Abdom Imaging 27:309–314 (2002)
DOI: 10.1007/s00261-001-0058-z

Abdominal Imaging

Hyperglycemia attenuates erythromycin-induced acceleration of solid-phase gastric emptying in healthy subjects

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Received: 23 October 2000/Revision accepted: 4 April 2001

Abstract
Background: Acute hyperglycemia has been associated with delayed gastric emptying of solid foods in healthy control subjects. Erythromycin has been found to be a gastrointestinal prokinetic agent in humans. We examined whether acute steady-state hyperglycemia reduces the erythromycin-induced acceleration of gastric emptying of a solid meal after a fasted state in healthy subjects.
Methods: Twelve healthy subjects ate standard solid meals that had been radiolabeled. Gastric emptying was measured by scintigraphy during normoglycemia (5–8.9 mmol/L glucose) and hyperglycemia induced by intravenous glucose (16–19 mmol/L glucose) after administration of placebo or 200 mg of erythromycin intravenously. Emptying was measured randomly on 4 different days.
Results: Administration of erythromycin during normoglycemia or induced hyperglycemia compared with placebo accelerated the gastric emptying of the solid meal but did not completely normalize the delay caused by hyperglycemia versus normoglycemia ($p < 0.001$). In both conditions, erythromycin versus placebo significantly reduced the lag-phase duration (9.7 ± 2.3 min and 22.0 ± 3.9 min vs. 38.3 ± 5.7 min and 49.5 ± 6.0 min, respectively; $p < 0.001$), gastric emptying of the half meal (39.2 ± 4.0 min and 52.0 ± 7.1 min vs. 75.7 ± 11.8 min and 94.0 ± 13.4 min, respectively; $p < 0.001$), and the percentage of meal retained in the stomach 120 min postprandially ($p < 0.001$).
Conclusion: The erythromycin-induced acceleration effect on gastric emptying was related to the plasma glucose level. Hyperglycemia might have chosen a cholinergic antagonist pathway that delayed gastric emptying of solids. Even though induced hyperglycemia inhibited gastric emptying, erythromycin accelerated the gastric emptying rate through two distinct pathways: cholinergic and noncholinergic.

Key words: Hyperglycemia—Erythromycin—Scintigraphic gastric emptying—Gastric motility.

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Erythromycin recently has been found to be a gastrointestinal prokinetic agent in humans and other animals. Those effects are believed to be mediated by the ability of erythromycin to bind to the receptors of the gastrointestinal peptide motilin and not its antibiotic characteristics [1–4]. However, it is still uncertain as to whether erythromycin binds to motilin receptors on smooth muscle or nerve tissue [5]. Administration of low doses of erythromycin (40 mg) can induce phase III of the migrating motor complex (MMC) in humans [6] and dogs [7]. In addition, a 200-mg dose of erythromycin increases antral contractile activity during fasting and gastric emptying of solid foods in normal subjects, patients with gastroparesis, and patients with delayed gastric emptying after gastric surgery [8–13], increases the amplitude of antral contractions, and improves antroduodenal coordination [14, 15].

Acute hyperglycemia is associated with decreased pressure waves in the antrum, loss of phase III interdigestive MMC in the stomach, and slowing of gastric emptying [16–18]. Most studies have dealt with diabetic patients with neuropathy, but healthy individuals also have shown slowing of gastric emptying during acute hyperglycemia [19–21]. A recent study found that hyperglycemia reduces motility in the stomach and inhibits motility in the duodenum and jejunum, with a significant effect on small intestinal motility [22], whereas another recent study found no consistent effects of hyperglycemia on the duodenum or others parts of the small intestine except the stomach [23]. In that study, most of the sub-

