

Metoclopramide Therapy in Patients with Delayed Gastric Emptying

A Randomized, Double-Blind Study

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Twenty-eight patients with delayed gastric emptying as measured by an abnormal barium "burger" were treated with metoclopramide in a randomized, double-blind fashion. Five had diabetic gastroparesis, four had undergone vagotomy and pyloroplasty, and 19 were idiopathic. Patients received either metoclopramide or placebo for a three-week period and symptoms were scored prestudy, at weekly intervals, and at termination of the study. Ten of 14 patients on metoclopramide and four of 14 on placebo decreased their symptom score to a level below entry criteria, indicating a significant metoclopramide effect when compared to placebo. The mean total symptom score for the metoclopramide group was 18.4 prestudy and 7.2 poststudy while for placebo was 19.1 prestudy and 12.9 poststudy. Although improvement on placebo was significant, these patients were still symptomatic. The improvement on metoclopramide was significantly greater than the improvement on placebo. Metoclopramide is an effective agent in treating the symptom complex of delayed gastric emptying.

Inadequate gastric emptying of a solid meal may result in the symptom complex of nausea, vomiting, postprandial bloating, and early satiety. The vomitus often contains food ingested many hours earlier. Gastric outlet obstruction must be excluded by standard radiologic and endoscopic studies. The diagnosis of delayed gastric emptying is confirmed by demonstrating impaired emptying of a solid meal with either the "barium burger" test or by isotope studies showing prolonged gastric clearance of a test radionuclide.

Gastric atony may occur in patients with the autonomic neuropathy of diabetes mellitus and following gastric surgical procedures. These symp-

toms may also follow the use of drugs which retard gastric emptying, particularly those with anticholinergic properties. In addition, there is a group of patients with the symptoms and objective findings of gastric atony without an apparent predisposing cause, the idiopathic group. Therapy has been directed to the control of symptoms, mainly by the use of centrally acting antiemetics. Gastric stimulation with a cholinergic agent such as bethanechol (Urecholine) has also been tried. Metoclopramide, a derivative of procaine amide which has a central antiemetic effect, has been shown to enhance gastric emptying (1). This paper reports the effect of metoclopramide evaluated in a double-blind, randomized study of patients with the syndrome of delayed gastric emptying.

MATERIALS AND METHODS

The protocol for this study was reviewed and approved by the Human Investigations Committee of Emory University School of Medicine on February 7, 1975.

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Study Design. Twenty-eight patients with nonresected stomachs and the symptom complex of delayed gastric emptying participated in the study. All patients had an abnormal roentgenographic barium "burger" study with retention of food and barium beyond 6 hr (2). None were on medications known to retard gastric emptying, such as those with anticholinergic properties or narcotic analgesics. Gastric outlet obstruction was excluded by upper endoscopy and standard upper-gastrointestinal series. Each patient was asked to grade the following symptoms: meal tolerance, epigastric pain, postprandial bloating, heartburn, belching and regurgitation, nausea, vomiting, anorexia, and early satiety. Each symptom was graded as follows: 0 = none or not at all; 1 = slight, occasional; 2 = moderate, often but not all the time; 3 = marked, occurs quite frequently; 4 = extreme, severe, almost constant. A total symptom score of greater than six was required for entry into the study.

After obtaining an informed consent, each patient was randomized in a double-blind manner to receive either metoclopramide, 10 mg, or placebo orally four times daily for three weeks. Each patient maintained a diary and returned for weekly follow-up visits. Symptoms were re-scored at each visit and at the end of the study. The scoring for all patients was done by the same investigator (M.P.).

Patient Population. The study group consisted of 24 females and four males. The mean age was 43.9 years (range 22-67). Five patients had diabetic gastroparesis, four had undergone vagotomy and pyloroplasty, and 19 had idiopathic atony. Duration of symptoms ranged from three months to 38 years (mean 4.6 years). The post-vagotomy patients had been symptomatic for at least six months prior to entry into the study. Four of the diabetics were insulin dependent; all five had postural heart rate and blood pressure changes. Three of these had evidence of renal disease.

The idiopathic group included four women under 30 years of age whose symptoms began following an apparent viral illness. They had been symptomatic from three months to one year before entering the study. Other associated medical illnesses in the idiopathic group included two patients with scleroderma variant (esophageal motility disorder and Raynaud's phenomena), one with early rheumatoid arthritis, six with gastritis, and one each with healed gastric ulcer, uremia, reactive hypoglycemia, and postcholecystectomy and hiatal herniorrhaphy.

Barium Burger: After an overnight fast the patient ingested an egg sandwich which contained one scrambled egg and two strips of bacon followed by eight ounces of barium. Supine films of the abdomen were obtained after ingestion of the meal and at 2, 4, and 6 hr. Retention of food and barium on the 6-hr film was considered abnormal (2). Seven asymptomatic controls were studied, and emptying was complete by 4 hr in five, and by 6 hr in the other two.

