Hyperglycemia Attenuates the Gastrokinetic Effect of Erythromycin and Affects the Perception of Postprandial Hunger in Normal Subjects

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OBJECTIVE — The major aims of this study were to determine in normal subjects whether the effects of erythromycin on gastric emptying, postprandial hunger, and fullness are modified by the blood glucose concentration.

RESEARCH DESIGN AND METHODS — A total of 10 normal subjects (aged 20–39 years) underwent concurrent measurements of gastric emptying, blood glucose, hunger, and fullness on four separate occasions: twice during euglycemia (~4 mmol/l) and twice during hyperglycemia (~15 mmol/l). Either erythromycin (3 mg/kg) or saline (0.9%) was administered intravenously immediately before ingestion of a radioisotopically labeled solid meal.

RESULTS — Gastric emptying was slower ($P < 0.0001$) during hyperglycemia when compared with euglycemia after both erythromycin and saline administration. During hyperglycemia, erythromycin reduced the lag phase (77.8 ± 12.6 vs. 20.3 ± 7.3 min; $P < 0.05$) but had no effect on the postlag emptying rate (0.32 ± 0.077% per min vs. 0.24% per min). Hunger decreased ($P < 0.001$) and fullness increased ($P < 0.001$) after the meal. Postprandial hunger was less during hyperglycemia after saline infusion ($P < 0.05$) but not after erythromycin. Hunger was greater after erythromycin during both hyperglycemia and euglycemia ($P < 0.05$).

CONCLUSIONS — At a blood glucose concentration of ~15 mmol/l, *1*) gastric emptying of a solid meal is slower, when compared with euglycemia, even after administration of erythromycin; *2*) the effect of erythromycin on gastric emptying of a solid meal is attenuated; and *3*) the perception of postprandial hunger is reduced.

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Delayed gastric emptying occurs in 30–50% patients with long-standing diabetes and may be associated with gastrointestinal symptoms such as nausea, vomiting, and postprandial fullness, poor control of blood glucose concentrations, and impaired oral drug absorption (1–4). Although diabetic gastroparesis has been attributed to irreversible autonomic neuropathy (5), it has now been established that acute changes in the blood glucose concentration have a major, reversible effect on gastrointestinal motor function (6–17). For example, in both normal subjects (7,17) and patients with type 1 diabetes (6,18), gastric emptying is slower during marked hyperglycemia (~15 mmol/l) when compared with euglycemia, while hypoglycemia accelerates gastric emptying (19,20). It has recently been demonstrated that changes in blood glucose within the normal postprandial range also affect gastric motility (10,15), as well as motor function in other regions of the gastrointestinal tract (16,21).

Symptomatic diabetic gastroparesis is usually treated with prokinetic drugs (22). When acutely given in a dose of 200 mg intravenously, erythromycin appears to be the most potent of these drugs, and when given to patients with diabetic gastroparesis during euglycemia, may accelerate gastric emptying at a rate faster than normal (23). Erythromycin also increases the rate of gastric emptying in normal subjects but, as with other prokinetic drugs, the magnitude of its effect is less than that observed in patients with gastroparesis (24,25). In nearly all studies that have evaluated the effects of prokinetic drugs on gastrointestinal motor function in patients with diabetes, blood glucose concentrations have not been stabilized in the euglycemic range and, at least in most cases, not monitored at all. It is also controversial whether the beneficial effect of these drugs on gastric emptying in diabetes, seen after short-term administration, is sustained in the long term (26–28). The possibility that the blood glucose concentration may influence the motor response to prokinetic therapy has not been considered.

While there is a high prevalence of upper gastrointestinal symptoms in patients with type 1 diabetes (29), the relationship between symptoms and gastric emptying is relatively weak (1,2), indicating that other factors are likely to be important. Recent studies provide persuasive evidence that acute changes in the blood glucose concentration may modulate the perception of sensations arising from the gastrointestinal tract (12,30,31). For example, in normal subjects, the perceptions of

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Abbreviations: Eug/Ery, euglycemia with erythromycin; Eug/Sal, euglycemia with saline infusion; Hyper/Ery, hyperglycemia with erythromycin; Hyper/Sal, hyperglycemia with saline infusion.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

nausea and fullness induced by proximal gastric distention (12) and small intestinal nutrient infusion (30) are increased during hyperglycemia, and in patients with type 1 diabetes the sensation of postprandial fullness is related directly to the blood glucose concentration (31). It has not been established whether changes in the blood glucose concentration affect postprandial sensations, such as hunger and fullness, in normal subjects.

