Erythromycin Derivative Improves Gastric Emptying and Insulin Requirement in Diabetic Patients With Gastroparesis

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OBJECTIVE — To evaluate the effect of the erythromycin derivative EM523L on gastric emptying and postprandial insulin requirement in insulin-dependent diabetic patients with severe gastroparesis.

RESEARCH DESIGN AND METHODS — In six IDDM patients with severe gastroparesis (two men and four women, mean age 44.5 years [range 36–53]), the insulin infusion pattern during feedback control with an artificial endocrine pancreas device (Biostator) after intake of a test meal, the retention rate of residual isotope (^{99m}Tc-labelled Sn-colloid) in the stomach, and the time-concentration curve of plasma acetaminophen as the marker for liquid emptying were studied with EM523L or a control placebo

RESULTS — Time courses of insulin infusion rates peaked within 120 min after intake of the test meal in the EM523L phase, whereas no apparent peak rates were observed in the control phase. The total amount of insulin required in the first 90 min postprandial was significantly greater in the EM523L phase than in the control phase. EM523L significantly decreased the residual isotope ratio in the stomach at ≥50 min postprandial and increased the plasma acetaminophen concentrations at 30–120 min postprandial, compared with respective values in the control phase.

CONCLUSIONS — Preliminary results obtained from a small number of patients suggest that EM523L or erythromycin analogs, which have agonistic activity to motilin receptors as well as no antibacterial effect, may be useful to accelerate gastric emptying and improve insulin requirement patterns, thereby establishing more stable glycemic control.

Impaired gastric motility or gastroparesis is not rare in patients with long-standing diabetes (1). Gastroparesis is an important factor in causing unstable glycemic control in insulin-treated diabetic patients because of the discrepancy between onset of insulin action and release of nutrients into the intestines. In fact, an altered time course of postprandial glucose levels and insulin requirement patterns has been shown in IDDM patients with gastroparesis (2).

The pathogenesis of gastroparesis is not yet fully understood. Metoclopramide (3–5), domperidone (6), dopamine D2-receptor antagonists, and cisapride (7–9), the last of which probably enhances acetylcholine release at the myenteric plexus, have been used to reduce upper gastrointestinal symptoms associated with gastroparesis. Nevertheless, the treatment of this condition is difficult, and the efficacy of these prokinetic agents has often been disappointing. Recent evidence suggests that motilin, a 22–amino acid gastrokinetic peptide, is effective in accelerating gastric emptying in diabetic patients with gastroparesis (10,11). Similarly, erythromycin, a macrolide agent with agonistic activity to motilin receptors, has been suggested to have a gastrokinetic effect (12,13). Janssens et al. (12) demonstrated that erythromycin can shorten the prolonged gastric-emptying time. However, it is still unclear whether long-term use of erythromycin, an antibiotic drug, in relatively large doses would be entirely without harmful side effects. For example, prolonged use may cause some antibiotic-resistant organisms. Increased interest has therefore been focused on erythromycin analogs as possible candidate drugs for treatment of gastroparesis.

The erythromycin derivative EM523L (Shimizu Pharmaceutical, Tokyo, Japan) is a potent agonist to motilin receptors (i.e., ~18 times more potent than erythromycin) and has virtually no antibiotic action (14–18). This study was designed to assess the effects of EM523L on gastric emptying of both solid and liquid test meals and on postprandial insulin requirement in IDDM patients with severe gastroparesis.