jects showed a phase III–like activity in the duodenum within 15 min after the onset of hyperglycemia [23]. Barnett et al. [17] showed that the motility index in the duodenum did not change significantly during hyperglycemia. Modern computerized recordings and detailed analysis of individual gastroduodenal contractions have shown that the last part of phase III in the proximal duodenum works as a retroperistaltic pump [22]. It is not known whether that pattern is altered by metabolic factors. Our group recently demonstrated the attenuated effect of hyperglycemia on the erythromycin-induced acceleration of solid and liquid gastric emptying in patients with idiopathic and diabetic gastroparesis and diabetic type I, respectively [24, 25]. Further, we found a similar hyperglycemic effect not mediated by the vagus [26]. In those patients erythromycin accelerated gastric emptying during normoglycemia and hyperglycemia but did not completely normalize the delay caused by the induced hyperglycemia. In the present study, we examined the effects of acute steady-state hyperglycemia induced by intravenous glucose infusion and "clamping" of the glucose level on the erythromycin-induced (a motilin agonist) acceleration on gastric emptying of solid food after a fast in healthy subjects.

Patients and methods

Twelve healthy subjects (seven men, five women; mean age = 35.5 years, range = 24–58 years; mean body weight = 74 kg, range = 54–92 kg; mean body mass index = 22.1 kg/m^2, range = 18.9–25.1 kg/m^2) without gastrointestinal symptoms participated. All subjects gave written informed consent, and the Ethical Committee of the University of Crete approved the study protocol.

Protocol

In a double-blind fashion, gastric emptying was measured in all subjects during normoglycemia (5–8.9 mmol/L) or induced hyperglycemia (16–19 mmol/L) after administration of placebo or erythromycin on 4 different days at 1-week intervals and in random order. Subjects fasted 16 h (from 8 PM the previous day to 12 PM). Two cannulas were inserted into the anticubital veins in each arm; one cannula was used for the infusion of glucose and insulin and the other was used for administration of erythromycin or placebo. Blood samples were drawn from another (third) venous cannula on the dorsal surface of the hand, and the blood glucose concentration was measured every 10 min. Blood glucose concentrations were stabilized within the normoglycemic or hyperglycemic range for at least 1 h before consumption of the solid meal. After stable blood glucose concentrations were taken, subjects ate radioisotopically labeled test meals at approximately 12.00 PM. Gastric emptying of the standard solid meal was studied on four different occasions, 1 week apart, in random order, after intravenous administration of 40 mL of normal saline (placebo) or 200 mg of erythromycin lactobionate (Abbott Laboratories, Abbott Park, IL, USA), which increases antral contractile activity [6, 8, 10], diluted in 40 mL of water during normoglycemia or hyperglycemia. Any medication that might have influenced gastrointestinal motility was discontinued at least 3 days before each study.

Measurement of gastric emptying

The standard meal consisted of a hamburger and 140 g of fresh tomato. The hamburger consisted of 100 g of minced beef meat, 20 g of toasted bread, 10 g of olive oil, and half an egg that had been labeled with 500 μCi of ^{99m}Tc sulphur colloid. The meal contained 1633 kJ (32% protein, 52% fat, and 16% carbohydrate) of energy and was consumed within 10 min. Immediately after the meal was completed, a reference scan for time 0 was acquired; subjects were then given infusions of placebo or erythromycin for normoglycemia or hyperglycemia, which continued another 10 min. With subjects seated in front of a γ-camera (GE Maxi II; General Electric, Milwaukee, WI, USA) that had been fitted with a low-energy collimator, abdominal scans were acquired for 1 min, every 5 min, and for a total of 120 min. The same nuclear medicine technologist, who had no interest in the outcome of the study, measured the radioactivity over the gastric area that was defined by hand with the use of a light pen. The counts were corrected for movement, Compton scatter, γ-ray attenuation, and physical isotope decay [27]. The data were computer generated, expressed as a percentage over the initial value (first scan at time 0), and plotted against time to generate profiles of the gastric emptying. From those profiles the following parameters were obtained: (a) shape of the emptying curves; (b) duration of the lag phase, if present; (c) $t_{1/2}$ (the time between completion of the meal to the point at which half of the meal had left the stomach); (d) time from the onset of emptying into the duodenum to the point at which half the meal had left the stomach (postlag $t_{1/2} = t_{1/2} - t_{lag}$); and (e) the percentage of meal remaining in the stomach 120 min after the meal had been consumed.