In patients with diabetic gastroparesis, the relationship between the magnitude of symptomatic improvement and the change in gastric emptying resulting from prokinetic therapy is weak (27,32–34). In patients with diabetes, some studies have been unable to establish a beneficial effect of prokinetic therapy on symptoms (33, 34). While variations in the blood glucose concentration could potentially account for these apparent anomalies, there is also evidence that prokinetic drugs may modulate gastrointestinal symptoms by mechanisms unrelated to changes in gastric emptying per se (35–37).

The aims of this study were to determine in normal subjects whether *1*) the gastrokinetic effect of erythromycin is attenuated during hyperglycemia and *2*) the perceptions of postprandial hunger and fullness are affected by either the blood glucose concentration and/or erythromycin.

RESEARCH DESIGN AND METHODS

— A total of 10 healthy male subjects (median age 25.5 years, range 20–39; median BMI 24.5 kg/m^2, range 20–28) participated in the study. None of the subjects had a history of gastrointestinal disease or surgery or were taking medication. Smoking and strenuous exercise were prohibited in the 24-h period before each experiment. Written informed consent was obtained from each subject before enrollment in the study, and the study protocol was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital.

Protocol

Each subject underwent concurrent measurements of gastric emptying, blood glucose concentrations, and perceptions of hunger and fullness on either three or four occasions, each measurement separated by 4–7 days. When four tests were performed, blood glucose concentrations were maintained in the euglycemic range (4–6 mmol/l) on 2 days; on the other 2 days, experiments were performed during hyperglycemia (blood glucose 14–16 mmol/l). Either erythromycin (3 mg/kg) or placebo (0.9% saline) was administered intravenously in single-blind fashion during both euglycemia and hyperglycemia. The four phases of the study (euglycemia with saline infusion [Eug/Sal], euglycemia with erythromycin [Eug/Ery], hyperglycemia with saline [Hyper/Sal], and hyperglycemia with erythromycin [Hyper/Ery]) were performed in single-blind fashion, that is, the investigator but not the subject was aware of the blood glucose concentration. We initially believed that it might have been impractical for each volunteer to participate in four experiments, and for this reason we elected not to perform the Hyper/Sal arm of the study in the first four subjects. The remaining six subjects underwent all four studies. In all cases, the order of the experiments was randomized; that is, for the first four subjects, the order of the studies Eug/Sal, Eug/Ery, or Hyper/Ery were randomized, while for the last six subjects, the order of the entire four studies were randomized.

Each subject attended the Department of Nuclear Medicine at 9:00 A.M. after an overnight fast (14 h for solids, 12 h for liquids). Two intravenous cannulae were inserted into antecubital veins (one in each arm); one cannula was used for infusion of either 0.9% saline (Eug) or 25% dextrose (Hyper) and the other for venous blood sampling and infusion of either placebo (0.9% saline) or erythromycin. After blood glucose concentrations had been stabilized at the desired concentration for 30 min, erythromycin (3 mg/kg) as the lactobionate (David Bull Laboratories, Melbourne, Australia), was mixed in saline, or saline was administered over 15 min (total volume 150 ml). Immediately after completion of erythromycin or saline infusion, subjects started to eat the test meal. Gastric emptying was monitored for at least 180 min after completion of the meal while the desired blood glucose concentration was maintained.

