Effect of Metoclopramide on Normal and Delayed Gastric Emptying in Gastroesophageal Reflux Patients

STEVEN M. FINK, MD, ROBERT C. LANGE, PhD, and RICHARD W. McCALLUM, MD

Gastric emptying has an important role in the pathophysiology of gastroesophageal reflux disease. We investigated the effect of metoclopramide, a gastric prokinetic agent, in gastroesophageal reflux patients with normal as well as delayed emptying. Twenty-six patients with subjective and objective evidence of gastroesophageal reflux ingested an egg salad sandwich meal labeled with ^{99m}technetium-DTPA for a baseline study, and then again on a separate day after receiving oral metoclopramide, 10 mg, 30 min prior to the test meal. The mean percent isotope remaining in the stomach after 90 min improved significantly ($P < 0.001$) from 70.3 ± 3.9% (SEM) to 55.2 ± 4.2% after metoclopramide. Fourteen (54%) had a basal emptying in the normal range of 34–69% retention of isotope at 90 min, ($\bar{X} \pm 2$ SD), while it was slow in 12 (46%). For those with delayed basal gastric emptying, the mean retention of 88.9 ± 2.9% at 90 min was significantly ($P < 0.005$) decreased by metoclopramide to 68.6 ± 6.1%. In those patients with a normal basal gastric emptying and a mean retention of 54.4 ± 2.3% at 90 min, there was also significant improvement ($P < 0.025$) to 43.6 ± 3.6% after metoclopramide. These data indicate that metoclopramide increased gastric emptying in gastroesophageal reflux patients with normal as well as delayed gastric emptying. Therefore on a patient management level a trial of metoclopramide is warranted in patients with gastroesophageal reflux disease and is not limited by the gastric emptying status of the patient.

Metoclopramide (methoxy-2-chloro-5-procainamide) stimulates smooth muscle of the gastrointestinal tract (1), resulting in an increase in lower esophageal sphincter (LES) pressure (2), and has therapeutic efficacy in gastroesophageal reflux (GER) (3). Patients with GER disease may have a decreased LES pressure when compared to normal subjects (4–6), and recently gastric emptying was found to be delayed in 41–57% of patients with GER disease using different radionuclide meals (7, 8). The questions we address in this study are: (1) Does oral metoclopramide accelerate gastric emptying in GER? (2) If so, is metoclopramide's effect on gastric emptying only limited to slower-emptying GER patients or does it also increase an initially normal emptying rate?

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From the Departments of Medicine and Nuclear Medicine, Yale University School of Medicine, New Haven, Connecticut.

Address for reprint requests: Dr. Richard W. McCallum, Yale University School of Medicine, Gastroenterology Section, 92 LMP, 333 Cedar Street, New Haven, Connecticut 06510.

MATERIALS AND METHODS

These studies were approved by the Human Investigation Committee at the Yale-New Haven Hospital. Twenty-six patients with GER disease participated in this study. All patients had a typical history of heartburn and regurgitation. Heartburn was defined as a burning substernal pain radiating orad, and was relieved to varying degrees with antacids. Regurgitation was defined as the effortless appearance of gastric contents in the mouth. Patients with gastric or duodenal ulcer, previous gastric surgery, or vagotomy were excluded. No patient had evidence of Raynaud's phenomenon, scleroderma, diabetes mellitus, or autonomic neuropathies. None of the patients was taking medications known to influence gastric emptying.

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All patients underwent a Bernstein test (9). Upper gastrointestinal panendoscopy was performed to assess macroscopic esophagitis (10). Histologic evidence of esophagitis (11) was evaluated by esophageal suction biopsies (Quinton Instruments, Seattle, Washington). At least two of these esophageal functions were positive in meeting criteria for GER.

