

The New England Journal of Medicine

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VOLUME 341

JULY 15, 1999

NUMBER 3



NEOSTIGMINE FOR THE TREATMENT OF ACUTE COLONIC PSEUDO-OBSTRUCTION

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ABSTRACT

Background Acute colonic pseudo-obstruction — that is, massive dilation of the colon without mechanical obstruction — may develop after surgery or severe illness. Although it may resolve with conservative therapy, colonoscopic decompression is sometimes needed to prevent ischemia and perforation of the bowel. Uncontrolled studies have suggested that neostigmine may be an effective treatment.

Methods We studied 21 patients with acute colonic pseudo-obstruction. All had abdominal distention and radiographic evidence of colonic dilation, with a cecal diameter of at least 10 cm, and had had no response to at least 24 hours of conservative treatment. We randomly assigned 11 to receive 2.0 mg of neostigmine intravenously and 10 to receive intravenous saline. A physician who was unaware of the patients' treatment assignments recorded clinical response (defined as prompt evacuation of flatus or stool and a reduction in abdominal distention), abdominal circumference, and measurements of the colon on radiographs. Patients who had no response to the initial injection were eligible to receive open-label neostigmine three hours later.

Results Ten of the 11 patients who received neostigmine had prompt colonic decompression, as compared with none of the 10 patients who received placebo ($P < 0.001$). The median time to response was 4 minutes (range, 3 to 30). Seven patients in the placebo group and the one patient in the neostigmine group without an initial response received open-label neostigmine; all had colonic decompression. Two patients who had an initial response to neostigmine required colonoscopic decompression for recurrence of colonic distention; one eventually underwent subtotal colectomy. Side effects of neostigmine included abdominal pain, excess salivation, and vomiting. Symptomatic bradycardia developed in two patients and was treated with atropine.

Conclusions In patients with acute colonic pseudo-obstruction who have not had a response to conservative therapy, treatment with neostigmine rapidly decompresses the colon. (N Engl J Med 1999;341:137-41.)

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ACUTE colonic pseudo-obstruction consists of massive dilation of the colon in the absence of mechanical obstruction. This severe form of adynamic ileus, also known as Ogilvie's syndrome,¹ develops in hospitalized patients and is associated with a wide variety of medical and surgical conditions.^{2,3} The approximate risk of spontaneous perforation is 3 percent, with an attendant mortality rate of 50 percent.⁴ Most cases respond to conservative management.⁵ Although its value is unproved, colonoscopic decompression is often performed to prevent ischemia and perforation of the bowel in patients who have no response to conservative management. Colonoscopy in such patients is technically difficult, is not always successful, and can be accompanied by complications including perforation. Colonic distention may recur in up to 40 percent of patients despite initial decompression.⁴

The results of three uncontrolled studies suggest that the intravenous administration of neostigmine, an acetylcholinesterase inhibitor, produces rapid colonic decompression in patients with acute colonic pseudo-obstruction.⁶⁻⁸ This pharmacologic approach is based on the theory that acute colonic pseudo-obstruction results from ineffectual colonic motility caused by excessive sympathetic stimulation, parasympathetic dysfunction, or both.^{1,9-11} Therefore, we conducted a prospective, double-blind, placebo-controlled trial of neostigmine as a treatment for acute colonic pseudo-obstruction.