RESULTS

Fourteen patients received metoclopramide and 14 received placebo. The mean total symptom score prestudy for the metoclopramide group was 18.4

and for the placebo group was 19.1. There was no statistically significant difference between the total symptom score prestudy for the two groups ($P > 0.10$, Wilcoxon two-sample rank statistic).

The mean total symptom score poststudy was 7.2 for the metoclopramide group, and 12.9 for the placebo group. The total symptom scores pre- and poststudy in patients receiving placebo were compared, and a statistically significant effect of placebo therapy was found ($P < 0.01$, Wilcoxon signed-rank test). The total symptom scores pre- and post-study were examined in patients receiving metoclopramide; a statistically significant effect of metoclopramide was also noted ($P < 0.01$).

The effect of metoclopramide compared to the effect of placebo was also analyzed. Ten of 14 patients on metoclopramide decreased their symptom score to a level below entry criteria (Figure 1). Four of 14 patients on placebo decreased their symptom score to less than or equal to 6. Using Fisher's exact test, there is a statistically significant improvement of symptoms in the patients on metoclopramide when compared to those on placebo ($P = 0.0285$). In addition, when the difference between pre- and poststudy scores for the placebo group was compared to that for the metoclopramide group, there was a statistically significant metoclopramide effect beyond the placebo effect ($P < 0.05$ Wilcoxon two-sample rank statistic).

The mean symptom scores for the individual symptoms before and after study are diagrammed in Figure 2. The number of points on the symptom scale were too few to permit adequate discrimina-

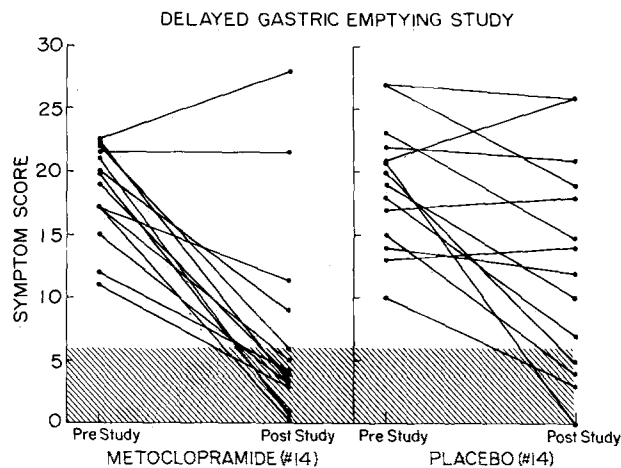


Fig 1. Total symptom scores pre- and poststudy for the patients on metoclopramide and placebo. A score of six or above was required for entry into the study.

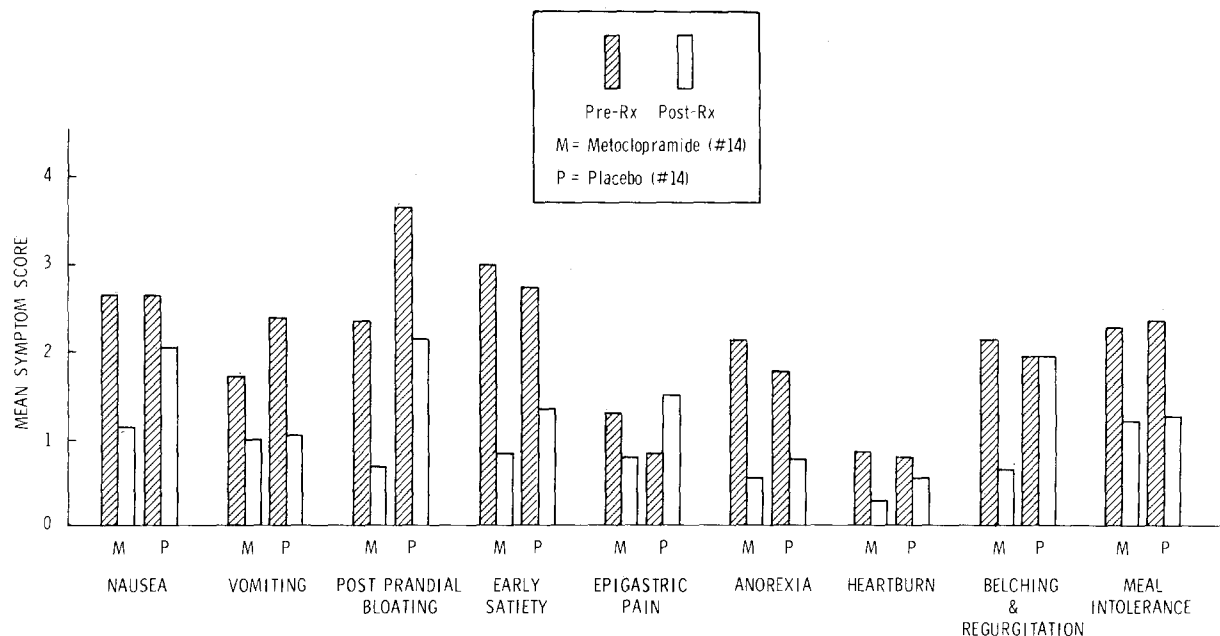


Fig 2. Mean pre- and poststudy symptom scores for individual symptoms for patients on metoclopramide and placebo.

tion of the changes statistically. However, the symptoms of nausea, postprandial bloating, and early satiety all showed greater improvement on metoclopramide.