Blood glucose stabilization

Normoglycemia and hyperglycemia were induced by intravenous infusion of 20% glucose and insulin (Actrapid, HM Novo Nordisk, Bagsvaerd, Denmark) [28]. The rate of 20% glucose was adjusted to maintain blood glucose concentrations at 5–8.9 or 16–19 mmol/L. Blood samples were drawn from the cannulas inserted into the dorsal

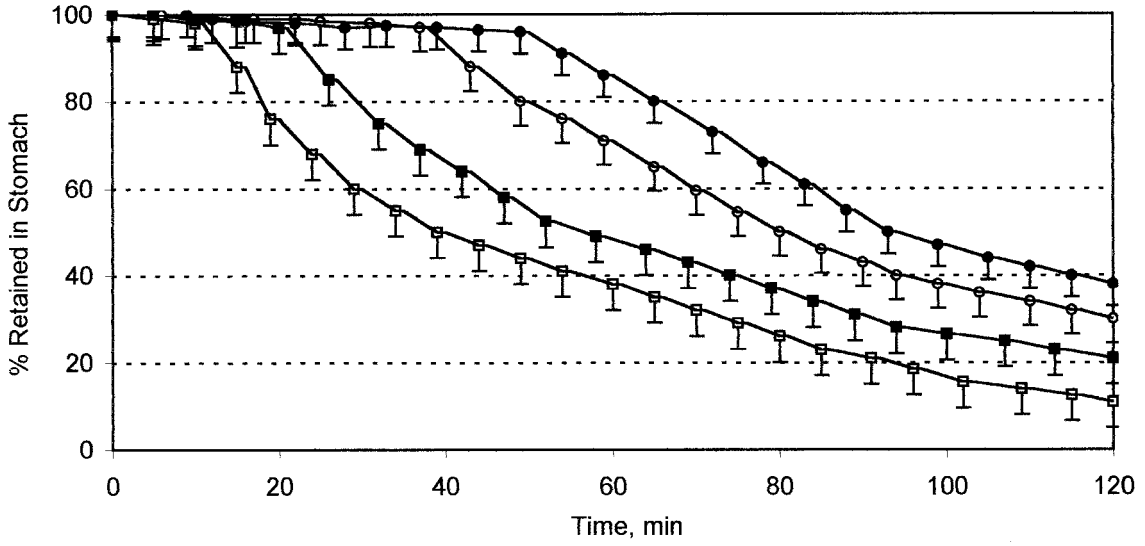

Fig. 1. Emptying curves of solids in healthy controls (mean ± SD). The typical dual-phase curve was obtained after placebo administration during normoglycemia (*open circles*) and a similar parallel curve was obtained with an increased lag-phase period during induced hyperglycemia (*solid circles*). Intravenous administration of 200 mg of erythromycin during normoglycemia (*open squares*) and induced hyperglycemia (*solid squares*) compared with placebo accelerated gastric emptying of solids by abolishing lag-phase duration and reducing the overall gastric emptying time; however, it did not completely normalize the delayed gastric emptying rate caused by hyperglycemia and thus produced two parallel emptying curves.

surfaces of the opposite hands; glucose concentrations were measured every 10 min with test strips (BM-test glycemie R 1-44, Boehringer, Mannheim, Germany).

The mean (SEM) blood glucose concentrations were 7.8 (0.5) mmol/L during normoglycemia and 17.5 (0.5) mmol/L during hyperglycemia. The glucose concentrations were 4.3 (0.8) mmol/L at 0 min and 8.2 (2.8) mmol/L at 60 min.

Statistical analysis

All values were expressed as mean ± SD, and $p < 0.05$ was considered significant. Analysis of variance for repeated measures measured differences between treatments.

