The Effects of Metoclopramide on Postoperative Ileus

A Randomized Double-blind Study

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Metoclopramide or placebo was administered postoperatively in a randomized, double-blind fashion to 115 patients undergoing laparotomy. The effect of metoclopramide on postoperative adynamic ileus (PAI) was evaluated. The patients were stratified into two groups: Group A—those with laparotomy without a gastrointestinal anastomosis or ostomy procedure, and group B—those with laparotomy undergoing an anastomosis or ostomy procedure. Metoclopramide reduced nausea and emesis postoperatively. However, the only significant effect on postoperative adynamic ileus was an earlier return to tolerance of solid foods in the patients in Group A.

POSTOPERATIVE ADYNAMIC ILEUS (PAI) is an expected concomitant of celiotomy. Efforts directed toward elimination or amelioration of ileus have been unsuccessful. Intestinal pacing via peroral gastric electrode stimulation[15] and transcutaneous electrical stimulation[18] have not reduced PAI. Pharmacologic stimulation via D-pantothenyl alcohol has also been ineffective.[14] Neostigmine has been used widely for prevention of PAI without good documentation of its efficacy.

Metoclopramide, a drug derived from procaine amide, has been shown to be an effective antiemetic agent with properties of enhancing gastrointestinal motility.[6,9,17] The drug stimulates gastric contractions and thereby accelerates gastric emptying.[7,11] The drug stimulates smooth muscle contraction in the small intestine which accelerates intestinal transit time.[10] Metoclopramide exerts minimal effect on colonic motility, though some *in vitro* and *in vivo* studies show stimulation of the colon with metoclopramide.[1,7] This study set out to examine the efficacy and safety of metoclopramide compared to placebo in the prevention of postoperative ileus.

Metoclopramide has been used extensively in Europe for prevention of PAI. Controlled studies by Breivak and Lind,[4] Makrigiannis and Gaca[13] and Friis[8] support its routine use in the patients undergoing celiotomy. Banke[2] did not show a reduction in time to first defecation in a double blind study of patients postvagotomy and pyloroplasty given postoperative metoclopramide.

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Submitted for publication: January 29, 1979.

Methods

Study Population

One hundred and twenty-five adult patients were enrolled in the study after careful explanation of the procedure, the medication and risks involved. All patients signed an approved institutional informed consent. One hundred and fifteen patients completed the study and were available for statistical analysis. The patients were categorized in two groups: Group A consisted of 58 patients undergoing abdominal surgery where no entry into the stomach, duodenum, small intestine or large intestine was made. Group B consisted of 57 patients where gastrointestinal entry, anastomosis or suture was performed. The patient population characteristics are listed in Table 1. All selected patients underwent intra-abdominal surgery with a total anesthesia time of more than one and one-half hours duration. All surgical patients were interviewed for the study except for those with Parkinson's disease or known seizure disorders, patients with known hypersensitivity to procaine amide or other related drugs, patients with severe renal, cardiac or hepatic disease and patients taking parasympathomimetic drugs or phenothiazines.

The patients were assigned to either the placebo or treatment group in a predetermined, randomized

0003-4932/79/0700/0024 $00.70

double-blind fashion. The code could only be broken if untoward reactions occurred. The patients were administered either metoclopramide 10 mg, or an intramuscular sterile buffer solution on the evening of surgery and at 7:30 a.m., 11:30 a.m. and 5:30 p.m. on the days following surgery. Similarly, the test medication was given orally in tablets when oral fluids were tolerated. Medication was stopped when solid food was tolerated and/or defecation had occurred.

The intraoperative course, recovery room time and postoperative symptoms were recorded for each patient. The following items were assessed three times daily at morning, noon and night in each patient each day until termination of the study: abdominal distention, abdominal cramping, nausea, vomiting, passage of flatus, passage of stool, presence or absence of bowel sounds, tolerance of oral fluids, tolerance of solid foods, nasogastric drainage, intravenous fluids given, drugs administered, and presence or absence of significant postoperative complications. In addition, all patients had temperature, blood pressure, pulse rate and measurement of abdominal girth recorded daily.