RESEARCH DESIGN AND METHODS

Patients

We studied six IDDM patients with gastroparesis (two men and four women, mean age 44.5 years [range 36–53]) after informed consent was obtained from each patient. All patients had diabetic autonomic neuropathy and peripheral neuropathy, such as orthostatic hypotension and paresthesia in the lower extremities. Gastroparesis was diagnosed by endoscopic observation of food residues in the stomach after a 12-h overnight fast. Patients with other types of organic or treatment-requiring gastropathy were not included in the study. None of the study patients were under any pharmacological treatment that would affect gastric motility and/or emptying. The patients refrained

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Table 1—*Clinical characteristics of patients*

Patient	Age (years)	Sex	BMI (kg/m²)	Diabetes duration (years)	Retinopathy	HbA_{1c} (%)	Serum creatinine (μmol/l)
1	50	F	23.5	17	Proliferative	8.2	159
2	40	F	17.2	16	Proliferative	6.3	194
3	40	M	18.7	17	Proliferative	8.1	80
4	53	F	21.1	40	Proliferative	10.3	150
5	36	M	24.4	10	Proliferative	7.2	274
6	43	F	17.9	16	Proliferative	7.6	97

from smoking and strenuous physical exercise for at least 24 h before the study. Clinical characteristics of the patients are summarized in Table 1.

Protocol and measurements

The effects of EM523L on gastric emptying and insulin requirement patterns (EM523L phase) and control placebo (control phase) were tested in an open study on two separate days with at least a 1-month interval between the tests. The assessment of postprandial insulin requirement and of liquid and solid gastric emptying was made according to a method described previously (2).

Briefly, the patients were connected to an artificial endocrine pancreas device (Biostator, Life Science Instruments, Miles, Elkhart, IN) at 0600 after an overnight fast. After a standardized test meal, the study started at 0900 after stabilization of the plasma glucose level in each patient. The postprandial insulin required to maintain the plasma glucose level at 5.0–6.0 mmol/l was evaluated for 180 min during feedback control with a Biostator (19). The patients received an intravenous infusion of EM523L (0.13 mg/min) dissolved in saline or a saline placebo dose over a 30-min period 15 min after intake of the test meal (15–45 min postprandial). The standardized test meal (2.6 MJ; 60 g carbohydrate, 28 g protein, and 30 g fat) was composed of solid and liquid parts: 100 g of scrambled eggs containing 37 MBq (1.0 MCi) of ^{99m}Tc-labelled Sn-colloid and 8 g of butter served with two slices of bread as a solid meal (12), and 250 ml of milk containing 20 mg/kg of acetaminophen as a liquid meal (20). After the patient consumed the test meal, scintigraphic images of the anterior abdomen were then collected by the physiological decay of the ^{99m}Tc. The time course of the ratio of each count to the maximum count obtained was used as the marker of solid emptying (12). In the same study, blood samples for the measurement of plasma acetaminophen concentration (21) were collected before and at 15, 30, 45, 60, 120, and 180 min after the test meal intake. The time course of plasma acetaminophen concentration was used as the marker of liquid emptying (22).

The results were analyzed by analysis of variance (ANOVA) with post hoc test. Data are expressed as means ± SE, and a P value <0.05 was considered to be significant.

RESULTS — Time courses of insulin infusion rates in the EM523L and control phases are shown in Fig. 1. After the test meal intake, no apparent peak rates were found in the control phase while the peak rates were observed within 120 min in the EM523L phase. The total amount of insulin to maintain the target plasma glucose level during the first 90 min (0–90 min postprandial) increased significantly with EM523L (from 2,652 ± 862 mU to 5,598 ± 459 mU). The total amount of insulin required during the following 90 min (90–180 min postprandial) was slightly but not significantly greater in the EM523L phase (2,268 ± 343 mU) as compared with the control phase (1,125 ± 459 mU).

The time courses of the residual isotope ratio after the test meal and the time-concentration curves for plasma acetaminophen are shown in Figs. 2 and 3, respectively. EM523L significantly decreased the residual isotope ratio in the stomach ≥50 min after the test meal intake, compared with that in the control phase. Similarly, EM523L significantly increased the plasma acetaminophen concentrations at 30–120 min postprandial. The plasma acetaminophen concentration at 45 min was 4.3 ± 0.7 μg/ml in the control phase and 9.1 ± 2.0 μg/ml in the EM523L phase, respectively.