Stabilization of blood glucose concentrations

Hyperglycemia was achieved using a modified glucose clamp technique (6,12). An intravenous bolus of 100 ml 25% dextrose was given over 2 min, followed by an infusion of 25% dextrose (via an IMED volumetric infusion pump, San Diego, CA) starting at a rate of 400 ml/h and adjusted to maintain the blood glucose concentration at ~15 mmol/l (6,12). During the experiments performed during euglycemia, normal saline was infused and the rate adjusted so that the total volume was likely to be similar to that infused during the hyperglycemic arms of the study. Starting immediately before the commencement of the intravenous infusions, venous blood samples for measurement of glucose were taken every 5 min. After consumption of the test meal, blood samples were taken at least every 10 min. Blood glucose concentrations were measured using a portable blood glucose meter (MediSense Companion 2 meter; Medisense, Waltham, MA) (35). The accuracy of these measurements has been confirmed using the hexokinase technique.

Measurement of gastric emptying

The test meal comprised 300 g lean minced beef labeled with 20 MBq of ^{99m}Tc-sulphur colloid chicken liver and 150 ml unlabeled water (38). The solid meal was consumed over 5 min, followed by the water. The water was not radioisotopically labeled because of limitations in the radiation dose that could be administered to normal volunteers. Scintigraphic data were acquired with the subject seated with their back against a gamma camera (Siemens, Chicago) in 1-min frames for the first 60 min and in 3-min frames for the following 120 min. Time zero was defined as the time when the meal was completed (38). Data were corrected for radionuclide decay, gamma ray attenuation, and subject movement (38).

A region of interest (ROI) was drawn around the total stomach, and this was divided into proximal and distal stomach regions (38). Gastric emptying curves, expressed as percentage retention over time, were derived from total, proximal, and distal stomach regions (38). For the total, proximal, and distal stomach the amount of the solid meal remaining at 15-min intervals between 0 and 180 min was derived. For the total stomach, the lag phase was determined visually as the time period before any of the solid meal had entered the small intestine (38). The post-lag emptying rate (percent per minute) between the end of the lag phase and 150 min was also calculated (35).

Measurement of fullness and hunger

Perceptions of fullness and hunger were quantified using a previously validated visual analog questionnaire (39). Questionnaires were administered at −45, −30, −15, 0, 15, 30, 45, 60, 75, 90, 105, 120,

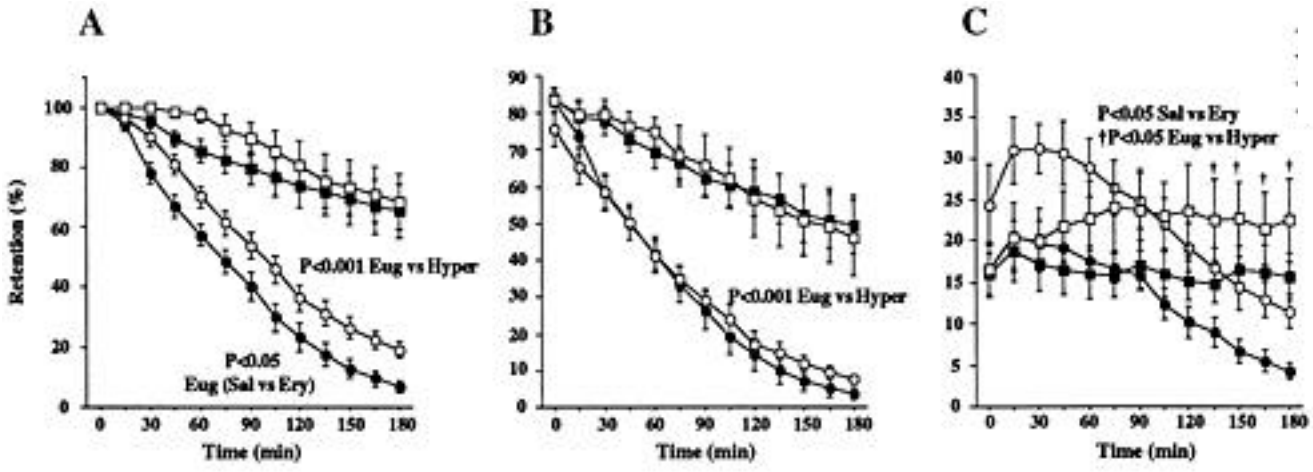

Figure 1—*Retention of the meal in total (A), proximal (B), and distal (C) stomach regions of interest for the four study days. Data are mean values ± SEM. ●, Eug/Ery (n = 10); ■, Hyper/Ery (n = 10); ○, Eug/Sal (n = 10); □, Hyper/Sal (n = 6).*

135, 150, 165, and 180 min, where time-zero was the time of meal completion.