Gastric emptying was determined basally for all 26 patients. Patients fasted 6–8 hr before ingestion of a labeled solid–liquid test meal. The meal was an egg salad sandwich, 100 g canned peaches, and 240 ml of low-fat milk. It contained 595 kcal consisting of 83 g carbohydrate, 20 g fat, and 20 g protein. One millicurie of ^{99m}technetium-labeled DTPA (diethylenetriaminepentaacetic acid) was employed as a marker and soaked into the bread of the sandwich. Within 15 min after beginning the meal, patients were positioned supine under a gamma camera. The stomach was identified on an oscilloscope and isolated by a triple layer of lead shielding and gamma emissions were counted every minute for 90 min while subjects remained as immobile as possible during the study (12). Gastric emptying was expressed as a percentage, (CTN/CTO) × 100, where CTN is the count at any minute over the 90-min study period after correction for isotope decay, and CTO is the initial count of isotope in the stomach. Normal gastric emptying rate for this meal was determined previously in 26 volunteers (7). Gastric emptying was found to be linear, and at 90 min, the mean percent of isotope remaining in the stomach was 51.8 ± 17.4% (2 SD), establishing a normal range of 34–69% of isotope remaining in the stomach at 90 min.

On a separate day, patients received metoclopramide 10 mg orally, 30 min prior to the same test meal. Gastric emptying was monitored using the same technique. Statistical evaluation used paired and unpaired Student's *t* test, and analyses of variance.

RESULTS

On the baseline day, the mean isotope remaining in the stomach after 90 min for all 26 patients was

TABLE 1. SUMMARY OF GASTRIC EMPTYING RESULTS

		Isotope remaining in stomach after test meal (%)					
		Basal			*Metoclopramide*		
Gastric emptying status	*Patient number*	*30 min*	*60 min*	*90 min*	*30 min*	*60 min*	*90 min*
Normal gastric emptying (basal)							
	1	79	63	48	98	75	53
	2	85	73	57	85	63	48
	3	88	77	64	70	56	43
	4	88	79	64	76	63	41
	5	92	73	54	72	52	35
	6	83	76	64	93	84	70
	7	85	61	45	100	77	60
	8	86	63	46	80	67	58
	9	82	66	53	80	60	41
	10	92	80	66	75	60	49
	11	100	92	59	72	36	21
	12	97	74	44	76	52	33
	13	72	54	41	68	46	33
	14	82	66	56	68	38	26
$\bar{X}$		86.5	71.2	54.4	79.5	59.2	43.6
SEM		1.9	2.6	2.3	2.9	3.7	3.7
Delayed gastric emptying (basal)							
	1	100	100	100	88	86	78
	2	100	100	88	75	48	31
	3	100	100	99	100	100	99
	4	100	100	79	100	79	61
	5	94	86	72	83	52	44
	6	96	89	78	100	72	43
	7	100	100	100	98	88	69
	8	92	92	84	99	80	72
	9	97	92	82	92	87	78
	10	100	95	90	96	85	70
	11	98	95	95	100	100	100
	12	100	100	100	95	84	78
$\bar{X}$		98.1	95.8	88.9	93.8	80.1	68.6
SEM		0.8	1.5	2.9	2.3	4.7	6.1

