Published in final edited form as:

Neurogastroenterol Motil. 2015 December ; 27(12): 1736–1746. doi:10.1111/nmo.12669.

Effect of Neostigmine on Gastroduodenal Motility in Patients With Suspected Gastrointestinal Motility Disorders

Gopanandan Parthasarathy¹, Karthik Ravi¹, Michael Camilleri¹, Christopher Andrews², Lawrence A. Szarka¹, Phillip A. Low³, Alan R Zinsmeister⁴, and Adil E. Bharucha¹

¹Clinical and Enteric Neuroscience Translational and Epidemiological Research Program (C.E.N.T.E.R.), Mayo Clinic, Rochester, MN, USA

³Department of Neurology, Mayo Clinic, Rochester, MN, USA

⁴Division of Biostatistics, Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota, USA

Abstract

Background—Acetylcholinesterase inhibitors (ACIs), e.g., neostigmine, are known to increase upper and lower gastrointestinal (GI) motility and are used to treat acute colonic pseudoobstruction. However, their effects on gastroduodenal motility in humans are poorly understood. Our hypotheses were that, in patients with suspected GI motility disorders, neostigmine increases gastric and small intestinal motor activity, and these effects are greater in patients with cardiovagal neuropathy, reflecting denervation sensitivity.

Methods—In this open label study, the effects of neostigmine (1mg intravenously) on gastroduodenal motor activity recorded with manometry were assessed in 28 patients with a suspected GI motility disorder. Cardiovagal function was assessed with the heart rate response to deep breathing and gastrointestinal transit by scintigraphy.

Key Results—The final diagnoses were gastroparesis (6 patients), gastroparesis with intestinal neuropathy (3 patients), intestinal neuropathy or pseudoobstruction (5 patients), functional dyspepsia (6 patients), chronic abdominal pain (3 patients), mechanical small intestinal obstruction (3 patients) and pelvic floor dysfunction (2 patients). Neostigmine increased both antral and intestinal phasic pressure activity ($P<.001$). Neostigmine increased antral and intestinal pressure activity in 81% and 50% of patients with reduced postprandial antral and intestinal contractile

Address for correspondence and reprint requests: Adil E. Bharucha, M.D., Clinical and Enteric Neuroscience Translational and Epidemiological Research Program, Mayo Clinic, 200 First St. S.W., Rochester, MN 55905, Telephone: 507-284-2687, Fax: 507-538-5820, bharucha.adil@mayo.edu.

²Current location: Division of Gastroenterology, University of Calgary, Calgary, AB, Canada

Disclosures: The authors have no personal financial interests to declare.

Author Contributions:

AEB designed the research study; AEB, MC, LAS, PAL & CA performed the research; GP, KR & ARZ analyzed the data; GP, AEB & MC wrote the manuscript.

Declaration of Funding:

This study was supported in part by USPHS NIH Grant R01 DK068055. This publication was supported by Grant Number UL1 TR000135 from the National Center for Advancing Translational Sciences (NCATS). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

responses to meal, respectively. The antroduodenal pressure response to neostigmine was not higher in patients with cardiovagal dysfunction.

Conclusions & Inferences—Neostigmine increased antral and intestinal motor activity in patients with hypomotility, including intestinal dysmotility. These responses to neostigmine were not greater in patients with cardiovagal dysfunction. The use of longer-acting ACIs for treating antroduodenal dysmotility warrant further study.

Graphical Abstract

Keywords

autonomic dysfunction; gastroparesis; intestinal pseudoobstruction; neostigmine

INTRODUCTION

Acetylcholine is the principal excitatory neurotransmitter in the gastrointestinal (GI) tract. By increasing the availability of acetylcholine, neostigmine and other acetylcholinesterase inhibitors increase GI motility. Several studies have shown that neostigmine increases colonic motility in healthy human controls (1–5). Neostigmine (intravenous, 1–2 mg) is used to diagnose colonic inertia during colonic motility testing in patients with chronic constipation (6), and to treat acute colonic pseudoobstruction (7). Pyridostigmine improved symptoms and accelerated colonic transit in constipated patients with an autonomic neuropathy and diabetes mellitus (8, 9).

Neostigmine also facilitated the clearance of intestinal gas and reduced abdominal symptoms and distention in patients with irritable bowel syndrome, abdominal bloating, and intestinal dysmotility (10, 11). However, acetylcholinesterase inhibitors are infrequently used in patients with upper GI symptoms. Indeed, our understanding of their effects on stomach and small intestine motility in humans is very limited. Neostigmine induced postprandial phasic contractions in the proximal stomach in 11 healthy people (12) and increased antral motor activity in 8 patients with idiopathic gastroparesis (13). Neostigmine increased jejunal contractile pressures in 10 patients with functional dyspepsia and 10 healthy subjects (14). However, these studies were relatively small and used a lower dose of neostigmine (0.5 mg) in comparison to studies that evaluated the colonic effects of

neostigmine. In the latter, the sensorimotor effects of intravenous neostigmine were dose-dependent between 0.25 and 1.5 mg (5).