CONCLUSIONS — We observed that 30-min intravenous administration of EM523L, an erythromycin derivative, changed the postprandial insulin requirement pattern in gastroparetic IDDM patients; however, the number of study patients might be too small to draw a conclusion. This drug-induced change to a more physiological pattern of insulin requirement can be explained by the drug-induced acceleration of gastric emptying,

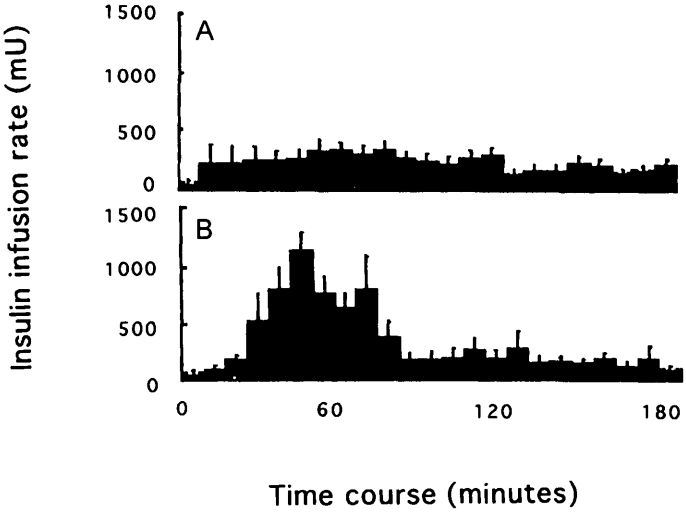

Figure 1—*Insulin infusion rates during feedback control with Biostator after test meals in six gastroparetic IDDM patients. The patients received an intravenous infusion of saline placebo* (A) *and EM523L (0.13 mg/min)* (B) *on 2 separate days. Data are shown as means ± SE.*

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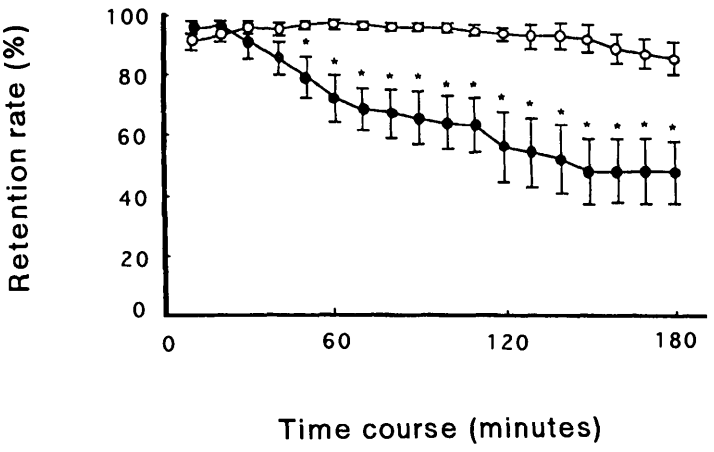

Figure 2—*Retention rate of ^{99m}Tc in the stomach after the test meal intake as a marker of solid emptying in the placebo (○) and EM523L (●) phases, respectively. Data are means ± SE; *P < 0.05.*

which shortened the time of propulsion of ingested food from the stomach into the duodenum. This assumption can be further strengthened by our previous observation that administration of EM523L caused a quicker rise in postprandial plasma glucose level after the intake of a test meal in gastroparetic IDDM patients (23). EM523L seems to be effective in accelerating gastric emptying of both solid and liquid parts of a meal, because the rate of the isotope remaining in the stomach, used as the marker for solid emptying, and the time course of plasma acetaminophen, used as the marker for liquid emptying, both improved with EM523L administration. Fraser et al. (24) have recently demonstrated that hyperglycemia itself may slow gastric emptying in IDDM patients, implying that glycemic status during the study is another factor influencing the results. In our study, plasma glucose levels were kept constant by using Biostator to exclude this possibility. Another plausible influencing factor is the kidney function of the patients. The difference in the degree of renal insufficiency in our study subjects might have influenced the pharmacokinetics of the drug, although we did not measure the plasma EM523L concentrations. Nevertheless, this is likely not the case, since the renal excretion rates of EM523L and its three major metabolites are relatively small (9.7, 0.9, 1.2, and 0.7 %, respectively; H. Toyoda, J.C. Cyong, K. Kodama, A. Yafune, S. Miyagawa, N. Suzuki, N. Furugen, K. Suzuki, T. Suzuki, unpublished observations).