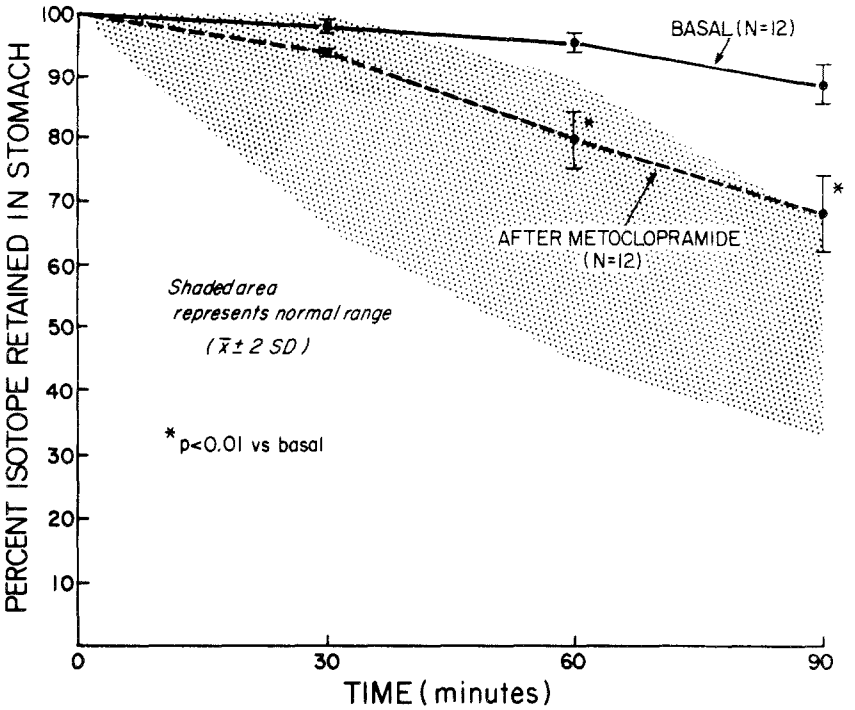

Fig 1. Gastric emptying results in 12 gastroesophageal reflux patients with delayed basal emptying rates, who were studied basally and after 10 mg oral metoclopramide. The data are expressed as the mean percent (±1 SEM) isotope remaining in the stomach for a period of 90 min after ingestion of an isotope-labeled test meal.

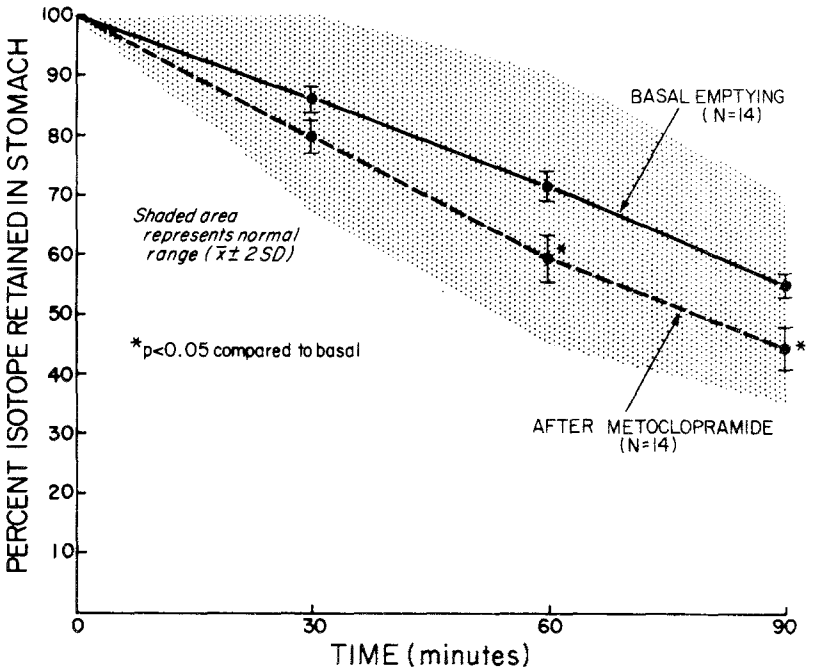

Fig 2. Gastric emptying in 14 gastroesophageal reflux patients with normal basal emptying rates, who were studied basally and after 10 mg oral metoclopramide. The data are expressed as the mean percent (± SEM) isotope remaining in the stomach for a period of 90 min after ingestion of an isotope-labeled test meal.

70.4 ± 3.9% (SEM). Of the group, 14 (54%) were found to have gastric emptying times within the normal range of 34–69% retention 90 min after the meal, as previously established, and their mean isotope retention was 54.4 ± 2.3% (SEM) after 90 min (range 41–66%). Twelve of the 26 GER patients (46%) had delayed gastric emptying of the test meal (Table 1), with a mean isotope retention after 90 min of 88.9 ± 2.9% (SEM) (range 72–100% isotope retention).

After metoclopramide, gastric emptying was accelerated and the mean isotope remaining in the stomach at 30, 60, and 90 min for the 26 patients decreased significantly ($P < 0.05$, $P < 0.001$, and $P < 0.001$, respectively), and at 90 min was 55.2% ± 4.2% (SEM). In the patients with delayed gastric emptying basally, the mean isotope remaining in the stomach at 60 and 90 min decreased significantly ($P < 0.001$), and at 90 min was 68.6 ± 6.1% (SEM) (Figure 1, Table 1). In those patients with normal gastric emptying basally, the isotope remaining in the stomach at 60 and 90 min also decreased significantly ($P < 0.05$), and at 90 min was 43.6 ± 3.7 (SEM) (Figure 2, Table 1).