Neostigmine increases GI motility by improving neurotransmission in the myenteric plexus and at the neuromuscular junction. Because it increases the availability of acetylcholine, it follows that neostigmine can increase motility only if acetylcholine release and smooth muscle function are relatively preserved. Hence, it is conceivable that the response to neostigmine is impaired in patients with a severe enteric neuropathy or a myopathy. Conversely, extrinsic denervation may result in cholinergic hypersensitivity with an exaggerated response to neostigmine, for example, after vagal injury (15–17). Also, neostigmine, but not nerve stimulation, increased gastric contractility in *W/W^v* mice, which lack interstitial cells of Cajal (ICC) in the intramuscular, but not in the myenteric plexus (18, 19). Taken together, these observations suggest that the motor response to neostigmine may be useful for understanding the pathophysiology of impaired postprandial antral and intestinal motor activity in humans. They also raise the possibility that a cholinesterase inhibitor may partly compensate for impaired contractility even in diseases characterized by deficient ICC such as gastroparesis and intestinal dysmotility resulting from either extrinsic denervation or deficiency of ICCs. Indeed, another cholinesterase inhibitor, acotiamide, increased GI motor activity in rats and dogs (20, 21) and improved gastric emptying and symptoms in patients with functional dyspepsia (22).

Therefore, we evaluated the effects of neostigmine in patients with a suspected upper GI motility disorder who were undergoing a clinically-indicated gastroduodenal manometry study of phasic pressure activity (which will be summarized as “motility” in the rest of this paper).

Our hypotheses were that: i) neostigmine will increase gastric and intestinal motor activity, and ii) patients with cardiovagal neuropathy will have an exaggerated contractile response to neostigmine due to denervation sensitivity.

MATERIALS AND METHODS

Overall Design

This open-label study investigated the effects of intravenous neostigmine on gastroduodenal motility in 30 patients undergoing a clinically-indicated gastroduodenal manometry (GDM) test. The study was approved by the Mayo Clinic Institutional Review Board. All participants signed informed written consent.

Patients

All patients who were undergoing a clinically-indicated GDM test were eligible to participate in this study. Exclusion criteria were as follows: prior gastric, duodenal, or jejunal surgery, clinically-suspected small intestinal mechanical obstruction, EKG abnormalities (i.e., second or third degree atrioventricular block, prolonged QT interval, or resting heart rate <45/minute), use of medications affecting GI transit, or clinically-significant cardiovascular, respiratory, or renal disease.

Gastroduodenal Manometry

After an overnight fast, an eight-lumen perfusion tube was introduced along a transoral guidewire whose tip was placed into the proximal jejunum using endoscopy and fluoroscopy (23–25). This catheter has 8 water-perfused sensors which are perfused at the rate of 0.5mL/hr by a pneumohydraulic pump and attached to strain gauge transducers (Sandhill Scientific, Highlands Ranch, CO). The sensors are located at the tip of the tube and at 10, 20, 30, 31, 32, 33, and 34 cm from the tip. The latter five openings were fluoroscopically placed across the antroduodenal region; thus, the tip of the tube lay about 10cm distal to the angle of Treitz. Pressures were recorded for 3 hours before and for 2 hours after a mixed solid-liquid meal (535 kcal) with 190 mL of water. Finally, pressures were recorded for 30 minutes following administration of neostigmine (intravenous, 1mg). This dose was previously proven to increase colonic motor activity in healthy people and constipated patients (5, 6). After intravenous administration, the half-life of neostigmine is 47 to 60 minutes (mean 53 minutes) (26).

Signals from the transducers were recorded by an eight-channel recorder (Sandhill Scientific, Highlands Ranch, CO). Two gastroenterologists (MC and AEB) inspected the recordings and identified the location of antral and intestinal sensors based on the number of contractions. The most distal antral recording site was identified as the catheter that recorded up to 3 waves per minute (antral waves) just proximal to the catheter that recorded up to 12 waves per minute (duodenal waves) or to the catheter that showed a mixture of antral and duodenal waves (25, 27). The phases of migrating motor complexes (MMC) were identified and characterized based on established criteria (28). Phase 3 of the MMC was considered to have a gastric component if antral contractions occurred at a frequency of 2–3 per minute for at least 2 minutes, in temporal relationship with a duodenal phase 3 and followed by a phase 1 or motor quiescence. In the small intestine, phase 3 was identified as a migrating burst of regular contractions with a frequency of >10/min, which lasted no less than 2 minutes and was followed by a phase 1.

A single physician (GP) analyzed all tracings, identified artifacts, and counted all phasic contractions with minimum amplitude of 4 mm Hg. In each subject, gastric antral and duodenal phasic pressure activity were summarized by the frequency, amplitude, and the motility index per hour (MI/hr), which was calculated as $\log_e (\text{Number of contractions} * \text{sum of amplitude of contractions}) / [\text{duration in hours}] + 1$. For duodenal phasic pressure activity, these parameters were calculated while fasting for 30 minutes, after the meal for 60 minutes, and before and after neostigmine (30 minutes each). Because antral motor activity during the fasting period was often sparse, it was challenging to identify the appropriate sensor with confidence. Hence, data for fasting antral motor activity are not shown.

The following criteria were used to interpret manometry studies. Antral hypomotility was defined by a postprandial antral frequency of less than 2 per minute, which is a more conservative cutoff than 1 per minute (25). Myopathy was excluded when the amplitude of contractions was normal (> 20 mm Hg) (29). Qualitative features were used to diagnose small intestinal manometric abnormalities as follows. In the presence of appropriate clinical features, abnormal MMC during fasting or brief and/or non-propagated small intestinal pressure response, uncoordinated pressure bursts, or clusters or presence of MMC during the

postprandial period were used to diagnose intestinal neuropathy (i.e., without intestinal dilatation) or pseudoobstruction (i.e., with intestinal dilatation) (30). Intestinal mechanical obstruction was identified by radiological features and when present, postprandial clustered contractions (>30-min duration) separated by quiescence or simultaneous prolonged (>8 s) or summated contractions (29). For the purpose of comparing responses to a meal and neostigmine, an increase in the MI/hr of 1(logarithmic) unit was deemed to represent a satisfactory response, which is consistent with the effects of cisapride on the distal antral MI (31). Responses to neostigmine were considered separately in the antrum and small intestine.

