the efficacy of a gastrokinetic compound.

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