

Comparison of Metoclopramide and Erythromycin in the Treatment of Diabetic Gastroparesis

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OBJECTIVE— To compare the effects of erythromycin and metoclopramide on gastric emptying and symptoms of gastroparesis in diabetic patients with delayed gastric emptying.

RESEARCH DESIGN AND METHODS— The study group consisted of 13 patients with symptoms of severe gastroparesis and delayed gastric emptying. Gastric emptying was evaluated using a radionuclide method, and gastrointestinal symptoms were scored. The patients were given either erythromycin (250 mg 3 times/day) or metoclopramide (10 mg 3 times/day) in random order for 3 wk, and after a washout period of 3 wk they were crossed-over to the other medication for another 3 wk. Parameters of gastric emptying were assessed before treatment and after both erythromycin and metoclopramide administration.

RESULTS— The half-time of gastric emptying in diabetic subjects was 110 (77–120) min before treatment. At 60 and 90 min, the median value of residual isotope activity was 66.5 (55–83.5) and 55% (43–74.3), respectively. The half-time decreased to 55 min (28.6–115) after 3 wk of treatment with erythromycin and percentages of meal retention in the stomach at 60 and 90 min were 49.9 (38.4–70) and 40.5% (29.7–60), respectively. After taking metoclopramide, the median value of half-time was 67 min (15–115) and percentages of meal retention at 60 and 90 min were 51 (34.5–93.9) and 42% (24–71.2), respectively. When compared with baseline values a significant difference in gastric emptying parameters was found after both erythromycin and metoclopramide. A significant improvement of the total score for gastrointestinal symptoms was observed with both drugs, but this improvement was more pronounced with erythromycin.

CONCLUSIONS— Erythromycin, a macrolide antibiotic and a motilin receptor agonist, appears to stimulate intestinal motility and seems to be an alternative agent for the treatment of gastroparesis caused by diabetic autonomic neuropathy.

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T1/2, half-time; ROI, region of interest; TAC, time activity curve; type I diabetes, insulin-dependent diabetes mellitus.

Gastroparesis diabeticorum is a serious and well-known condition that delays gastric emptying in patients with long-standing diabetes mellitus (1). The most effective approach to the treatment of gastroparesis is the use of drugs designed to increase the rate of gastric emptying by facilitating gastroduodenal motility (2,3). Although metoclopramide is an effective drug in the treatment of gastroparesis diabeticorum, evidence has been found that chronic oral administration of metoclopramide may result in a loss of the gastrokinetic properties of this drug (4). Recently, studies have shown that erythromycin stimulates gastrointestinal motor activity (5,6) and that it accelerates gastric emptying in patients with diabetic gastroparesis (7).

This single-blind, cross-over study was specifically designed to compare the effects of erythromycin and metoclopramide on gastric emptying and symptoms of gastroparesis in diabetic patients with delayed gastric emptying.

RESEARCH DESIGN AND METHODS

Thirteen patients with severe symptoms of gastroparesis and delayed gastric emptying were included in this study. Of the patients, 9 were being treated with insulin and 4 were receiving oral hypoglycemic agents. All were nonsmokers and were not taking drugs likely to interfere with gastrointestinal motility. None had a history of gastric surgery. Each patient gave informed consent before entering the study. Of these patients, 6 had peripheral neuropathy, 8 had cardiac autonomic neuropathy, 3 had diabetic nephropathy, and 3 had retinopathy.

After entering the study, each patient was given a standard questionnaire for symptoms of gastric retention, nausea, vomiting, abdominal pain, abdominal bloating, early satiety, diarrhea, constipation, and anorexia. The symptoms were graded as not present (0), mild (1), moderate (2), or severe (3), according to

Table 1—Characteristics of diabetic patients examined for gastric emptying

Patient characteristics	
Sex	
Female	9
Male	4
Diabetes type	
Type 1	5
Type 2	8
Age (yr)	46.5 ± 16.3 (19–68)
Duration of diabetes (yr)	10 (1–21)*
BMI (kg/m ²)	25.3 ± 4.4 (20.2–35.4)
Insulin dose (U/day)	46.0 ± 9.4 (28–62)
BUN (mM)	6.4 ± 2.5 (2.8–12.1)
Creatinine (μM)	88.4 (53–150)*
Creatinine clearance (ml/s)	1.1 (0.32–1.08)*
Microalbuminuria (mg/day)	10.6 (6–350)*

Data are means ± SD.

*Median and range values are given (nonhomogen distribution).

Horowitz et al (8). The maximum possible total score was 24 for gastric symptoms.