A three-way factorial analysis of variance on the gastric emptying results of the total patient group ($N = 26$) revealed that metoclopramide explained 8% ($P < 0.001$) of the total variation in gastric emptying. When a two-way analysis of variance was applied on the gastric emptying data for the delayed patient group only ($N = 12$), metoclopramide's influence on gastric emptying was augmented to 18% ($P < 0.001$). A similar analysis was performed for the normal ($N = 14$) emptying patient group; however, metoclopramide explained only 7% ($P < 0.001$) of the total variability in gastric emptying. Based on these analyses, metoclopramide improves gastric emptying in the delayed as well as the normal emtpying groups, and this effect is more pronounced in the group with slow gastric emptying.

DISCUSSION

The present study indicates that metoclopramide increases the rate of gastric emptying in GER patients, independent of whether they initially had normal or delayed gastric emptying. Of patients with GER, 43–57% have delayed gastric emtpying utilizing radionuclide techniques (7, 8), and this disturbance is related to abnormal antral motility. Behar et al (13) found that antral contractility in GER patients, as measured by perfused catheters, was significantly lower than in normal subjects. McCallum et al (8) demonstrated that when specific markers are used for the liquid and solid components of a meal, there is a delay in gastric emptying of the solid component in 57% of GER patients, while liquid emptying remains normal, implying antral dysfunction. In the present study, 46% of our population of patients with GER disease had delayed gastric emptying of the test meal, confirming these previous reports of the high incidence of this abnormality. In the majority of patients this was a latent defect in that no specific symptoms related to gastric retention were elicited.

Metoclopramide, a procainamide derivative, stimulates the smooth muscles of the upper gastrointestinal tract in animals and man (14–19). It increases LES pressure in both normal subjects and in patients with GER disease (1, 2, 20–22). It was reported previously that metoclopramide did not accelerate gastric emptying of a liquid (18, 23) or solid meal (24, 25), in normal subjects. Metoclopramide does, however, increase gastric emptying of liquids (18) or solids (24–27) in patients in whom these emptying rates are delayed.

We observed that metoclopramide significantly enhanced gastric emptying in the subgroups of GER patients with slow as well as normal emptying rates. The improvement in the group of normal emptying esophagitis patients was greater than that reported by Metzger et al (25), in normal volunteers, using the same test meal. Our result was obtained in a larger population and, although significant, the mean decrement of 10.8%, 90 min after the meal, was only half the improvement achieved with metoclopramide in the slow emptying reflux patients (20.3%). For a given patient, this improved emptying rate, although still in the "normal" range, may be clinically important by reducing the residual gastric volume available to reflux, particularly when combined with the purported reduction in duodenogastric reflux attributed to metoclopramide. These effects, augmented by the accompanying increase in LES pressure, may promote less gastroesophageal reflux. Consistent with these conclusions of a role for metoclopramide on the LES and on gastric emptying are unpublished observations from our laboratory. Six of the 26 patients in the present report underwent esophageal motility studies with metoclopramide as part of additional clinical studies. LES pressure with 10 mg metoclopramide increased from 14.1 ± 3.4 mm Hg to 24.7 ±

6.6 mm Hg ($\bar{X} \pm$ SEM) at 90 min, while, in comparison, their gastric emptying improved from 83.3 ± 4.9% to 65.7 ± 4.9 ($\bar{X} \pm$ SEM) isotope retention at 90 min.

Academically, and from a pathophysiologic point of view, investigations of gastric emptying remain an important aspect of research in GER patients. Such endeavors have already identified the gastric emptying abnormality as specific for the solid food component (8), and this forms the basis for advising a diet which stresses smaller, semisolid, or soft meals for those patients. The usual recommendation for adherence to a low-fat diet in the management of reflux esophagitis is based not only on the ability of fat to decrease LES pressure (28) but also to markedly inhibit gastric emptying (29). Methodology for gastric emptying can be easily adopted by nuclear medicine sections at both university and community hospital settings. From a patient management approach, a trial of a gastric "prokinetic" agent such as metoclopramide in GER is warranted and is not limited by the status of the patient's gastric emptying. If a gastric emptying test is not readily available, our findings support initiating therapy and monitoring the patient's clinical parameters.

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