Pseudo-Obstruction of the Bowel
Therapeutic Trial of Metoclopramide

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In some patients with classic signs and symptoms of mechanical bowel obstruction, it is difficult to identify an unequivocal cause for ileus. This may occur in diseases that involve the bowel wall and interfere with intestinal motility, such as scleroderma (1) or amyloidosis (2). A similar syndrome is associated with disturbances of neuromuscular transmission, as seen in myxedema (3), hypoparathyroidism (4), myotonia dystrophica, Hirschprung's disease, or after treatment with anticholinergics, phenothiazines, or opiates. Moreover, transient obstruction of the bowel may occur, particularly in elderly patients, in a variety of systemic diseases, such as pancreatitis, heart failure, uremia, and electrolyte imbalance (5, 6). After all these conditions have been excluded, there remains a small but distinct group of patients with recurrent episodes of seemingly mechanical bowel obstruction for which no cause can be found. This clinical condition has been termed idiopathic pseudo-obstruction of the bowel. Detailed clinical descriptions appear to differentiate this entity clearly from other causes of acute and chronic bowel obstruction (7, 8).

Idiopathic pseudo-obstruction of the bowel was first described by Dudley and colleagues (9) in 1958. Since then, 14 additional cases have been described (10–14). The condition usually becomes manifest in adolescence. Symptoms consist of recurrent episodes of abdominal pain, distention, nausea, and vomiting leading to weight loss and eventually to malnutrition. Diarrhea frequently accompanies acute episodes and steatorrhea may occur secondary to bacterial overgrowth within segments of hypotonic small bowel (8, 12, 14). The disease course may extend over several decades during which the patients usually undergo multiple surgical procedures for apparent mechanical obstruction. Among the 13 well-documented cases reported in the literature, six are known to have succumbed to their disease.

During acute episodes plain films of the abdomen invariably demonstrate air fluid levels in the small bowel and occasionally in the large bowel. Barium studies consistently indicate dilation of small bowel and delayed transit. Roentgenologic contrast studies of the esophagus, stomach, and colon frequently are normal, but motility disorders in the lower two-thirds of the esophagus (8) and dilation of the colon (7) have been reported.

Motility studies, manometric studies, or both often show infrequent or absent peristaltic activity throughout the body of the esophagus and low pressure within the lower esophageal sphincter. Hypomotility and weak spontaneous contractions of the proximal small bowel associated with normal gastric and colonic motility also have been recorded (8, 13).

Pathogenesis of idiopathic pseudo-obstruction is unknown. Histologic examination of full-thickness biopsy specimens of bowel wall have shown no detectable abnormalities at all or, at best, "nonspecific" changes characterized by infiltration of round cells within the mucosa of the small bowel. Ganglion cells have been demonstrated in all portions of the bowel, excluding the diagnosis of aganglionosis of the small intestine. Attempts to stimulate motor activity of the bowel by intraluminal instillation of acetylcholine (13) or intravenous administration of neostigmine (8) have been unsuccessful. The failure of cholinergic agents to stimulate the atonic musculature of the small bowel, to-

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gether with the presence of structurally normal ganglion cells, suggests that the primary disorder may be one of defective end-organ response.

Therapy for idiopathic pseudo-obstruction has been uniformly disappointing. A variety of bypass procedures have been performed (8), but none is known to have provided lasting benefit. Moderate symptomatic improvement was reported in one patient after resection of 115 cm of jejunum combined with construction of an end-to-end duodenoileostomy, but no information is available about the further course of this patient (11). Treatment with broad-spectrum antibiotics may be helpful in reducing steatorrhea in patients with bacterial overgrowth, but it does not alter the overall course of disease (7, 8, 14). Cholinergic drugs, steroids, and dietary manipulations were found to be without benefit (8).

We decided to undertake a double-blind trial of metoclopramide (methoxy-2-chloro-procainamide) in a patient with idiopathic pseudo-obstruction of the bowel because of the reported stimulatory effect of this drug on gastrointestinal motility (15–18). Studies *in vitro* have shown that administration of metoclopramide results in contraction of isolated strips of intestinal smooth muscle; this effect is enhanced by acetylcholine but antagonized by atropine (19). Ganglionic blocking agents and vagotomy do not appear to reduce the effect of metoclopramide. Jacoby and Brodie (18) have suggested that metoclopramide acts either by activation of peripheral intramural cholinergic neurons or by depression of nonadrenergic pathways.

Experiments in animals have demonstrated that metoclopramide greatly accelerates gastric emptying without concomitant stimulation of gastric secretions and without the general parasympathomimetic stimulation usually associated with agents that stimulate gastrointestinal motility (18). In humans, metoclopramide has been shown to increase the strength of gastric antral contractions with simultaneous dilation of the pylorus; thus, the combined effect results in rapid emptying of the stomach and reduced intestinal transit time (15). Metoclopramide has been employed as a radiologic "hurrying" agent to reduce the time required for barium to traverse the small bowel (16, 17).