Gastric emptying

A semisolid gastric emptying study was performed after an overnight fast (9–11). The test meal, which consisted of 1 egg, 2 slices of bread, 25 g of cheese, and 200 ml of milk containing 2 mCi of ^{99m}Tc-DTPA, was ingested. Immediately after finishing the meal, each patient was positioned supine under a single-head γ -camera (Toshiba GCA-501, Tokyo, Japan) equipped with a low-energy, all purpose, parallel hole collimator. Sixty sequential images (each 2 min) were recorded for 120 min with a matrix size of 64 × 64. The gastric region was drawn using ROI, and the TAC of ROI was obtained. Using the monoexponential analysis of the TAC, the T1/2 and the amount of radioactivity remaining in the stomach at 60 and 90 min were calculated.

In our laboratory a normal range (mean T1/2 55 ± 10 min) for gastric emptying has been obtained with an identical test meal in normal volunteer subjects. A value >2 SD above the mean of this group was accepted as delayed gastric emptying.

The patients were randomly assigned to receive either metoclopramide (10 mg 3 times/day) or erythromycin (250 mg 3 times/day), 30 min before each meal. Each medication was taken for 3 wk. After a 3-wk washout period, patients taking metoclopramide were given erythromycin and vice versa for another 3 wk. Patients were seen each week to review their clinical status and discuss any side effects. Medication compliance was assessed by counting the number of tablets returned. The patients had taken 99.4% of the prescribed tablets.

The gastric emptying test was repeated after each treatment period while the patients continued to take the medications, and gastrointestinal symptom scores were recorded again at these times.

GHb, fasting, and postprandial blood glucose concentrations were measured in each patient before and during each treatment period. GHb was measured by the liquid chromatography method and blood glucoses were determined by the glucose oxidase method.

Statistical analysis

The results were expressed as median (range) and means ± SD. The signifi-

cance of the results was tested using the Kruskal-Wallis analysis. $P < 0.05$ was considered significant (12).

RESULTS— Characteristics of diabetic patients examined for gastric emptying are summarized in Table 1. In the pre-treatment period, the median value of gastric emptying was 110 min (77–120). At 60 and 90 min the residual activity was 66.5 (15–115) and 55% (43–74.5). The median score for gastric symptoms was 8 (2–11). Table 2 shows gastric emptying in patients with diabetes before therapy and also after metoclopramide and erythromycin treatment. A significant improvement was observed in gastric emptying T1/2 and meal retention percentages at 60 and 90 min following both erythromycin and metoclopramide treatments. Yet no significant difference was found between the effects of erythromycin and metoclopramide.

After erythromycin and metoclopramide treatment, a significant improvement was detected in the total score for gastrointestinal symptoms. The symptom score calculated after 3 wk of erythromycin therapy (2 [0–5]) was significantly less ($P < 0.05$) than the post-metoclopramide therapy score of 3 (0–11).

Although no serious side effects caused by metoclopramide were observed, 2 patients complained of weakness, sedation, and leg cramps. Another patient had palpitation, and 1 other had drowsiness. None of the subjects reported side effects after erythromycin.

CONCLUSIONS— Of the patients with diabetes, ~50% have delayed gastric emptying, which is the most sensitive indicator of gastric motor dysfunction in diabetes mellitus (8). Metoclopramide was the first drug introduced for the treatment of diabetic gastroparesis. Given on a chronic basis, it will reduce symptoms of stasis such as bloating, early satiety, nausea, and vomiting. Although metoclopramide shortens the gastric emptying rate effectively, tol-

Table 2—Effects of oral administration of metoclopramide and erythromycin on gastric emptying in gastroparetic patients with diabetes

Number	Symptom			T1/2(min)			60 min (%)			90 min (%)		
	B	M	E	B	M	E	B	M	E	B	M	E
1*	10	7	2	77.2	40.0	53.0	67.7	35.8	49.0	46.9	25.4	40.5
2*	2	0	0	120	15.0	55.0	66.5	34.5	49.9	60.5	25.9	34.6
3	5	—	5	100	—	80.0	68.9	—	65.0	59.9	—	45.0
4	11	2	4	120	100	82.5	83.5	93.9	63.9	74.3	71.2	49.7
5*	9	2	1	120	42.0	84.0	65.0	38.0	68.0	52.5	24.0	45.0
6*	7	6	3	78.3	110	48.7	62.9	63.0	45.2	43.0	56.0	29.7
7	7	3	3	110	80.0	88.0	66.6	60.0	62.3	60.9	40.0	49.0
8	5	5	2	77.0	67.0	49.0	60.0	51.0	44.5	46.6	42.0	36.7
9	8	2	2	108	115	115	61.5	73.3	70.0	55.0	60.0	60.0
10*	8	6	0	120	100	88.0	70.0	62.8	66.6	64.4	56.7	50.0
11	5	2	0	120	60.0	40.0	75.0	50.0	42.3	70.0	42.2	32.0
12	11	11	—	95.0	40.0	50.0	61.6	39.4	44.4	53.4	28.5	33.8
13	6	—	1	78.0	—	28.6	55.0	—	38.4	49.0	—	30.0
Median	8	3	2	110	67	55	66.5	51	49.9	55	42	40.5
Range	2–11	0–11	0–5	77–120	5–115	28–115	55–83.5	34.5–93.9	38.4–70	43–74.3	24–71.2	29.7–60

B, Baseline; M, Metoclopramide; and E, Erythromycin.