METHODS

Patients

Patients with acute colonic pseudo-obstruction who were 18 years of age or older were recruited for the study between August 1995 and November 1997 from inpatient medical and surgical

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wards of hospitals affiliated with the University of Washington. Acute colonic pseudo-obstruction was defined as marked colonic distention in the absence of mechanical obstruction. To be eligible for the study, patients had to have a cecal diameter of at least 10 cm on plain radiographs. Mechanical obstruction was ruled out by the finding of air throughout all colonic segments including the rectosigmoid on plain abdominal radiographs. When air was not demonstrable in the rectosigmoid colon, mechanical obstruction was ruled out by radiographic contrast enemas. Patients were enrolled in the study if colonic distention, documented by clinical examination and abdominal radiographs, failed to improve after 24 hours of conservative management that included administering nothing by mouth, nasogastric suction, and intravenous fluid and electrolyte replacement. Any drugs that could adversely affect colonic motility, specifically narcotics and anticholinergic agents, were discontinued when possible. One patient, who was subsequently randomly assigned to the placebo group, was enrolled after only 18 hours of conservative therapy, when the consulting gastroenterologist determined that urgent decompression was warranted.

Exclusion criteria included a base-line heart rate of less than 60 beats per minute or systolic blood pressure of less than 90 mm Hg; signs of bowel perforation, with peritoneal signs on physical examination or free air on radiographs; active bronchospasm requiring medication; treatment with prokinetic drugs such as cisapride or metoclopramide in the 24 hours before evaluation; a history of colon cancer or partial colonic resection; active gastrointestinal bleeding; pregnancy; or a serum creatinine concentration of more than 3 mg per deciliter (265 μ mol per liter).

The human-subjects committee of the University of Washington and its affiliated hospitals approved the study protocol. All patients provided written informed consent.

Study Design

Patients were randomly assigned to receive 2.0 mg of neostigmine intravenously over a period of three to five minutes or identical-appearing saline placebo. The injections were given by a physician who was unaware of the patients' treatment assignments. All patients were monitored by electrocardiography; atropine was available at the bedside, and 1.0 mg was given intravenously as needed for symptomatic bradycardia. Patients were instructed to remain supine for at least 60 minutes after the injection. Vital signs were recorded immediately before the injection and five minutes and three hours afterward.

The physician administering the infusion monitored the clinical response for 30 minutes after the injection. The maximal abdominal circumference and the diameter of the cecum, ascending colon, and transverse colon on plain radiographs were measured before and three hours after the injection by an investigator who was unaware of the patients' treatment assignments.

Three hours after the infusion, patients who did not have a reduction in colonic distention on both clinical examination and radiographs were eligible to receive open-label neostigmine (2.0 mg intravenously) administered by a physician who was unaware of the identity of the study drug. The three-hour period was chosen because of the short half-life of neostigmine. Three hours later, abdominal circumference, colonic diameters, and clinical response were again measured. Patients were monitored for adverse effects during the initial treatment and during open-label treatment and were then followed for the remainder of their hospitalization. The treatment assignments were not revealed to the investigators, treating physicians, or patients until the last patient had been discharged from the hospital.

Assessment of Outcomes

The outcomes assessed included an immediate clinical response to the study drug, changes in abdominal girth and colonic diameters on abdominal radiographs three hours after treatment, and the need for colonoscopic decompression or surgery during hospitalization. An immediate clinical response was defined as the passage of flatus or stool with a reduction in abdominal distention

TABLE 1. CHARACTERISTICS OF THE PATIENTS AT BASE LINE.

CHARACTERISTIC	NEOSTIGMINE (N=11)	PLACEBO (N=10)
Age (yr)		
Median	67	64
Range	40-82	43-83
Sex (M/F)	11/0	8/2
Duration of pseudo-obstruction (days)*		
Median	3	3
Range	1-6	1-10
White-cell count ($\times 10^{-3}/\text{mm}^3$)		
Median	13	13
Range	7-25	6-19
Maximal temperature in preceding 24 hr ($^{\circ}\text{C}$)		
Median	37.2	37.8
Range	36.5-40.0	37.1-39.8
Abdominal circumference (cm)		
Median	113	106
Range	102-146	85-132
Cecal diameter (cm)†		
Median	16	13
Range	10-24	11-23
Diameter of ascending colon (cm)†		
Median	12	9
Range	9-15	6-12
Diameter of transverse colon (cm)†		
Median	12	9
Range	7-14	5-12
No. with mechanical obstruction ruled out by radiographic contrast enemas	5	4
No. receiving mechanical ventilation	0	1
No. receiving narcotics, anticholinergic agents, or both before study entry	6	7
No. with history of recent surgery	5	6

*The duration of pseudo-obstruction was measured from the time of radiologic diagnosis to randomization.