The data were examined and computer coded and separated into two categories for analytic purposes. The first category consisted of the presence or absence of nausea, vomiting, abdominal cramping, abdominal distention and need for an indwelling nasogastric tube. The data were analyzed by both the number of patients with or without symptoms and the total frequency of the symptoms. These data were analyzed for the day of surgery and the first two postoperative days only while the patients were all receiving injectable drug.

The second category analyzed the length of time until tolerance of oral fluids and of solid food, the timing of the first occurrence of passage of flatus and of stool and the appearance of bowel sounds in relationship to the time of surgery. These data were analyzed by considering the total number of doses administered, whether parenteral or oral.

The statistical methods included log linear analysis of nominal qualitative data by the method of maximum likelihood, the chi-square test of difference of proportions and Fischer's exact test. Data were analyzed for both population groups. Ten patients were eliminated from the study: three refused to participate postoperatively and seven either died or had life threatening complications requiring removal from the protocol. One hundred and fifteen patients completed the protocol and their data were analyzed.

TABLE 1. *Mean Age, Range of Age and Sex of Study Patients*

	Group A		Group B	
	Age (Range)	M/F	Age (Range)	M/F
Placebo	52.1 yrs (21–84)	13/16	49.7 yrs (30–77)	15/13
Metoclopramide	48.8 yrs (20–81)	14/15	52.8 yrs (19–81)	16/13
Total subjects		27/31		31/26

TABLE 2. *Nausea and Emesis During the First Two and One-half Postoperative Days*

		Metoclopramide	Placebo	Significance
Group A				
Nausea	Present	14	10	ns
	Absent	15	19	
Emesis	Present	1	7	$p < 0.05$
	Absent	28	22	
Group B				
Nausea	Present	5	12	$p < 0.05$
	Absent	24	16	
Emesis	Present	1	1	ns
	Absent	28	27	

Results

Table 2 shows the effect of the test drug on the occurrence of postoperative nausea and emesis. The number of patients having nausea in Group B in the two day postsurgical period was significantly less than patients in the placebo group ($p < 0.05$). When both Groups A and B were pooled, the overall number of reports of nausea was statistically less in the metoclopramide treated patients than in the placebo group ($p < 0.05$). Emesis was significantly reduced only in the Group A patients receiving metoclopramide when compared to placebo ($p = 0.027$ single tailed test).

Table 3 shows that in Group A patients the time until tolerance of solid food was significantly lower in the metoclopramide treated group than in the placebo treated group. This difference did not appear in Group B patients. The number of patients achieving food tolerance is less than the number of patients in each group. This discrepancy occurred because in some

TABLE 3. *Total Drug Doses (i.e. Time) Until Tolerance of Solid Food in Group A and Group B Patients*

		Median Doses—10 Less Than or Equal to Median Number of Doses	Greater Than Median Number of Doses
Group A	Metoclopramide	24	4
	Placebo	14	10
		$p < 0.05$	
Group B	Metoclopramide	7	17
	Placebo	10	13
		ns	

patients the study medication was discontinued at first defecation prior to resumption of a solid food diet.

There were no other statistically significant differences in the other variables measured. Abdominal pain and cramping, return of bowel sounds, passage of flatus and stool and tolerance of fluids showed no significant differences in Group A or Group B patients between metoclopramide and placebo treated groups. The findings on physical examination, temperature, pulse, blood pressure, laboratory determinations including electrolytes, were not different in placebo or drug treated patients.

In the metoclopramide treated group, side effects reported included one patient with marked and eight with mild sedation. Mild sedation, however, was also noted in six patients who received the placebo. Restlessness was reported in three patients on metoclopramide and two patients on placebo. Dystonia was recorded for three patients on placebo but was not noted in cases taking metoclopramide. No other untoward symptoms were attributable to either test drug. The overall incidence of adverse reactions was 10.4% in the metoclopramide group and 9.6% in the placebo treated group.