*Patients with type I diabetes.

erance to its action may develop during long-term use (4). Perhaps the failure to respond to chronic administration of the drug reflects receptor downregulation or depletion of neural cholinergic stores.

Janssens et al. (7) studied the effect of erythromycin on gastric emptying in 10 patients with type I diabetes and gastroparesis. They found that erythromycin acutely and markedly improves impaired gastric emptying in patients with severe diabetic gastroparesis, and the drug is active when given orally for 4 wk (7).

In this study, which compares the effect of metoclopramide and erythromycin stearate on diabetic gastroparesis for the first time, the gastric emptying rate of semisolid food was used as an index of gastric function. In support of previous clinical studies, both agents were found to have strong and similar gastrokinetic effects. Gastric emptying is modified by blood glucose control, and acute hyperglycemia slows gastric emptying in diabetic patients (13). Because no change was indicated in blood glucose levels during our study (data not

shown), the beneficial effects of both agents can not be attributed to better glycemic control. Furthermore, erythromycin was more effective in ameliorating the symptoms of gastric stasis than metoclopramide. Side effects, such as weakness, drowsiness, cramps, and tachycardia, were observed in 30% of our patients given metoclopramide, whereas the incidence in the literature is ~10–20%. Side effects were not noted with erythromycin.

In conclusion, although erythromycin has been given for only 3 wk, it seems to be an alternative to metoclopramide in the treatment of diabetic gastroparesis, especially since it provides greater symptomatic relief.

References

1. Kassander P: Asymptomatic gastric retention in diabetics (gastroparesis diabetorum). *Ann Intern Med* 48:797–812, 1958
2. McCallum RW: Review of current status of prokinetic agents in gastroenterology. *Am J Gastroenterol* 80:1008–16, 1985
3. Reynolds JC: Prokinetic agents: a key in the future of gastroenterology. *Gastro Clin North Am* 18:437–56, 1989
4. Schade RR, Dugas MC, Lhotsky DM, Gavaler JS, Van Thiel DM: Effect of metoclopramide on gastric liquid emptying in patients with diabetic gastroparesis. *Dig Dis Sci* 30:10–15, 1985
5. Itoh Z, Nakaya M, Suzuki T, Arai H, Wakabayashi K: Erythromycin mimics exogenous motilin in gastrointestinal contractile activity in the dog. *Am J Physiol* 247:688–94, 1984
6. Otterson MF, Sama SK: Gastrointestinal motor effects of erythromycin. *Am J Physiol* 259:355–63, 1990
7. Janssens J, Peeters TL, Vantrappen G, Tack J, Urbain JL, De Roo M, Muls E, Bouillon R: Improvement in gastric emptying in diabetic gastroparesis by erythromycin. *New Engl J Med* 322:1028–31, 1990
8. Horowitz M, Maddox AF, Wishart JM, Harding PE, Chatterton BE, Shearman DJC: Relationship between oesophageal transit and solid and liquid gastric emptying in diabetes mellitus. *Eur J Nucl Med* 18:229–34, 1991
9. Chaudhuri TK: Use of Tc-DTPA for measuring gastric emptying time. *J Nucl Med* 15:391–95, 1974

10. Rocha AFG, Zuccaro AM, Marquiotti M: Relationship between severity of clinical symptoms and delay in gastric emptying in chronic gastritis: studied with ^{99m}Tc -DTPA scintigraphy. *Eur J Nucl Med* 12: 91–95, 1986
11. Corinaldesi R, Stanghellini Y, Calamelli R, Salgemini R, Zarabini GE, Barbara L: Validation of radioisotopic labelling techniques in gastric emptying studies. *J Nucl Med Allied Sci* 31:207–12, 1987
12. Conover WJ: *Practical Nonparametric Statistics* 2nd ed. New York, John Wiley, 1980
13. Fraser RJ, Horowitz M, Maddox AF, Harding PE, Chatterton BE, Dent J: Hyperglycaemia slows gastric emptying in type I (insulin-dependent) diabetes mellitus. *Diabetologia* 33:675–80, 1990