CASE REPORT

A 23-year-old woman was transferred to the Santa Clara Valley Medical Center from a local community hospital in late November 1973. She gave a history of recurrent episodes of indigestion and vomiting since childhood. At the age of 15 she had had surgery for correction of the so-called superior mesenteric artery syndrome, but the operation brought no relief. Since the age of 20 the frequency of her attacks, all of which simulated mechanical obstruction of the bowel, had progressively increased. In early November 1973, an exploratory laparotomy had been performed which revealed distended loops of small bowel, but no specific cause of the obstruction could be detected. There was no history or evidence of arthralgia, Raynaud's phenomenon, or the skin involvement of scleroderma.

Physical examination on admission was unremarkable except for a midabdominal surgical scar. Laboratory studies showed a hematocrit of 37%, white blood cell count of 7,600 with a normal differential count, and a normal platelet count. Concentrations of serum sodium, potassium, bicarbonate, calcium, phosphorus, blood urea nitrogen, fasting blood glucose, and cholesterol were normal. Additional laboratory values were as follows: antinuclear antibody, unreactive; rheumatoid factor, negative; serum thyroxine, 6.9 μg per 100 ml; and qualitative test for urinary porphobilinogen, negative. Serum immunoglobulins were within normal range by agar gel electrophoresis. Upper gastrointestinal series showed a generalized decrease in motility throughout the esophagus, stomach, and small bowel and a grossly dilated second portion of the duodenum without evidence of a stricture. The normal contour of the esophagus and stomach were preserved. No barium had entered the ascending colon even on the 9-hr film. A barium enema demonstrated a dilated colon with loss of haustral markings. Endoscopy identified aperistalsis of the esophagus, stomach, and proximal duodenum, and mild exudative esophagitis. Esophageal motility studies demonstrated an abnormal lower esophageal sphincter characterized by low pressure (+ 4 mm Hg), low amplitude peristaltic waves, and frequent lack of peristaltic waves in the body of the esophagus in response to deglutition. Specimens from peroral biopsy of the small bowel appeared normal under light microscopy with the H and E stain. Between November 1973 and February 1975 the patient continued to have frequent episodes that simulated mechanical bowel obstruction and that required hospitalization on six occasions. During this period she lost 26.3 kg of weight.

A trial of metoclopramide was initiated in February 1975. Informed consent of the patient and approval from the Research Committee of the Santa Clara Valley Medical Center was obtained. For four courses of 28 days each, the patient was given either 40 mg of metoclopramide per day or an identically appearing placebo tablet. Instructions were to take one 10-mg tablet 0.5 hr before each meal and at bedtime. The four 28-day courses were randomized in such a way that the attending physician (A.L.) was unaware of which medication the patient was receiving. The effects of metoclopramide and placebo were evaluated by the following clinical criteria: (a) number of days of hospitalization during each 28-day course; (b) alteration in weight; and (c) daily record of symptoms noted by the patient and expressed by a prearranged numerical code.

In the patient described, metoclopramide appeared to

TABLE 1. DOUBLE-BLIND TRIAL OF METOCLOPRAMIDE IN IDIOPATHIC PSEUDO-OBSTRUCTION*

	Day																											
Treatment	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
A. Placebo	1	1	1	1	0	0	2	2	1	1	1	3	2	4	4	4	4	4	4	4	0	0	0	0	0	0	0	0
B. Metoclopramide	0	0	0	0	0	1	4	4	4	4	4	4	4	4	4	4	4	4	2	1	1	1	1	1	1	1	4	4
C. Metoclopramide	1	1	1	1	1	1	1	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
D. Placebo	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1

*0: no symptoms; 1: symptoms of nausea, vomiting, abdominal pain, abdominal distension, not resulting in reduced dietary intake; 2: symptoms as above but resulting in reduced dietary intake; 3: symptoms as above precluding oral intake for 24 hr; 4: hospitalization.

provide no advantage compared to placebo during the course of this trial. As outlined in Table 1, during the time the patient received metoclopramide there was no appreciable symptomatic improvement and no reduction in hospitalization time when compared to periods during which the patient received placebo. The lack of symptomatic response to metoclopramide is also reflected by changes in body weight occurring during the study. During two 28-day courses of metoclopramide the patient lost a total of 4.1 kg, but she gained 3.2 kg during the two 28-day courses of placebo. Metoclopramide produced no detectable systemic or organ-specific side effects.

SUMMARY

A patient with chronic idiopathic pseudo-obstruction is reported and the results of a double blind therapeutic trial of metoclopramide are described. Within the limits of this trial metoclopramide was ineffective by all clinical criteria.

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