Side Effects. Restlessness, with an uncomfortable feeling in the arms and legs, occurred in four patients on metoclopramide. Dose reduction eliminated this symptom in three patients while one required withdrawal from the study. One patient in the placebo group reported mild restlessness. No other side effects were recorded.

DISCUSSION

Recent studies have demonstrated that liquids and solids are handled in different ways by the stomach; liquid emptying is regulated primarily by the body of the stomach whereas the contractions of the antrum regulate emptying of solids (3). Patients with delayed gastric emptying may empty liquids adequately, and therefore they may have a normal standard upper-gastrointestinal radiologic study. Often patients with atony are labeled as having functional disease. Diagnosis may not be made for long periods of time as evidenced by seven of our patients who had symptoms for more than five years. The importance of evaluating the gastric emptying of solids in the presence of the aforementioned symptom complex and the absence of

gastric outlet obstruction must be emphasized. When the physiologic abnormality is properly identified, specific therapy can then be undertaken.

The idiopathic group was identified only after gastric emptying of a solid meal was studied. In four patients with atony, an apparent viral illness antedated their gastrointestinal symptoms. In a recent study (4), a transient delay of gastric emptying of liquids was demonstrated when nonbacterial gastroenteritis was induced in normal volunteers. Thus a viral etiology may be responsible for this syndrome in some of our patients in the idiopathic group.

Antiemetic therapy may not improve these patients' symptoms. In uncontrolled studies, bethanechol, a cholinergic agent, was shown to alleviate the symptoms of gastric atony in patients with prior gastric surgery (5, 6). These studies included patients who were symptomatic both in the immediate (5) and long-term (6) postoperative periods.

Metoclopramide has a central antiemetic effect (1) and also increases the amplitude of antral contractions (7), increases the intraluminal gastric pressure (8), and coordinates antral duodenal contractions (7, 8). In dogs, this increased antral motility has been shown to be blocked by pretreatment with atropine (9). Metoclopramide increases gastric motor activity in patients with diabetic gastroparesis and postvagotomy stasis (10). It has been

shown to improve the gastric emptying of the water test meal (11) and solid test meal (12-14). In *in vitro* studies using human smooth muscle, Eisner (15) proposed that metoclopramide acted by sensitizing the smooth muscle to acetylcholine. Hay (16), using isolated longitudinal muscle strips from guinea pig stomach, reported that metoclopramide may act by increasing the amount of acetylcholine released at the postganglionic cholinergic nerve ending. A role as a dopamine antagonist has been suggested for metoclopramide with respect to its central antiemetic effect (17). Dopamine has been postulated as a possible neurotransmitter in controlling gastric relaxation (18); therefore, dopamine antagonism may also be a contributing factor in the drug's mechanism of enhancement of gastric emptying.

Several uncontrolled studies have described favorable results of oral metoclopramide in the treatment of diabetic gastroparesis (19-21). In one study, improvement in the symptoms of gastric atony occurred in 14 of 20 patients who had undergone gastric surgery (22). Emptying of solids was measured by the barium burger study (22). Stadaas and Aune found in a double-blind cross-over study that oral metoclopramide was superior to carbachol (a cholinergic agent) and placebo in relieving the symptoms of gastric stasis in patients who had had vagotomy and a drainage procedure at least two years prior to study. Gastric emptying of solids was not measured (23). In a double-blind cross-over trial versus placebo, Berkowitz and coworkers (24) showed that metoclopramide improved the symptom complex of delayed gastric emptying for diabetic and postsurgical patients. In a double-blind cross-over trial, metoclopramide was more effective than placebo in the treatment of flatulent dyspepsia (25). The symptoms of these patients were essentially those of the symptom complex of delayed gastric emptying. Upper gastrointestinal x-ray studies were normal, but gastric emptying of a solid meal was not assessed (25).

In our study, metoclopramide was significantly superior to placebo in reducing the symptom complex associated with delayed gastric emptying. Although an improvement in the gastric emptying of a solid test meal has been shown in other studies after administration of this drug, the present study does not demonstrate which property of metoclopramide was primarily responsible for the symptomatic improvement. However, most of our patients had been treated unsuccessfully with antiemetic therapy. Of note in this study is that a significant placebo

effect was also demonstrated. However, despite improvement on placebo, these patients still had symptoms, and the improvement of the patients on metoclopramide was significantly better than those on placebo. Thus, metoclopramide is an effective therapeutic agent in ameliorating the symptom complex of delayed gastric emptying.

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