Discussion

This study confirms previous studies in demonstrating a statistically significant difference for reduction in the frequency of postoperative nausea and vomiting in patients receiving injectable metoclopramide.[6,9,17] The aforementioned studies showed that metoclopramide was effective in reducing postoperative nausea and vomiting after single dose administration, particularly in patients who were concomitantly receiving narcotic analgesics. The present study, where patients received the injectable drug over a period of two and one-half days postoperatively, demonstrated significant reduction in the frequency of vomiting in Group A patients and in nausea in Group B patients. There was also an overall significant reduction in nausea when both groups were pooled.

Metoclopramide exerts an antiemetic action by its activity on the vomiting center and on the chemoreceptive trigger zone. The drug also enhances gastric motility and improves gastric emptying, which may further contribute to its antiemetic properties. A combination of these two effects, central and gastric, should be additive in reducing postoperative vomiting.

This study does not support the European studies[4,8,13] concerning the effects of metoclopramide on postoperative ileus. With the exception of the significant reduction in the time until tolerance of solid foods in patients undergoing abdominal operation without entry into the gastrointestinal tract, there was no significant effect exerted by metoclopramide on any of the other parameters measured. No other indicators of ileus achieved significance. Abdominal distention, abdominal girth, cramping pain, toleration of oral fluids, and the passage of the first stool were similar in both drug and placebo treated patients in both Group A and Group B. Although the drug did not significantly reduce the period of symptomatic postoperative ileus, none of the 115 patients experienced prolonged postoperative ileus. We have used metoclopramide successfully for the treatment of an established ileus, but the effect of the drug cannot be isolated from the general postoperative care measures instituted concurrently. Kronberger[12] has reported excellent results using metoclopramide in treating prolonged PAI.

Electrophysiologic studies have shown that abdominal laparotomy initially produces a loss of spike potentials and contractions in the entire intestine and these return within 12–24 hours after surgery.[5,16] In the experimental animal, coordinated propulsion of intestinal contents down the gut is, however, inhibited for periods of three to seven days after laparotomy.[16] Gastric pacing via peroral electrode could not be expected to diminish PAI in the small intestine and perhaps most importantly the colon would not be stimulated. The right colon may be the site of maximum delay in PAI: Neostigmine can produce gut contraction but does not restore coordinated propulsion and may be dangerous if any mechanical component of obstruction is present.

Metoclopramide may increase gut contraction by acting as a dopamine antagonist.[3] It does not produce spasm and it does restore coordinated contraction in the gastrointestinal tract. The lack of effect on PAI may reflect the drug's inability to stimulate the colon *in vivo*. The study by Friis[8] would suggest that higher doses of metoclopramide may be needed to reduce PAI.

Conclusions

Metoclopramide, an agent which enhances gastrointestinal motility and acts centrally as an antiemetic, was given to 115 patients undergoing major abdominal surgery. Patients were stratified into those with and those without gastrointestinal suture or anastomosis. The major effects of metoclopramide when compared to placebo included a significant reduction in postoperative emesis in patients without gut anastomosis. There was a significant reduction in nausea in patients with gastrointestinal anastomoses and in the total frequency of nausea in both groups.

Overall postoperative ileus was unaffected by metoclopramide with the exception of a statistically significant earlier return to solid food diet in patients not

undergoing gastrointestinal anastomosis. All other parameters indicative of ileus remained the same for metoclopramide and placebo treated patients.

Acknowledgment

The authors wish to thank Dr. V. A. Vokac, A. H. Robins Co., Richmond, Va., for providing metoclopramide and Dr. J. R. Amerson, Dr. W. C. McGarity, Dr. G. D. Perdue and Dr. R. B. Smith, III, for providing study patients.

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