Statistical analysis

Data were evaluated using repeated measures analysis of variance (ANOVA), using the time points at 0, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, and 180 min. Contrasts were used to test preplanned hypotheses of interest, enabling comparisons at specific time points. The lag phase and rate of gastric emptying were assessed using the Wilcoxon's signed-rank test. Given that 4 of the 10 subjects only completed three of the four studies (the Hyper/Sal arm not completed), comparisons between Hyper/Sal and Eug/Sal, Hyper/Ery, Eug/Ery were performed using the data from six subjects. In all other comparisons, data from the entire group of 10 subjects were used. Data are shown as mean values ± SEM. A P value <0.05 was considered significant in all analyses.

RESULTS

— All of the subjects tolerated the studies well, and there were no untoward events. Mean blood glucose was 4.8 ± 0.4 mmol/l during euglycemia and 14.4 ± 0.2 mmol/l during hyperglycemia. There was no difference in the volume infused intravenously between the four study days.

Gastric emptying

Total stomach. In all cases, gastric emptying approximated a linear pattern after an initial lag phase (Fig. 1*A*). The lag phase was longer during hyperglycemia when compared with euglycemia after administration of saline (Eug/Sal 17.8 ± 3.6 vs. Hyper/Sal 77.8 ± 12.6 min; $P = 0.02$), but not after erythromycin (Eug/Ery 10.6 ± 1.4 min vs. Hyper/Ery 20.2 ± 7.3 min). After administration of both saline and erythromycin, the postlag emptying rate was slower ($P < 0.0001$) during hyperglycemia. The lag phase was shorter after administration of erythromycin when compared with saline during both euglycemia (Eug/Sal 17.9 ± 11.5 vs. Eug/Ery 10.6 ± 1.4 min; $P < 0.05$) and hyperglycemia (Hyper/Sal 77.8 ± 12.6 vs. Hyper/Ery 20.1 ± 7.3 min; $P < 0.05$). Erythromycin accelerated the postlag emptying rate during euglycemia (Eug/Sal 0.56 ± 0.02 vs. Eug/Ery 0.63 ± 0.02% per min; $P < 0.05$), but not hyperglycemia (Hyper/Sal 0.32 ± 0.07 vs. Hyper/Ery 0.24 ± 0.07% per min).

Proximal stomach. The retention in the proximal stomach was greater during hyperglycemia when compared with euglycemia after both saline ($P < 0.0005$) and erythromycin ($P < 0.001$) (Fig. 1*B*). Erythromycin did not affect the content of the proximal stomach during hyperglycemia or euglycemia.

Distal stomach. The content of the distal stomach was greater during hyperglycemia when compared with euglycemia after administration of both saline ($P < 0.05$) and erythromycin ($P < 0.05$) (Fig. 1*C*).