Autonomic Functions

Cardiovascular functions were evaluated with the subject supine by heart rate responses to deep breathing, 6 breaths per minute (32).

Scintigraphic Transit: Gastric Emptying, Small Bowel, and Colonic Transit

Gastric and small bowel transit was measured in 24 and 22 patients, respectively. GI transit was measured by standard, validated scintigraphic methods (33, 34). Gastric and small bowel transit was measured by 99m -labeled technetium (^{99m}Tc). Gastric emptying was categorized as delayed, normal, or accelerated based on normal ranges for the estimated proportion emptied at 2 hours (31%–67% in women, 36%–79% in men) and at 4 hours (81%–100% in women and 87–100% in men). The proportion of ^{99m}Tc reaching the colon at 6 h (normal range is 2%–86% in women and 13%–98% in men) was used as a surrogate marker for small bowel transit.

Statistical Analysis

The postprandial and post-neostigmine antral, and separately, duodenal MI were compared with a paired t test. The association between manometric responses and other features was assessed with Fisher's exact test. Data are presented as mean $\pm$ SD.

RESULTS

Demographic and Clinical Characteristics

Of the 30 patients, vomiting and technical factors precluded administration of neostigmine and analysis of the GDM recording, respectively, in 1 patient each. Twenty-four of 28 remaining patients were women. The age was 37.5 ± 2.6 years and the BMI was 23.6 ± 1.1 kg/m².

All patients presented with clinical features suggestive of gastric and/or small intestinal dysmotility (Table 1). Based on the clinical assessment, radiological testing, and GDM, the final diagnosis (i.e., after all tests, including gastroduodenal manometry) was gastroparesis without (7 patients) or with (2 patients) intestinal neuropathy, intestinal neuropathy or pseudoobstruction (5 patients), functional dyspepsia (6 patients), chronic abdominal pain (3 patients), mechanical small intestinal obstruction (3 patients), and pelvic floor dysfunction (2 patients). Eight patients had at least one significant underlying medical condition: diabetes mellitus (4 patients), Raynaud's phenomenon (2 patients), dysautonomia (1

patient), anorexia nervosa (1 patient), myelodysplastic syndrome (1 patient), multiple sclerosis (1 patient), celiac disease (1 patient), and mixed connective tissue disease (1 patient). Nine patients reported a weight loss of greater than 10%. One patient received enteral and 2 received parenteral nutritional supplementation. Seven patients had one or more major GI surgeries, including partial resection of the ileum (5 patients), a diverting loop ileostomy (4 patients), and rectosigmoid resection (3 patients).

Gastrointestinal Transit and Cardiovascular Vagal Functions

Of 24 patients, 6 had normal, 11 had delayed, and 7 had accelerated gastric emptying. Small bowel transit (i.e., colonic filling at 6 hours) was measured and normal in 22 patients. Colonic transit was measured in 17 patients; 6 patients were assessed as delayed. Cardiovascular vagal function was assessed in 21 patients, of whom 8 had vagal dysfunction.

Effects of a Meal on Antral Pressure Activity

During the gastroduodenal manometry study, 27 patients consumed sufficient calories to evoke a fed pattern in the gastric antrum; 21 patients ingested 400 kcal or more, and 6 had between 200 and 400 kcal. One patient ingested less than 200 kcal. The manometric sensors were optimally positioned to record postprandial antral activity in 24 subjects and intestinal activity in 28 patients (Table 2). While the amplitude of postprandial antral pressure activity was normal in all patients, the frequency was 2 per minute or greater in only 7 patients, indicative of a preserved response.

Effects of Neostigmine on Antral Pressure Activity

The manometric sensors were optimally positioned to record antral motor activity after neostigmine in 22 patients who had normal (>2 distal antral contractions per minute in the postprandial period; 6 patients) or reduced (<2 contractions per minute; 16 patients) postprandial antral pressure activity, suggestive of neuropathic antral hypomotility. After neostigmine, antral pressure activity had a frequency of 1.9 ± 0.9 contractions per minute, an amplitude of 60.4 ± 39.7 mm Hg and a MI/hr of 13.2 ± 1.3 (Table 2, Figures 1 and 2). Neostigmine increased ($P < .001$) the antral MI/hr. However, the antral MI/hr was not significantly different compared to the postprandial period ($P = .13$).

Of 22 patients, 18 (82%) had an adequate antral pressure response to neostigmine, as gauged by an increase of 1 unit or greater in the MI/hr. A comparison of the antral pressure responses to a meal and neostigmine demonstrates that the antral pressure response to neostigmine was normal in a similar proportion of patients with a normal (5 of 6 patients [83%]) and a reduced (13 of 16 patients [81%]) contractile response to a meal.

Neostigmine induced antral contractions of amplitude >100 mm Hg in 8 patients (Figure 3). The effect of neostigmine on the antral MI/hr was impaired in all 7 patients with vagal dysfunction and 7 of 10 (70%) patients without vagal dysfunction. Hence, the antral response to neostigmine was not associated with vagal dysfunction. All 5 patients with both vagal dysfunction and an impaired antral contractile response to meal ingestion had an adequate response (increase in MI/hr >1) to neostigmine.