†The diameter was measured on plain radiographs.

on physical examination within 30 minutes after the injection. Treatment was considered to have failed if open-label neostigmine, colonoscopic or surgical intervention, or both were required because of the recurrence or persistence of colonic distention.

Statistical Analysis

On the basis of prior reports, we estimated that 10 patients would be required in each group for the study to have the power at an alpha level of 0.05, with a beta error of 0.2, to detect a significant difference between groups, assuming a response rate of 80 percent in the neostigmine group and 30 percent in the placebo group. We used Fisher's exact test to compare the frequency of clinical responses and treatment failures in the two groups.¹² We evaluated the changes in abdominal circumference and colonic diameters with the use of Wilcoxon's rank-sum test.¹² All tests were two-tailed.

RESULTS

Eleven patients were randomly assigned to receive neostigmine, and 10 to receive saline placebo. All patients had acute abdominal distention. Fifteen patients (71 percent) reported abdominal pain at base line. The two groups were similar with regard to age, sex, duration and degree of colonic distention, use of narcotics and anticholinergic medications, his-

TABLE 2. RESULTS OF INITIAL TREATMENT.

RESULT	NEOSTIGMINE (N=11)	PLACEBO (N=10)
Immediate clinical response — no. (%)	10 (91)	0*
Change in abdominal circumference — cm		
Median	-7	-1†
Range	+2 to -26	+2 to -4
Change in cecal diameter — cm		
Median	-5	-2‡
Range	+1 to -10	+1 to -5
Change in diameter of ascending colon — cm		
Median	-4	0§
Range	+1 to -12	+2 to -4
Change in diameter of transverse colon — cm		
Median	-4	0¶
Range	-2 to -10	-2 to +2
Recurrence of colonic distention — no. (%)	2 (18)	NA

*P<0.001 by Fisher's exact test.

†P=0.007 by Wilcoxon's rank-sum test.

‡P=0.03 by Wilcoxon's rank-sum test.

§P=0.01 by Wilcoxon's rank-sum test.

¶P<0.001 by Wilcoxon's rank-sum test.

||NA denotes not applicable.

tory of recent surgical procedures, and severity of illness (Table 1). In two patients, the underlying medical diagnosis was spinal cord injury with paralysis, and one patient each had bleeding peptic ulcer, cerebrovascular accident, pneumonia with respiratory failure, liver failure due to primary sclerosing cholangitis, sepsis, wrist fracture with urinary tract infection, graft-versus-host disease after bone marrow transplantation, renal transplantation, and metastatic insulinoma. The underlying surgical diagnoses included total knee replacement in two patients, coronary-artery bypass grafting in two patients, and total hip replacement, amputation of a leg after a burn, prostatectomy, lumbar laminectomy, exploratory laparotomy after a gunshot wound, and open reduction of multiple fractures, with internal fixation, in one patient each.

After treatment, there was prompt evacuation of flatus or stool with a reduction in abdominal distention on physical examination in 10 patients in the neostigmine group (91 percent) and none in the placebo group (P<0.001) (Table 2). The median time to response was 4 minutes (range, 3 to 30). There were also significant reductions in abdominal circumference and colonic diameters in the neostigmine group as compared with the placebo group (Table 2). An example of the response to neostigmine is shown in Figure 1.

Treatment was considered to have failed in three patients who received neostigmine (27 percent) and eight who received placebo (80 percent, P=0.04). One of the three patients in the neostigmine group



A



B

Figure 1. Plain Abdominal Radiographs Obtained before the Administration of Neostigmine (Panel A) and 24 Hours Afterward (Panel B) in a 72-Year-Old Man with Acute Colonic Pseudo-Obstruction.

