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Evaluating the Safety and the Effects on Colonic Compliance of Neostigmine during Motility Testing in Patients with Chronic Constipation

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Abstract

Background—Neostigmine, an acetyl cholinesterase inhibitor, stimulates colonic motor activity and may induce vagally-mediated cardiovascular effects. Our aim was to evaluate effects of i.v. neostigmine on colonic compliance and its safety in patients with chronic constipation.

Methods—We retrospectively reviewed medical records of a randomly selected group of 144 outpatients with chronic constipation who were refractory to treatment. These patients had undergone intracolonic motility and compliance measurements with an infinitely compliant balloon linked to a barostat. Data abstracted included barostat balloon mean volumes with increases in pressure (4mmHg steps from 0–44mmHg) before and after i.v. neostigmine. Vital signs and oxygen saturation before and after neostigmine were recorded.

Key Results—Of the 144 patients, 133 were female, mean age was 41.0 ± 15.4 years (SD), and duration of constipation was 12.9 ± 13.8 years. Among patients who had undergone colonic transit measurement by scintigraphy, the overall colonic transit at 24 hours [GC24 (n=115)] was 1.5 ± 0.7 (normal >1.3), and at 48 hours [GC48 (n=75)] it was 2.3 ± 0.9 (normal >1.9). Neostigmine decreased colonic compliance at lower distension pressures [e.g. 12 and 20mmHg (both $P < 0.001$)], but not at 40mmHg. There were expected minor changes in vital signs in response to neostigmine in 144 patients; however, 1 patient developed unresponsiveness, significant bradycardia, hypotension, and muscular rigidity that responded to 400mcg i.v. atropine.

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Conclusions & Inferences—Neostigmine significantly decreases colonic compliance in patients with refractory chronic constipation. Symptomatic bradycardia in response to neostigmine should be promptly reversed with atropine.

Keywords

neostigmine; colonic compliance; motility testing; chronic constipation

Constipation is a common disorder affecting women more than men (1). Among constipated patients who do not respond to laxatives (2,3), assessments to identify pelvic floor dysfunction, slow transit constipation (4), and colonic inertia (5) should be considered when appropriate. Colonic inertia is diagnosed by an inadequate contraction in response to a physiological stimulus (i.e., a meal) and in response to a pharmacological stimulus (e.g., intraluminal bisacodyl or parenteral neostigmine) as assessed with manometry, myoelectrical activity and/or a barostat (6,7). Intraluminal assessments document colonic motor dysfunction and may facilitate selection of therapy. Thus, a colectomy with ileorectal anastomosis is efficacious in patients with medically refractory constipation who do not have pelvic floor dysfunction (8–10). Ravi et al. previously reported the Mayo Clinic experience with measurements of colonic phasic pressure activity, tone and compliance in patients with chronic constipation and showed that, compared with healthy subjects, colonic compliance was reduced in isolated slow transit constipation and defecatory disorders, but not in patients with normal transit constipation (6). In addition, fasting and/or postprandial colonic tone were reduced, reflecting motor dysfunctions, even in some patients with normal transit constipation (6). In the same report, the colon was less compliant (i.e., stiffer) after neostigmine, as evidenced by a higher Pr50 (pressure at half maximum volume) in all subtypes of constipation. However, the effect on colonic compliance was not associated ($r_s = 0.05$; $p = 0.66$) with the tonic contractile response to a meal, a physiological response reflecting colonic motility (6). The relationship between colonic compliance and colonic transit has not been evaluated.

We recently reported on colonic compliance, including the effects of neostigmine, in patients with chronic megacolon, in whom the colon's diameter typically exceeds 6.5cm at the pelvic brim (11). In the human colon, subtypes of muscarinic receptors are present on multiple cell types within the enteric circuits underlying motility, secretory and vasoactive reflexes (12). Neostigmine is an acetylcholinesterase inhibitor which increases colonic tone and phasic pressure activity in healthy people by increasing the availability of acetylcholine (13). Neostigmine is used to treat colonic dysfunction in acute colonic pseudo-obstruction (Ogilvie's syndrome) and spinal cord injury (14).

The aims of this study were to appraise the effects of intravenous neostigmine on colonic compliance and its safety in patients with treatment-refractory chronic constipation undergoing measurements of colonic motility in a clinical laboratory.

MATERIALS AND METHODS

Mayo Clinic Institutional Review Board approved this study for patients who had consented to the use of their medical records for research.

Patients

We studied 144 patients with medically-refractory constipation who underwent a colonic motility study at Mayo Clinic between January 2010 and April 2015. Patients with chronic megacolon diagnosed by radiographic studies (15) or a colonic motility study (11) were excluded from this analysis.