Intestinal Motor Activity

During the fasting period, one or more MMC in the small intestine were observed in 14 patients. The amplitude, frequency of propagation, and velocity were normal in all patients. These MMC were preceded with a gastric component in 11 patients. However, 1 patient had 5 MMC, suggestive of vagal dysfunction.

Intestinal pressure activity increased after a meal ($P<.001$) and after neostigmine ($P<.001$). The amplitude of contractions was normal in all patients. In 14 of 28 patients, intestinal pressure activity summarized as MI/hr increased by 1 unit after ingestion of the meal. The remaining 14 patients had intestinal neuropathy or pseudoobstruction (4 patients), gastroparesis with intestinal neuropathy (2 patients), gastroparesis without intestinal neuropathy (2 patients), or other conditions (e.g., dyspepsia, chronic abdominal pain, mechanical small intestinal obstruction [6 patients]). None of the 3 patients with radiological features and a final diagnosis of intermittent obstruction had manometric features of obstruction. Of interest, 3 of 4 patients with an intestinal neuropathy without pseudoobstruction but none of 3 patients with intestinal pseudoobstruction had an intestinal response to neostigmine ($P = .14$). The most frequently observed intestinal response to neostigmine was increased phase 2 activity in 14 patients (Figure 4); intestinal phasic pressure bursts (1 patient, Figure 5) and tonic and summated contractions (1 patient) were uncommon. The pressure response to a neostigmine was normal (i.e., increased by 1 MI/hr) in 9 of 14 patients (64%) with a normal intestinal contractile response to a meal and in 7 of 14 patients (50%) with a reduced contractile response to a meal. The association between the intestinal response to a meal and neostigmine was not significant. Six of 7 patients with reduced contractile responses to both a meal and neostigmine had intestinal neuropathy or pseudoobstruction (3 patients), gastroparesis with intestinal neuropathy (1 patient), gastroparesis without neuropathy or pseudoobstruction (1 patient), chronic abdominal pain (1 patient), or dyspepsia (1 patient). The effects of neostigmine on intestinal pressure activity were not significantly different in patients with versus without intestinal neuropathy or pseudoobstruction (Table 3).

Four of 8 patients (50%) with and 9 of 13 patients (69%) without vagal dysfunction had a normal response to neostigmine. Vagal dysfunction did not predict ($P=.65$) the intestinal response to neostigmine.

DISCUSSION

In this study, neostigmine significantly increased antral and intestinal motor activity even in some patients with antroduodenal hypomotility. In the antrum, neostigmine significantly increased the frequency but not the amplitude of contractions in a group of patients with normal amplitude baseline contractions. By contrast, neostigmine increased both the amplitude and frequency of pressure waves in the small intestine. The antral and intestinal pressure wave responses to neostigmine were not significantly associated with cardiovascular vagal dysfunction.

After neostigmine administration, on average, the antral MI/hr increased by 2.6 units in the log scale, which translates to a 13.4-fold increase in the MI. Allowing for differences in the

method for calculating the MI, these effects were substantially greater than the approximately 2.5-fold increase in antral MI with acotiamide (oral, 30 mg/kg) in dogs (21) and rats (20). These differences may be explained by the fact that neostigmine is 20-fold more potent than acotiamide for increasing acetyl cholinesterase activity in rats (20). Indeed, based on the contractile response to electrical vagal stimulation, the effective dose of acotiamide is 1000-fold greater than neostigmine in rats (20).

While neostigmine induced sustained giant antral pressure waves in 8 patients, the overall effect on the amplitude of these events was not significant. By contrast, erythromycin (intravenous, 200 mg) induced giant antral contractions but did not affect antral frequency in healthy people (27). Four possible explanations for these differences are offered. First, it is conceivable that neostigmine cannot augment the amplitude of antral contractions when the release of acetylcholine and/or smooth muscle function are impaired, as occurs in patients with enteric neuropathy and myopathy, respectively. Second, while neostigmine augments the concentration of endogenously-released acetylcholine, erythromycin directly stimulates motilin receptors on nerve and smooth muscle (35). Third, the patients who participated in this study did not have low baseline contractions in the stomach or duodenum (<20 mm Hg) to suggest myopathic disease (29). Fourth, the essential defect in neuropathic dysmotility is not in the muscle but in the neural control; when there is normal neural input, the muscle is able to produce a normal amplitude response that is not augmented further by enhancing the availability of the transmitter that simulated the muscarinic cholinergic receptor on the muscle cells.

The antral pressure wave response to neostigmine was preserved in 13 of 16 patients with an impaired antral contractile response to a meal. There are 4 possible explanations for an impaired antral contractile response to a meal: extrinsic denervation, enteric neuropathy, loss of ICCs, and myopathy. Since an antral response to neostigmine requires relatively preserved acetylcholine release and smooth muscle contractility, it seems more likely that a loss of ICC, partial loss of enteric nerves, or extrinsic denervation rather than a complete loss of enteric nerves or myopathy are responsible for an impaired antral response to a meal in these patients. Indeed, the gastric response to neostigmine is preserved in *W/W^v* mice that lack intramuscular ICC (18, 19). It has been suggested that normally, close apposition of ICC to enteric motor neurons compartmentalizes acetylcholine, which might hasten its metabolism by cholinesterase (19). However, in the absence of ICC, the neostigmine-mediated increase in acetylcholine has better access to cholinergic receptors in smooth muscle, leading to an increased contractile response (19).