Abdominal distention developed one day after knee arthroplasty. Distention persisted despite conservative therapy. On the fourth postoperative day, an abdominal radiograph (Panel A) demonstrated dilation of the cecum (maximal diameter, 15 cm), ascending colon, and transverse colon. Treatment with neostigmine resulted in prompt evacuation of flatus and stool. Three hours after the infusion, radiography showed that the cecum was 9 cm in diameter. An abdominal radiograph obtained 24 hours after the infusion (Panel B) showed that there was little remaining colonic gas.

had no immediate clinical response to initial treatment but did have a response to open-label therapy, with no recurrence of dilation. The other two patients required colonoscopic decompression for recurrence of colonic distention. One of these two also received atropine for symptomatic bradycardia and underwent colonoscopic decompression three hours after receiving neostigmine. The other pa-

TABLE 3. RESULTS OF OPEN-LABEL TREATMENT WITH NEOSTIGMINE IN EIGHT PATIENTS.*

RESULT	VALUE
Clinical response (%)	100
Recurrence (%)	0
Time to response (min)	
Median	4
Range	3–30
Reduction in abdominal circumference (cm)	
Median	4
Range	2–7
Reduction in cecal diameter (cm)	
Median	7
Range	2–11

*Seven of the patients had initially been assigned to the placebo group, and one had been assigned to the neostigmine group.

tient, who had metastatic insulinoma, had a clinical response to a second dose of neostigmine given 24 hours after the initial injection. However, distention recurred, leading to colonoscopic decompression. After a third recurrence of colonic dilation, the patient underwent subtotal colectomy.

Three of the 10 patients who were assigned to the placebo group did not receive open-label therapy. At the discretion of their attending physicians, two were treated with conservative measures alone, and colonic distention gradually resolved over the next 48 to 72 hours. One patient did not receive open-label treatment, because of the development of renal failure. This patient underwent two unsuccessful attempts at colonoscopic decompression and was found at laparotomy to have ischemic colonic necrosis that required bowel resection.

The results of open-label treatment with neostigmine are given in Table 3. Of the eight patients who received open-label therapy, one had previously received neostigmine and seven had received placebo. All eight patients had an immediate clinical response, and none had a recurrence of dilation or required colonoscopic or surgical decompression. Of the 18 patients who received neostigmine, either initially or during open-label treatment, 17 (94 percent) had an immediate clinical response and 2 (11 percent) had recurrent colonic dilation.

The most frequent adverse effect of neostigmine treatment was abdominal pain, which occurred in 13 patients; it was described as mild cramping by 9 and as moderate-to-severe cramping by 4. In all patients, the abdominal pain was transient and had no sequelae. Eight patients had excessive salivation, and two vomited. Symptomatic bradycardia requiring atropine occurred in two patients: one patient

had a syncopal episode while walking to the bathroom 30 minutes after receiving neostigmine (a violation of the protocol), and the other felt lightheaded within minutes after the infusion. None of the patients in the placebo group had an adverse effect.

Two patients (both of whom were in the neostigmine group) died, but in neither patient was death related to acute colonic pseudo-obstruction or its treatment. One patient, who had metastatic insulinoma, underwent hepatic-artery chemoembolization and died of multiorgan failure 16 days after receiving neostigmine. The other patient, who had end-stage liver disease from primary sclerosing cholangitis, underwent liver transplantation 16 days after receiving neostigmine and died of invasive aspergillosis 17 days after transplantation.