Our results with EM523L are in accordance with the erythromycin observations by Janssens et al. (12). They show that an intravenous infusion and a 4-week oral administration of erythromycin improved gastric emptying in patients with gastroparesis. The time lag between postprandial insulin requirement in gastroparetic IDDM patients and absorption and action of insulin from subcutaneous injection is a cause of unstable plasma glucose levels and unwanted hypoglycemia. The present results suggest that EM523L (and erythromycin as well, presumably) can improve postprandial insulin requirement by stimulating gastric emptying, effects considered clinically beneficial for patients.

The gastrokinetic action of EM523L is considered to be mediated through the stimulation of motilin receptors on gastrointestinal smooth muscle (14–18), as reported with erythromycin. Motilin receptors are mainly confined to the gastric antrum and proximal duodenum, and physiological doses of motilin have been shown to stimulate interdigestive gastric motility. Meanwhile, Kawamura et al. (17) reported an increase in plasma motilin concentration after administration of EM523L in nondiabetic humans, suggesting that motilin itself may be partially involved in the mechanism.

Diabetic gastroparesis is often associated with severe autonomic neuropathy (9,25,28) and is the cause of poor quality of life for patients because of uncomfortable upper gastrointestinal symptoms such as nausea, vomiting, and abdominal distention. A defect of the autonomic innervation of the gastrointestinal tract has been proposed to be the underlying cause of the disorder (25–28); however, the precise mechanism of the condition has not yet been elucidated. Plasma motilin levels in gastroparetic diabetic patients are reported to be slightly elevated within normal cyclic fluctuation (9,29,30), but the role of endogenous motilin in the pathogenesis of diabetic gastroparesis is, as yet, inconclusive. Metoclopramide (3–5), domperidone (6), and cisapride (7–9) have a prokinetic property to accelerate gastric emptying and are reported to be effective in reducing the upper gastrointestinal symptoms, but often to an unsatisfactory extent. In the present study, EM523L was effective in shortening both the liquid and solid emptying time and in improving the insulin requirement in severe gastroparetic IDDM patients. These preliminary results obtained from a small number of patients suggest that EM523L or erythromycin analogs may be useful for future treatment of severe gastroparesis in diabetic patients. Nevertheless, the results obtained from this study should be viewed as a preliminary basis for future investigations until such studies ascertain the beneficial effect and therapeutic value of this class of agents in diabetic patients with gastroparesis.

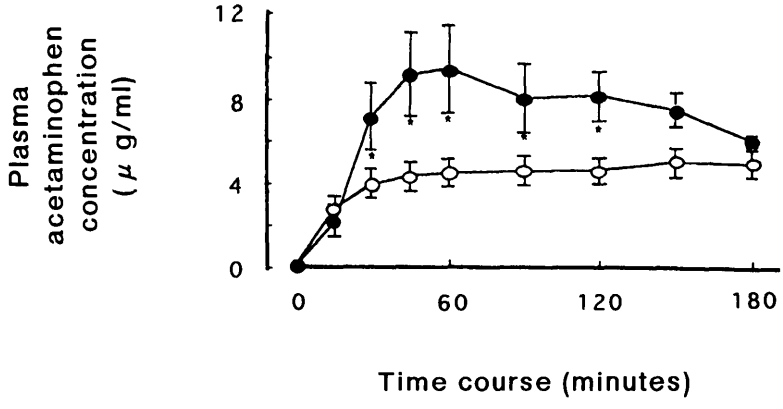

Figure 3—*Time-concentration curves for plasma acetaminophen after the test meal intake as a marker of liquid emptying in the placebo (○) and EM523L (●) phases, respectively. Data are means ± SE; *P < 0.05.*

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