Neostigmine also increased pressure wave activity in the small intestine. The most frequent pattern was increased phasic activity at a frequency of 10–12/minute, similar to a fed pattern. In contrast to octreotide or a lower dose of erythromycin (40 mg), neostigmine did not induce MMC in any patients (36, 37). Three of 4 patients with an intestinal neuropathy without pseudoobstruction but none of 3 patients with intestinal pseudoobstruction had an intestinal response to neostigmine. While the comparison was not statistically significant, these observations support the concept that an impaired intestinal response to neostigmine probably reflects more severe disease since intestinal dilation generally reflects more severe disease in patients with a neuropathy.

These findings have diagnostic and therapeutic implications. It is conceivable that the response to neostigmine, particularly in the small intestine, may be useful for assessing the severity of neuromuscular dysfunction. Compared to no response, a preserved pressure wave response to neostigmine reflects at least partially-preserved neuromuscular function in patients with antral hypomotility or an intestinal neuropathy or pseudoobstruction. Similarly, Battle and Snape observed that the colonic motor response to neostigmine was partly preserved in patients with early, but absent in patients with severe progressive systemic sclerosis (38). Likewise, a preserved colonic contractile response to neostigmine predicted the pyridostigmine-induced acceleration of colonic transit (8). While the effects of neostigmine on gastric emptying have not been evaluated, it is conceivable that neostigmine-induced increased antral motility may facilitate gastric emptying. These effects may be particularly useful since the efficacy of erythromycin is limited by tachyphylaxis, drug interactions, and the risk of prolonged QT interval (39).

A major limitation of this study is that it was uncontrolled. Antroduodenal manometry is an invasive and relatively cumbersome test. While the criteria for diagnosing intestinal neuropathy or myopathy were predominantly established in patients with a known underlying disorder (eg, diabetes mellitus), the correlations between these criteria and enteric neuropathology are limited (29). The response to neostigmine was characterized as normal, exaggerated, or reduced with rational criteria that need to be refined with further studies in healthy people. Not all patients had all tests, and the number of patients in individual groups (e.g., diabetes mellitus) was small, limiting conclusions. In summary, neostigmine significantly increased antral and intestinal motor activity even in some patients with antroduodenal hypomotility.

References

1. Chaudhary NA, Truelove SC. Human colonic motility: a comparative study of normal subjects, patients with ulcerative colitis, and patients with the irritable colon syndrome. II. The effect of prostigmin. *Gastroenterology*. 1961; 40:18–26. [PubMed: 13692638]
2. Bassotti G, Chiarioni G, Imbimbo BP, Betti C, Bonfante F, Vantini I, Morelli A, Whitehead WE. Impaired colonic motor response to cholinergic stimulation in patients with severe chronic idiopathic (slow transit type) constipation. *Dig Dis Sci*. 1993; 38:1040–5. [PubMed: 8508698]
3. Grotz RL, Pemberton JH, Levin KE, Bell AM, Hanson RB. Rectal wall contractility in healthy subjects and in patients with chronic severe constipation. *Ann Surg*. 1993; 218:761–8. [PubMed: 8257226]
4. Hammer HF, Phillips SF, Camilleri M, Hanson RB. Rectal tone, distensibility, and perception: reproducibility and response to different distensions. *Am J Physiol*. 1998; 274:G584–90. [PubMed: 9530161]
5. Law NM, Bharucha AE, Undale AS, Zinsmeister AR. Cholinergic stimulation enhances colonic motor activity, transit, and sensation in humans. *Am J Physiol Gastrointest Liver Physiol*. 2001; 281:G1228–37. [PubMed: 11668032]
6. Ravi K, Bharucha AE, Camilleri M, Rhoten D, Bakken T, Zinsmeister AR. Phenotypic Variation Of Colonic Motor Functions In Chronic Constipation. *Gastroenterology*. 2009; 138:89–97. [PubMed: 19660461]
7. De Giorgio R, Barbara G, Stanghellini V, Tonini M, Vasina V, Cola B, Corinaldesi R, Biagi G, et al. Review article: the pharmacological treatment of acute colonic pseudo-obstruction. *Aliment Pharmacol Ther*. 2001; 15:1717–27. [PubMed: 11683685]