Data Extraction from Medical Records

The data extracted for this study included age, sex, BMI, years of constipation, colonic transit measured with scintigraphy (16), and effects of neostigmine on measurements during the colonic motility study (i.e., barostat balloon volumes before and after neostigmine administration, with a primary focus on volumes at 12, 16, 20, and 40mmHg). We also assessed vital signs (heart rate, systolic blood pressure, diastolic blood pressure, oxygen saturation, and time to maximal drop in heart rate).

Measurement of Colonic Motor Activity

Each patient underwent an intracolonic motility study including measurement of colonic compliance with a 10cm-long polyethylene balloon controlled by a rigid piston barostat. After discontinuing medications which have potential effects on colonic motility for 48 hours, the colon was cleansed with 2–5 liters of polyethylene glycol 3350 electrolyte solution, and the patients fasted the night before the procedure. Colonic motor functions were measured with an assembly that contains 6 manometric sensors and a 10cm-long infinitely compliant balloon linked to an electric rigid piston barostat. The balloon was positioned in the left colon with the aid of unsedated flexible sigmoidoscopy, as described previously (17). A conditioning distension, in which the pressure was increased from 0 to 44mmHg at 4mmHg steps at 15-second intervals, was performed in preparation for compliance measurement (17). Thereafter, compliance (volume response to imposed pressure in the infinitely compliant polyethylene balloon) was measured while the patient was fasting by balloon inflation from 0–44mmHg using 4mmHg steps at 30-second intervals. After evaluating the colonic contractile response for 1 hour after a 1000kcal liquid meal, neostigmine (1mg, diluted in 5mL of saline) was administered over 1–2 minutes into a forearm vein. Colonic compliance was reassessed with an identical protocol thereafter. The colonic contractile response to a meal is not analyzed in this report.

As part of the clinical assessment of colonic motor function, before referring the patient for colectomy for severe constipation, the colonic motility test included study of the effects of neostigmine, unless there was a clinical contraindication to the administration of neostigmine (detailed in patients eligibility section).

Neostigmine

Neostigmine was administered by a physician with continuous hemodynamic monitoring, as described above. In 1 study (18), initial and peak hemodynamic effects after intravenous neostigmine were observed within 1 minute and at 20 minutes, respectively. In another study (19), the elimination half-life averaged 53 minutes (range 47 to 60 minutes).

Colonic Transit Measurement by Scintigraphy

On days separate from the colonic motility test, 115 of the 144 patients underwent colonic transit. Patients who had undergone colonic measurements elsewhere did not have the test repeated.

Colon transit was assessed with a well-validated method involving ingestion of a methacrylate-coated gelatin capsule containing indium-111 charcoal in the morning after an overnight fast (17). When the capsule had been demonstrated to have emptied from the stomach, all participants received a standard breakfast (218kcal egg meal) at time 0, and were instructed to ingest meals of ~530kcal at 4 hours and ~750kcal at 8 hours.

Scans to measure colonic transit were obtained at 4 and 24 hours and, in most patients, at 48 hours after ingestion of the isotope. Colonic transit was summarized as the geometric center (weighted average of counts in 4 colonic regions and stool) at 24 and 48 hours (16,20). Results obtained were compared with normal data previously published from our laboratory (21).

Data Analysis

The data are reported as mean ($\pm$ SD) or median (interquartile range, IQR) as appropriate.

Colonic Compliance Measurements

Previous studies suggest that the effects of pharmacological modulation with α_2 adrenergic and cholinergic agents on colonic compliance are most pronounced when the colon is distended over low to moderately high pressures of 4 and 24mmHg (13,22,23). By contrast, colonic distension by higher pressures (i.e., 28–44mmHg) is generally sufficient to overcome the effects of pharmacologically-increased colonic tone. Hence, the assessment of colonic pressure-volume relationships at pressures ranging from 28 to 44mmHg is typically more useful in patients with megacolon (11).

Therefore, in the current study, the primary endpoints were a comparison of the mean volumes of a 10cm-long balloon distended with a barostat to 12, 20, and 40mmHg before and after neostigmine administration with Wilcoxon's Signed Rank test. In order to control for potential differences in the starting colonic volume before distension, we subtracted the balloon volume at 4mmHg distension from the volume measured at 12, 20 and 40mmHg. In these analyses, a p-value <0.017 was considered significant, given the selection of three separate pressures (12, 20 and 40mmHg, corrected for volumes at 4mmHg distension) for comparison.

When a single pressure level was required to reflect the responsive part of the compliance curve, we used volumes at a pressure of 16mmHg. The correlation between colonic transit measured in the absence of the intraluminal device and colonic compliance (using the volume at 16mmHg) before neostigmine was assessed using Spearman correlation analysis.

All analyses were performed using JMP software (Statistical DiscoveryTM from SAS) and plotted using SigmaPlot12 (Systat Software, Inc).