Results

During normoglycemia after placebo administration, gastric emptying of the meal was fitted to a typical dual-phase (lag phase: virtually no emptying, postlag phase: actual emptying) curve, according to a linear model (Fig. 1). During normoglycemia, administration of erythromycin as opposed to placebo almost abolished the lag phase (9.7 ± 2.3 min vs. 38.3 ± 5.7 min, respectively; $p < 0.001$) and the appearance of the curve was almost that of the linear model (Fig. 1). Erythromycin as opposed to placebo significantly reduced the $t_{1/2}$ of gastric emptying (39.2 ± 4.0 min vs. 75.7 ± 11.8 min, $p < 0.001$) but did not affect the postlag $t_{1/2}$ of gastric emptying. Significantly less food was retained in the stomach 120 min postprandially after erythromycin than after placebo administration (11.8 ± 2.8% vs. 30.0 ± 3.4%, respectively; $p < 0.001$).

During induced hyperglycemia after administration of placebo or erythromycin, the emptying curves shifted to the right compared with those obtained during normoglycemia, and ran parallel, as shown in Figure 1, because of the prolonged lag phase, dual-phase curve, and decrease in the overall gastric emptying rate.

During induced hyperglycemia, erythromycin versus placebo administration significantly accelerated the overall gastric emptying rate. Erythromycin administration during induced hyperglycemia significantly decreased the lag phase (22.0 ± 3.9 min vs. 49.5 ± 6 min, $p < 0.001$), $t_{1/2}$ of gastric emptying (52.0 ± 7.1 min vs. 94.0 ± 13.4 min, $p < 0.001$), and the percentage of retained meal in the stomach at 120 min postprandially (21.2 ± 3.3% vs. 39.6 ± 5.3%, $p < 0.001$). However, erythromycin did not normalize the delay caused by the hyperglycemic conditions versus normoglycemia. After erythromycin administration, the lag phase was significantly prolonged, producing a dual-phase curve compared with the linear model after erythromycin administration in normoglycemia (22.0 ± 3.9 min vs. 9.7 ± 2.3 min, $p < 0.001$). Placebo administration during induced hyperglycemia

versus normoglycemia significantly prolonged the lag phase (49.5 ± 6.0 min vs. 38.3 ± 5.7 min, $p < 0.001$).

The postlag phase of actual emptying was similar to that of the linear model after administration of placebo or erythromycin during hyperglycemia. Further, hyperglycemia versus normoglycemia after administration of placebo or erythromycin significantly increased $t_{1/2}$ of gastric emptying (94.0 ± 13.4 min vs. 75.7 ± 11.8 min and 52.0 ± 7.1 min vs. 39.2 ± 4.0 min, respectively; $p < 0.001$) but did not affect the postlag $t_{1/2}$ of the gastric emptying rate. The percentage of meal remaining in the stomach at 120 min postprandially after administration of placebo or erythromycin during hyperglycemia was significantly greater compared with the percentage during normoglycemia (39.6 ± 5.3% vs. 30.0 ± 3.4% and 21.2 ± 3.3% vs. 11.8 ± 2.8%, respectively; $p < 0.001$).

Discussion

Gastric emptying of solids has two phases known as lag and postlag [27, 29]. The lag phase corresponds to food coursing from the fundus to the antrum and trituration of that food to particles no larger than approximately 1 mm by the antral mill [29, 30]. The duration of the lag phase is inversely related to antral pressure [29]. The postlag phase corresponds to propulsion of food particles through the pylorus into the duodenum [29–31]. The emptying rate during that period is directly related to antral pressure [29]. However, the resistance of the pylorus and the motility of the duodenum also affect postlag emptying [29, 31, 32]. Houghton et al. [33] found that, during the lag phase of emptying, the stomach gets rid of excess fluid and leaves the solid ball of food in the fundus and that trituration is minimal. Grinding of solid food to small particles by antral contractions and emptying into the duodenum occur during the postlag period.