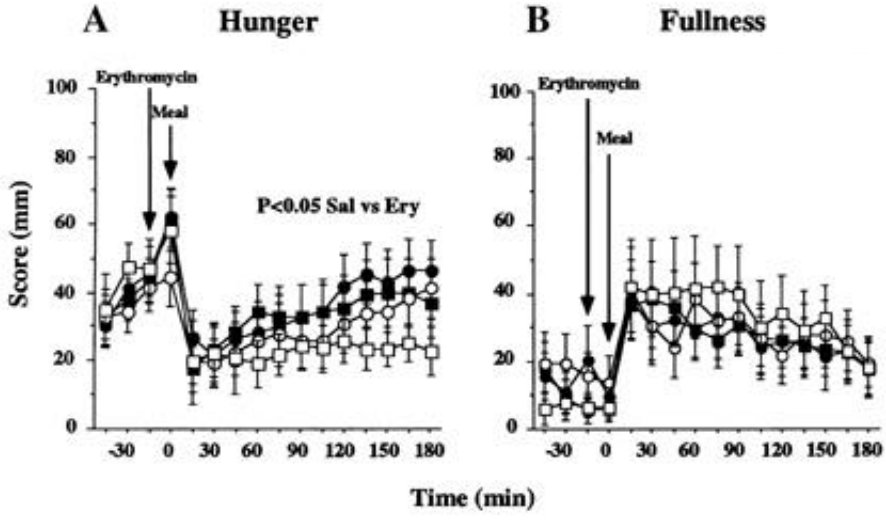

Figure 2—*Scores for hunger (A) and fullness (B) before and after meal ingestion for the four study days. Data are mean values ± SEM. ●, Eug/Ery (n = 10); ■, Hyper/Ery (n = 10); ○, Eug/Sal (n = 10); □, Hyper/Sal (n = 6).*

During both euglycemia and hyperglycemia, the retention in the distal stomach was less after erythromycin ($P < 0.05$).

Hunger and fullness

Hunger. There were no significant differences between the groups in the score for hunger before meal ingestion (Fig. 2*A*). Hunger decreased ($P < 0.0001$) after the meal on all study days. Hunger was less during hyperglycemia than euglycemia after administration of saline ($P < 0.05$), but not erythromycin. The score for hunger was greater after erythromycin on both study days when compared with saline ($P < 0.05$). There was no significant difference in the score for hunger on the Hyper/Ery study day when compared with control (Eug/Sal).

Fullness. Before ingestion of the meal, there were no differences in scores for fullness (Fig. 2*B*); fullness increased ($P < 0.0001$) after the meal on all study days. The mean score for fullness between 0 and 180 min was greater during hyperglycemia after administration of saline, but not erythromycin (Eug/Sal 28.0 ± 8.4 vs. Hyper/Sal 32.4 ± 11.1 mm; $P < 0.05$ and Eug/Ery 26.4 ± 8.0 vs. Hyper/Ery 26.6 ± 7.4 mm; NS).

CONCLUSIONS — We demonstrated in normal subjects that at a blood glucose concentration of ~15 mmol/l *1*) after administration of erythromycin (3 mg/kg i.v.), gastric emptying of a solid meal is much slower than during euglycemia; *2*) the effect of erythromycin on gastric emptying of a solid meal is attenuated; and *3*) the perception of postprandial hunger is reduced. Our study also suggests that erythromycin has the capacity to modulate the sensation of postprandial hunger.

The beneficial effect of intravenous erythromycin on gastric emptying in both normal subjects and patients with diabetes (23–25,40–42) is well established. The magnitude of the observed reduction in the lag phase and the acceleration of the postlag emptying of a solid meal by erythromycin during euglycemia are similar to that reported in previous studies in normal subjects (24,25). It has also been established that administration of erythromycin is associated with stimulation of high amplitude antral pressure waves (41,43,44), a reduction in the number of pressure waves localized to the pylorus (44) and an increase in proximal gastric tone (45). The use of erythromycin is known to be associated with the delivery of larger solid particles into the small intestine (46), as indicated by the reduction in the lag phase. In contrast to a previous study from our group (25), the increased postlag emptying rate observed in this study was not associated with a more rapid emptying from the proximal stomach, but with a reduced content of the distal stomach. This apparent discrepancy may reflect differences in the composition (941 vs. 550 kcal) and volume (730 vs. 450 ml) of the test meal between studies, particularly the nutrient content of the liquid component of the meal (25).

Marked hyperglycemia slows gastric emptying in both normal subjects (7,17) and patients with diabetes (6,18); the magnitude of the slowing of emptying during hyperglycemia that we observed is consistent with these previous studies. Marked hyperglycemia is known to be associated with the stimulation of pyloric motility (47), suppression of antral pressure waves (10), as well as a change in their organization (48), and a reduction in fundic tone (12,30). Our observation that the slowing of gastric emptying by hyperglycemia is associated with increased retention of the meal in the proximal stomach may be attributable to fundic relaxation (12,30).