8. Bharucha AE, Low PA, Camilleri M, Burton D, Gehrking TL, Zinsmeister AR. Pilot study of pyridostigmine in constipated patients with autonomic neuropathy. *Clin Auton Res.* 2008; 18:194–202. [PubMed: 18622640]
9. Bharucha AE, Low PA, Camilleri M, Veil E, Burton D, Kudva YC, Shah P, Gehrking T, et al. A randomised controlled study of the effect of cholinesterase inhibition on colon function in patients with diabetes mellitus and constipation. *Gut.* 2013; 62:708–15. [PubMed: 22677718]
10. Caldarella MP, Serra J, Azpiroz F, Malagelada JR. Prokinetic effects in patients with intestinal gas retention. *Gastroenterology.* 2002; 122:1748–55. [PubMed: 12055580]
11. Serra J, Villoria A, Azpiroz F, Lobo B, Santos J, Accarino A, Malagelada JR. Impaired intestinal gas propulsion in manometrically proven dysmotility and in irritable bowel syndrome. *Neurogastroenterol Motil.* 2010; 22:401–6. e91–2. [PubMed: 20047636]
12. Di Stefano M, Vos R, Klersy C, Lee KJ, Janssens J, Tack J. Neostigmine-induced postprandial phasic contractility in the proximal stomach and dyspepsia-like symptoms in healthy volunteers. *Am J Gastroenterol.* 2006; 101:2797–804. [PubMed: 17227525]
13. Bortolotti M, Cucchiara S, Sarti P, Brunelli F, Mazza M, Bagnato F, Barbara L. Comparison between the effects of neostigmine and ranitidine on interdigestive gastroduodenal motility of patients with gastroparesis. *Digestion.* 1995; 56:96–9. [PubMed: 7750675]
14. Greydanus MP, Vassallo M, Camilleri M, Nelson DK, Hanson RB, Thomforde GM. Neurohormonal factors in functional dyspepsia: insights on pathophysiological mechanisms. *Gastroenterology.* 1991; 100:1311–8. [PubMed: 1672858]
15. Tinker J, Kocak N, Jones T, Glass HI, Cox AG. Supersensitivity and gastric emptying after vagotomy. *Gut.* 1970; 11:502–5. [PubMed: 5430377]
16. Osinski MA, Bass P. Chronic denervation of rat jejunum results in cholinergic supersensitivity due to reduction of cholinesterase activity. *J Pharmacol Exp Ther.* 1993; 266:1684–90. [PubMed: 8371166]
17. Leelakusolvong S, Bharucha AE, Sarr MG, Hammond PI, Brimijoin S, Phillips SF. Effect of extrinsic denervation on muscarinic neurotransmission in the canine ileocolonic region. *Neurogastroenterol Motil.* 2003; 15:173–86. [PubMed: 12680916]
18. Ward SM, Beckett EA, Wang X, Baker F, Khoyi M, Sanders KM. Interstitial cells of Cajal mediate cholinergic neurotransmission from enteric motor neurons. *J Neurosci.* 2000; 20:1393–403. [PubMed: 10662830]
19. Sanders KM, Ward SM, Koh SD. Interstitial cells: regulators of smooth muscle function. *Physiol Rev.* 2014; 94:859–907. [PubMed: 24987007]
20. Kawachi M, Matsunaga Y, Tanaka T, Hori Y, Ito K, Nagahama K, Ozaki T, Inoue N, et al. Acotiamide hydrochloride (Z-338) enhances gastric motility and emptying by inhibiting acetylcholinesterase activity in rats. *Eur J Pharmacol.* 2011; 666:218–25. [PubMed: 21651906]
21. Nagahama K, Matsunaga Y, Kawachi M, Ito K, Tanaka T, Hori Y, Oka H, Takei M. Acotiamide, a new orally active acetylcholinesterase inhibitor, stimulated gastrointestinal motor activity in conscious dogs. *Neurogastroenterol Motil.* 2012; 24:566–74. e256. [PubMed: 22429221]
22. Kusunoki H, Haruma K, Manabe N, Imamura H, Kamada T, Shiotani A, Hata J, Sugioka H, et al. Therapeutic efficacy of acotiamide in patients with functional dyspepsia based on enhanced postprandial gastric accommodation and emptying: randomized controlled study evaluation by real-time ultrasonography. *Neurogastroenterol Motil.* 2012; 24:540–5. e250–1. [PubMed: 22385472]
23. Malagelada JR, Stanghellini V. Manometric evaluation of functional upper gut symptoms. *Gastroenterology.* 1985; 88:1223–31. [PubMed: 3979747]
24. Camilleri M, Malagelada JR, Brown ML, Becker G, Zinsmeister AR. Relation between antral motility and gastric emptying of solids and liquids in humans. *Am J Physiol.* 1985; 249:G580–5. [PubMed: 4061646]
25. Thumshirn M, Bruninga K, Camilleri M. Simplifying the evaluation of postprandial antral motor function in patients with suspected gastroparesis. *Am J Gastroenterol.* 1997; 92:1496–500. [PubMed: 9317071]