The properties of erythromycin as a motilin agonist explain its action on the gastric emptying of solids in healthy individuals and patients with gastroparesis or delayed emptying after gastric surgery [6, 8, 10–13]. Motilin receptors in humans are confined to the stomach and duodenum [34], and increased plasma motilin concentrations in blood are detected when phase III of the MMC begins from the stomach [35]. Erythromycin increases antral and not jejunal postprandial motor activity in healthy individuals and patients with diabetic gastroparesis [7, 8, 10, 30, 36]. One recent found that erythromycin also affects proximal gastric tone in humans [37], whereas some in vivo studies suggested an indirect action through a cholinergic pathway [38–40]. Erythromycin also induces powerful contractions that obliterate the lumen of the gastric antrum [8], and antral motor activity is inversely related to the duration of the lag phase [29]. Moreover, erythromycin enhances the gastric emptying and accelerates the emptying rate of liquids and solids, thereby overcoming the inhibitory enterogastric osmotic reflex or antroduodenal coordination [8, 10]. The present findings confirmed those of previous reports [6, 10] in which 200 mg of intravenous erythromycin increased gastric contractile activity during fasting and accelerated gastric emptying in healthy subjects by almost abolishing the lag phase and reducing by half the overall gastric emptying period, thereby overcoming antroduodenal coordination, which controls trituration and emptying of solid food.

Hyperglycemia decreases the rate of gastric emptying in healthy subjects [16]. Acute hyperglycemia affects antral activity with loss of antral MMC phase III [17, 26]. The pressure activity in the antrum, expressed as the motility index, is significantly reduced after the onset of hyperglycemia as opposed to normoglycemia, and the absence of MMC phase III in the antrum during hyperglycemia seems to abolish this component in healthy subjects [27]. Björnsson et al. [22] found that acute hyperglycemia is accompanied by a decrease in gastric interdigestive motility and a significant inhibition of contractions in the duodenum and proximal jejunum, although long clusters of contractions were more common during hyperglycemia in healthy subjects. They also found that hyperglycemia decreases motilin and pancreatic polypeptide (PP) levels, probably by suppressing cholinergic transmission, and that efferent activity in the vagal nerve might be disturbed in some way during acute hyperglycemia as evident by the inhibition of gastric and small intestine motility [22]. Samson et al. [41] found that hyperglycemia delays gastric emptying of solids by prolonging the lag phase and decreasing the postlag emptying rate. The present study confirmed the role of blood glucose level and its metabolic control in the gastric emptying of solids and the results of Samson et al. [41], further showing that acute hyperglycemia rather than normoglycemia attenuates the erythromycin-induced acceleration on gastric emptying of solids. Nevertheless, erythromycin accelerated gastric emptying of solids during hyperglycemia but did not normalize the delay caused by hyperglycemia compared with normoglycemia. Despite the administration of erythromycin, a motilin agonist that overcomes the inhibitory effect of excited antroduodenal coordination on gastric emptying of solids [6, 10, 22], the gastric emptying rate decreased significantly during hyperglycemia compared with normoglycemia. Therefore, hyperglycemia likely uses a cholinergic antagonist pathway that suppresses the cholinergic transmission and efferent activity of the vagal nerve and reducees gastrointestinal motility. Hence, we confirmed the results of Björnsson et al. [22] by showing that suppression of cholinergic transmission is probably mediated through activation of a cholinergic antagonist pathway that also attenuates the erythromycin-induced acceleration of gastric emptying and its indirect action via a cholinergic pathway [38–40]. In that way, erythromycin

may act through two distinct pathways, cholinergic and noncholinergic, hence, its effect in patients with vagotomy [26].

The present findings also might be relevant for diabetics. Intestinal dysmotility was found in most patients with diabetes mellitus and gastroparesis [42–44]. Moreover, gastric emptying during hyperglycemia was delayed in subjects with diabetes mellitus type I or II [18]. In diabetic patients with gastroparesis, 40% had an affected gastric component of the MMC [42]. The blood glucose level might affect gastric emptying in diabetic patients or healthy control subjects [18, 27]. Pioneer studies of gastric emptying after placebo or erythromycin administration in diabetic patients might not have controlled the metabolisms of those patients in an optimal way. Therefore, the changes in gastric emptying, at least part, might have been due to inadequate regulation of glucose level rather than irreversible neuropathy.

The erythromycin-induced acceleration effect on gastric emptying is related to the plasma glucose level. Hyperglycemia might use a cholinergic antagonist pathway that delays gastric emptying of solids. Erythromycin accelerated gastric emptying during normoglycemia and hyperglycemia by acting through cholinergic and noncholinergic pathways and might be a useful prokinetic agent even during hyperglycemia.

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