Erythromycin stimulates gastrointestinal motility by acting as an agonist of the gastrointestinal hormone motilin; this may reflect direct activation of motilin receptors located on smooth muscle cells (49) and/or the stimulation of acetylcholine release from motilin receptors on cholinergic nerves (42,43,50). The latter mechanism is likely to be more important in humans (42). Our study has not addressed the mechanisms responsible for the effect of hyperglycemia on the gastrokinetic effect of erythromycin, but modifications in cholinergic activity or sensitivity to motilin are potentially important. In healthy subjects, hyperglycemia reduces plasma motilin (51) and suppresses secretion of pancreatic polypeptide; the latter effect is indicative of a reduction in vagal cholinergic activity (8). Exogenous administration of motilin has been shown to accelerate gastric emptying in patients with diabetic gastroparesis, but blood glucose concentrations were apparently not monitored (52). In the study by Janssens et al. (23), which established the marked effect of intravenous erythromycin (200 mg) on gastric emptying in diabetic gastroparesis, oral administration of erythromycin (250 mg t.i.d.) for 3 weeks had a lesser effect on gastric emptying. The effects of intravenous erythromycin were assessed when blood glucose concentrations were maintained in the euglycemic range (23); however, this was not the case for oral erythromycin (J. Janssens, personal communication). In view of our observations, evaluation of the effects of hyperglycemia on the motor effects of other prokinetic drugs, particularly those that are not motilin agonists, such as cisapride, domperidone, and metoclopramide, would be of interest. While it is appropriate to determine whether the effects of erythromycin on gastric emptying in patients with diabetes are modified by the blood glucose concentration, it is likely that the effects would be similar to those observed in normal subjects because the magnitude of the effects of hyperglycemia on gastric emptying in patients with diabetes is comparable to that observed in normal subjects (6,7,15,17,18). Our observations suggest that in evaluating the effects of prokinetic drugs in patients with diabetes, blood glucose concentrations should ideally be maintained in the euglycemic range; to date, this has been the case in only a few studies (23,53).

The factors that influence postprandial upper gastrointestinal sensations and appetite are poorly defined. Acute changes in the blood glucose concentration affect sensations arising from the gastrointestinal tract (9,12,14,16,21,31,35). In patients with type 1 diabetes, gastrointestinal symptoms occur more frequently in those patients with poor long-term glycemic control as assessed by the glycosylated hemoglobin concentration (29). The mechanisms mediating the effects of the blood glucose concentration on gastrointestinal sensation are unknown. In this study, we have demonstrated that marked hyperglycemia reduced postprandial hunger in normal subjects. These observations are consistent with a previous study in patients with type 1 diabetes (31) and may potentially relate to an increase in intragastric volume caused by slowing of gastric emptying (6,7,15,17,18). It is, however, of interest that both pre- and postprandial fullness have been reported to be increased in hyperglycemic patients with type 2 diabetes when compared with age-matched normal volunteers, although in this study there was little difference in gastric emptying between the two groups (35). It should be recognized that the symptomatic response to prokinetic therapy is also likely to be dependent on factors that are not related directly to the blood glucose concentration. For example,

Camilleri et al. (54) have reported that patients with extrinsic vagal damage are less likely to respond.

The sensation of postprandial hunger was greater after erythromycin during both euglycemia and hyperglycemia. Furthermore, an effect of hyperglycemia on postprandial hunger was not evident after administration of erythromycin. These observations are unlikely to be attributable to differences in intragastric volume, since erythromycin had little effect on gastric emptying during hyperglycemia. Previous studies of the effects of prokinetic therapy on gastrointestinal symptoms in patients with diabetes have not considered the potential impact of the blood glucose concentration. Recent studies also indicate that prokinetic agents such as cisapride (55) and erythromycin (36) may alter gastrointestinal sensation by mechanisms unrelated to gastric emptying. For example, we have reported in normal subjects that cisapride increased preprandial hunger and reduced the satiating effect of a meal containing discrete oil and aqueous components (55), and more recently, it has been reported in abstract form that intravenous erythromycin (200 mg) increases the threshold perception of discomfort during proximal gastric distention (36).

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