26. Cronnelly R, Stanski DR, Miller RD, Sheiner LB, Sohn YJ. Renal function and the pharmacokinetics of neostigmine in anesthetized man. *Anesthesiology*. 1979; 51:222–6. [PubMed: 382915]
27. Annese V, Janssens J, Vantrappen G, Tack J, Peeters TL, Willemse P, Van Cutsem E. Erythromycin accelerates gastric emptying by inducing antral contractions and improved gastroduodenal coordination. *Gastroenterology*. 1992; 102:823–8. [PubMed: 1537520]
28. Rees WD, Malagelada JR, Miller LJ, Go VL. Human interdigestive and postprandial gastrointestinal motor and gastrointestinal hormone patterns. *Dig Dis Sci*. 1982; 27:321–9. [PubMed: 7067584]
29. Camilleri M, Bharucha AE, di Lorenzo C, Hasler WL, Prather CM, Rao SS, Wald A. American Neurogastroenterology and Motility Society consensus statement on intraluminal measurement of gastrointestinal and colonic motility in clinical practice. *Neurogastroenterol Motil*. 2008; 20:1269–82. [PubMed: 19019032]
30. Stanghellini V, Camilleri M, Malagelada JR. Chronic idiopathic intestinal pseudo-obstruction: clinical and intestinal manometric findings. *Gut*. 1987; 28:5–12. [PubMed: 3817584]
31. Camilleri M, Malagelada JR, Abell TL, Brown ML, Hench V, Zinsmeister AR. Effect of six weeks of treatment with cisapride in gastroparesis and intestinal pseudoobstruction. *Gastroenterology*. 1989; 96:704–12. [PubMed: 2644150]
32. Low, PA. Laboratory evaluation of autonomic failure. In: Low, PA., editor. *Clinical Autonomic Disorders: Evaluation and Management*. Boston: Little, Brown and Company; 1993. p. 169-95.
33. Deiteren A, Camilleri M, Bharucha AE, Burton D, McKinzie S, Rao AS, Zinsmeister AR. Performance characteristics of scintigraphic colon transit measurement in health and irritable bowel syndrome and relationship to bowel functions. *Neurogastroenterol Motil*. 2010; 22:415–23. e95. [PubMed: 20025675]
34. Camilleri M, Iturrino J, Bharucha AE, Burton D, Shin A, Jeong ID, Zinsmeister AR. Performance characteristics of scintigraphic measurement of gastric emptying of solids in healthy participants. *Neurogastroenterol Motil*. 2012; 24:1076–e562. [PubMed: 22747676]
35. Coulie B, Tack J, Peeters T, Janssens J. Involvement of two different pathways in the motor effects of erythromycin on the gastric antrum in humans. *Gut*. 1998; 43:395–400. [PubMed: 9863486]
36. Tack J, Janssens J, Vantrappen G, Peeters T, Annese V, Depoortere I, Muls E, Bouillon R. Effect of erythromycin on gastric motility in controls and in diabetic gastroparesis. *Gastroenterology*. 1992; 103:72–9. [PubMed: 1612359]
37. Haruma K, Wiste JA, Camilleri M. Effect of octreotide on gastrointestinal pressure profiles in health and in functional and organic gastrointestinal disorders. *Gut*. 1994; 35:1064–9. [PubMed: 7926907]
38. Battle WM, Snape WJ Jr, Wright S, Sullivan MA, Cohen S, Meyers A, Tuthill R. Abnormal colonic motility in progressive systemic sclerosis. *Ann Intern Med*. 1981; 94:749–52. [PubMed: 7235416]
39. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L. American College of Gastroenterology. Clinical guideline: management of gastroparesis. *Am J Gastroenterol*. 2013; 108:18–37. quiz 8. [PubMed: 23147521]

KEY MESSAGES

- Our aim was to evaluate the effect of neostigmine on gastroduodenal activity in patients with a suspected GI motility disorder
- A total of 28 patients with gastroparesis, intestinal neuropathy/pseudoobstruction, or other upper gastrointestinal motility disorder underwent antroduodenal manometry in the study
- Neostigmine significantly increased both antral and intestinal pressure activity, even in some patients with antroduodenal hypomotility. Neostigmine increased both the amplitude and frequency of pressure waves in the small intestine. The antral and intestinal responses to neostigmine were not significantly associated with cardiovascular vagal dysfunction

Figure 1. Effect of neostigmine on antral motility

Solid lines indicate a normal response, as defined by an increase in the motility index/hour of 1 unit or greater. Dashed lines indicate an increase of less than 1 unit. Data refers to patients in whom the manometric sensors were optimally positioned, N= 22.

Figure 2. Effects of meal (left panel) and neostigmine (right panel) on antral motility
Left panel: Postprandial antral hypomotility. Right panel: Neostigmine-induced antral motor activity (Channel 3 represents antrum).

Figure 3. Giant antral contractions induced by neostigmine (Channel 2 represents antrum)

Figure 4. Effect of neostigmine on intestinal motility

Left panel: Pre neostigmine period; Right panel: Post neostigmine period (Channel 1 represents intestine)

Figure 5. Intestinal bursts induced by neostigmine (Channel 5 represents intestine)

Table 1

Individual Patient Characteristics

No.	Presenting clinical features	Final diagnosis ^a	GE ^b	Vagal Function ^c	Fasting MMC ^d	Meal response by Manometry ^e		Intestinal manometry - qualitative abnormalities	Neostigmine response ^f	
						Antrum	Intestine		Antrum	Intestine
1	Chronic AP, narcotic dependence	Pelvic floor dysfunction	0	0	2	+	-	None	-	++
2	FD	Functional dyspepsia, diarrhea, SIBO, status post subtotal colectomy	1	0	2	NA	+	None	NA	++
3	FD, GERD	Idiopathic gastroparesis	1	0	0	-	+	None	-	+
4	Intermittent AP, N/V	Intermittent mechanical small intestinal obstruction, status post partial colectomy, ileostomy	2	0	0	+	+	None	NA	-
5	Chronic N/V	Intestinal neuropathy status post ileostomy, partial colectomy	0	1	2	-	+	F - Clusters of phasic activity	++	++
6	Chronic N/V	FD, recurrent vomiting.	0	0	0	-	-	None	++	-
7	Chronic AP, N/V	Chronic intestinal pseudoobstruction	NA	1	2	-	-	PP - Propagated clusters of phasic activity	+	-
8	Intermittent AP, N/V	Intermittent mechanical small intestinal obstruction	2	0	0	-	-	None	++	+
9	Chronic AP, N/V	Functional abdominal bloating	2	0	0	-	+	None	-	+
10	Intermittent AP, N/V	Intermittent mechanical small intestinal obstruction, DM, myelodysplastic syndrome	1	NA	2	-	+	PP - Propagated clusters of phasic activity	-	+(burst)
11	Chronic AP	Chronic intestinal pseudoobstruction, SIBO	2	NA	2	NA	-	Paucity of contractile activity, and presence of common cavity waves	NA	-
12	Intermittent AP, N/V	Intestinal neuropathy status post ileostomy	NA	0	0	-	-	PP - Poor conversion to fed pattern	++	+
13	Chronic vomiting	FD with vomiting	2	0	0	NA	+	None	NA	-