DISCUSSION

Although the pathophysiology of acute colonic pseudo-obstruction is not fully understood, it is thought to result from an imbalance in the regulation of colonic motor activity by the autonomic nervous system. In 1948, Ogilvie described two patients with colonic pseudo-obstruction resulting from malignant infiltration of the celiac plexus and attributed the syndrome to sympathetic deprivation.¹ There is now a better understanding of the autonomic innervation of the colon. The parasympathetic nervous system increases contractility, whereas the sympathetic nerves decrease motility.¹¹ Multiple pharmacologic and metabolic factors, as well as spinal and retroperitoneal trauma, can alter the autonomic regulation of colonic function, leading to excessive parasympathetic suppression, sympathetic stimulation, or both. This imbalance results in colonic atony or pseudo-obstruction and forms the rationale for pharmacologic manipulation of the autonomic innervation of the colon in patients with this condition.

We found that neostigmine decompressed the colon in patients with acute colonic pseudo-obstruction who had not responded to conservative therapy. Colonic distention recurred infrequently. Even though the elimination half-life of neostigmine is short, most patients had sustained improvement. This result may reflect resolution of the underlying problem with continued use of conservative measures. Our results confirm those of uncontrolled studies.^{6–8} However, our study was too small to evaluate the effect of neostigmine treatment on the risk of colonic perforation and mortality.

In most patients with acute colonic pseudo-obstruction, conservative management will result in the resolution of colonic distention within three days.⁵ Decisions about the need for medical therapy, colonoscopy, or surgery should be individualized and should be based on the patient's clinical status. The risk of colonic perforation is reportedly increased

when the cecal diameter exceeds 12 cm and when distention has been present for more than six days.^{2,13}

Colonoscopy is successful in about 70 percent of patients with acute colonic pseudo-obstruction, as determined by a reduction in radiographically measured cecal diameter.^{4,14} The recurrence rate of approximately 40 percent may be decreased by placement of a decompression tube at the time of the procedure.⁴ In this setting, colonoscopy is a difficult procedure and has a morbidity rate of 3 percent and a mortality rate of 1 percent.⁹ Surgical intervention is associated with high morbidity and mortality rates and should be reserved for patients with signs of ischemia or perforation or those in whom colonoscopic decompression fails.²

Although the majority of side effects in our study were minor, the use of parasympathomimetic agents such as neostigmine is not without risk. Patients with underlying bradyarrhythmias or those receiving β -adrenergic antagonists may be more susceptible to neostigmine-induced bradycardia. Similarly, neostigmine increases airway secretions and bronchial reactivity, which may exacerbate active bronchospasm. Concomitant treatment with neostigmine and the anticholinergic agent glycopyrrolate has been reported to diminish the central cholinergic effects of neostigmine without reducing the increases in colonic motility.¹⁵ Thus, the combination of neostigmine and glycopyrrolate merits further study in patients with colonic pseudo-obstruction.

The elimination half-life of neostigmine after intravenous infusion averages 80 minutes.¹⁶ Neostigmine is hydrolyzed by plasma cholinesterase and is metabolized by microsomal liver enzymes. Renal excretion accounts for the clearance of 50 percent of the drug, and the serum half-life is prolonged in patients with renal dysfunction.¹⁶ Therefore, patients with renal impairment may have an increased or prolonged vagomimetic response after the administration of neostigmine.¹⁷

A 2-mg ampule of neostigmine for parenteral use costs \$3. The cost of neostigmine to the patient after storage and handling fees are included is approximately \$15 — substantially less than the cost of colonoscopy. In addition, colonoscopic decompression can be a technically demanding and unpleasant procedure that involves a considerable amount of effort and time on the part of physicians. The procedure is

often done at the bedside, and preparation of the colon may not be possible.

In summary, we found that treatment with neostigmine was an effective way to decompress the colon in patients with acute colonic pseudo-obstruction. The use of neostigmine should be considered before colonoscopy is performed in patients with acute colonic pseudo-obstruction who have not had a response to conservative management.

Supported by a grant from the American Society for Gastrointestinal Endoscopy.

We are indebted to Dr. Jason Dominitz for his contribution to the statistical analyses.

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