No.	Presenting clinical features	Final diagnosis ^a	GE ^b	Vagal Function ^c	Fasting MMC ^d	Meal response by Manometry ^e		Intestinal manometry - qualitative abnormalities	Neostigmine response ^f	
						Antrum	Intestine		Antrum	Intestine
14	Chronic vomiting	DM gastroparesis with intestinal neuropathy	1	1	1	+	+	PP - Poor conversion to fed pattern	++	+
15	Connective tissue disorder and vomiting	FD, Morphea	2	1	2	-	-	None	NA	+
16	Chronic vomiting and early satiety	Idiopathic gastroparesis	1	0	2	-	-	None	+	+
17	FD	Diabetic gastroparesis	NA	1	0	+	-	None	++	++
18	Chronic anorexia, constipation and weight loss	Pelvic floor dysfunction, abdominal distension, multiple sclerosis	0	1	2	+	+	None	++	-
19	Eating disorder with gastric dilation and retention	Small intestinal pseudoobstruction, anorexia nervosa, constipation, status post rectopexy, ileostomy and ileal resection	2	1	0	-	-	F and PP - Sustained incoordinated phasic activity and repetitive bursts of phasic activity	++	-
20	Chronic N/V	Gastroparesis, celiac disease in remission	1	1	2	-	+	None	+	-
21	Chronic vomiting	Diabetic gastroparesis, dysautonomia	NA	NA	0	+	+	None	++	+
22	Chronic AP and weight loss	Chronic abdominal pain, superior mesenteric artery compression syndrome	1	NA	2	-	+	None	+	-
23	Chronic AP and weight loss	Chronic abdominal pain, narcotic bowel syndrome	1	NA	2	NA	-	None	NA	-
24	Chronic N/V	FD	0	0	0	+	-	None	++	+
25	Chronic N/V	Gastroparesis	1	0	0	-	-	None	++	-
26	FD	FD, POTS	0	0	0	-	+	None	++	+
27	Gastroparesis	Gastroparesis	1	NA	2	-	+	None	++	++
28	Gastroparesis with weight loss	Gastroparesis with intestinal neuropathy	1	NA	0	-	-	F - phasic pressure bursts and incompletely propagated MMC without distal quiescence	+	-

Abbreviations: GE, gastric emptying; MMC, migrating motor complex; SIBO, small intestinal bacterial overgrowth; POTS, postural orthostatic tachycardia syndrome; GERD, gastroesophageal reflux disease; FD, functional dyspepsia; AP, abdominal pain; N/V, nausea/vomiting; DM – diabetes mellitus; F-fasting, PP - postprandial

^aThe final diagnosis takes into consideration the clinical features and objective findings, including the results of the gastroduodenal manometry study.

^b0 Normal, 1: Delayed, 2 Rapid. Delayed emptying was defined on the basis of delayed emptying at 2 or 4 hours while rapid emptying was defined on the basis of increased emptying at 1 or 2 hours.

^c0 Normal, 1 Abnormal

^d0 Normal, 1 Abnormal, 2 Not observed

^e+ Response present, – Reduced or absent response (i.e., postprandial increase of less than 1 MI/hr), NA Suboptimal catheter placement

^f₊₊₊ Response exaggerated, + Response present, – No response, NA: Poor recording

Table 2Characteristics of Gastric Antral and Intestinal Motor Activity After a Meal and Neostigmine ^a

	Post Meal	Pre Neostigmine	Post Neostigmine
Antral Amplitude, mm Hg ^b	49.9 ± 22.0	42.2 ± 24.6	60.4 ± 39.7
Antral Frequency, cpm ^b	1.6 ± 0.8	0.7 ± 0.6	1.9 ± 0.9 ^d
Antral MI/hr ^b	12.7 ± 1.3	10.6 ± 1.6	13.2 ± 1.3 ^d
Intestinal Amplitude, mm Hg ^c	27.4 ± 9.8	25.1 ± 10.4	40.2 ± 18.7 ^{d,e}
Intestinal Frequency, cpm ^c	7.0 ± 2.2	6.1 ± 2.9	7.8 ± 2.3 ^d
Intestinal MI/hr ^c	15.2 ± 1.1	14.7 ± 1.2	15.8 ± 1.1 ^{d,e}

Abbreviations: cpm, contractions per minute; MI/hr, motility index per hour

^aValues are mean ± SD^bN = 22,^cN = 28^d*P* < .01 for Post Neostigmine vs Pre Neostigmine^e*P* < .05 for Post Neostigmine vs Post Meal

Table 3

Comparison of Antral and Intestinal Responses to a Meal and Neostigmine in Patients With Gastrointestinal Motility Disorders^a

	Gastroparesis (N = 9)	Intestinal Neuropathy or Pseudoobstruction (N = 5)	Other ^b (N = 14)
Meal			
Increase in antral activity	0.3 ± 2.2	3.0 ± 0.9	0.5 ± 1.7
Increase in intestinal activity	1.2 ± 1.1	0.5 ± 1.4	1.6 ± 1.7
Neostigmine			
Increase in antral activity	2.7 ± 1.4	4.2 ± 2.0	1.8 ± 2.6
Increase in intestinal activity	1.4 ± 0.9	0.4 ± 1.2	1.0 ± 0.8

^aValues are mean ± SD

^bOther conditions include functional dyspepsia (n=6), chronic abdominal pain (n=3), mechanical small intestinal obstruction (n=3) and pelvic floor dysfunction (n=2)