RESULTS

Patient Eligibility and Demographics

Of 178 patients screened, 144 were enrolled and the rest were excluded, as described in Figure 1. Post-neostigmine compliance was not evaluated or completed in 11 patients because of potential contraindications to neostigmine (3 patients: 1 with bradyarrhythmia, 1 with premature ventricular complexes, and 1 with AV block), development of side effects to neostigmine (4 patients: 1 with nausea, hypotension, bradycardia and tonic-clonic seizure requiring atropine administration; the others with fainting, pain, or undescribed reaction, but atropine was not required), patients who declined neostigmine administration (2 patients), and two patients received bisacodyl during the 48 hours prior to the test.

The mean age of the 144 patients (133 female) was 41.0 ± 15.4 years. The average duration of constipation was 12.9 ± 13.8 years.

Colonic Transit

The average overall colonic transit (geometric center, GC) at 24 hours (GC24) in 115 patients was 1.5 ± 0.7 (compared to 5th percentile in healthy volunteers < 1.3), and at 48 hours (GC48) in 75 patients it was 2.3 ± 0.9 [compared to < 1.9 in healthy volunteers (21)]. Eight-four patients had normal and 59 had slow colonic transit.

Colonic Compliance after Neostigmine Administration

Figure 2 compares mean barostat balloon volumes at different distending pressures before and after injection of neostigmine. After neostigmine, colonic balloon volumes (corrected for volumes at 4mmHg distension) were lower, reflecting decreased compliance, at 12mmHg and 20mmHg (both $p < 0.001$; median and interquartile and full ranges in Figures 2 and 3). In contrast, neostigmine did not significantly decrease the volume of a colonic balloon distended to 40mmHg (corrected for volumes at 4mmHg distension) (Figure 4).

Correlation between Colonic Compliance and Colonic Transit

In order to appraise the association of colonic compliance and colonic transit before neostigmine administration, there was a significant correlation between colonic transit (GC24) and the volume of colonic balloon at 16mmHg distension, as a surrogate for colonic compliance (Figure 4).

Effects of Neostigmine on Hemodynamic Parameters

Heart rate and systolic blood pressure declined, but diastolic blood pressure increased after neostigmine (Table 1). However, oxygen saturation dropped only by an average of 1.7%, which suggests that none of the patients were exposed to significant drops in arterial pO_2 , based on the expected oxygen saturation curves in these relatively healthy patients. However, a significant and severe adverse event was observed in one patient who required reversal with intravenous atropine. This patient was an insulin-dependent diabetic with gastroparesis, but no documented record of autonomic dysfunction. Within one minute of neostigmine administration, the patient developed nausea, chest pain, hypotension (111/67mmHg, dropping to undetectable), bradycardia (93bpm, dropping to 30bpm), tonic

seizure-like activity, rigidity and unresponsiveness. After administration of 400mcg of atropine intravenously, the patient's hemodynamic parameters improved and she regained consciousness within 2–3 minutes. After subsequent monitoring in the emergency room, she was discharged home without long-term sequelae. Blood glucose was above 80mg/dL during the entire adverse event in this patient.

DISCUSSION

This study shows that neostigmine decreases colonic compliance, suggestive of increased colonic tone, in patients with chronic constipation who did not have megacolon. While neostigmine (1mg, i.v.) reduced heart rate and systolic blood pressure, oxygen saturation was unchanged in most patients. These observations in a large cohort of 144 patients with constipation of varying severity suggest that intravenous neostigmine can be administered safely in a clinical motility laboratory and support its use to augment colonic motor activity in acute colonic pseudo-obstruction. Similar to the small intestine, it is conceivable that the colonic contractile response to neostigmine may be useful for assessing the severity of neuromuscular dysfunction (24). Moreover, the acute effects of intravenous neostigmine on colonic transit and, separately, on colonic motility also predicted the effect of oral pyridostigmine on colonic transit in patients with autonomic neuropathy and constipation (25).

These findings expand on previous studies documenting that neostigmine reduced colonic compliance and accelerated colonic transit in healthy volunteers (13). Neostigmine also increased colonic contractility during the post-operative phase after left colonic or rectal resection for rectal cancer or recurrent diverticulitis (26). By contrast, the tonic response to neostigmine was reduced in chronic constipation (27). Neostigmine also reduced colonic volumes in patients with megacolon, but the effects were not statistically significant (11). In the prior study, at a distending pressure of 20mmHg, a volume greater than 300mL for a 10cm-long intracolonic balloon is virtually diagnostic of chronic megacolon. At 44mmHg pressure distension, the median balloon volume was 584mL (IQR 556.5–600) in patients with megacolon compared to 251mL (IQR 212–281) in healthy controls, 241mL (210.8–277.5) in diarrhea-predominant irritable bowel syndrome, and 240mL (IQR 207–286) in constipation-predominant irritable bowel syndrome (11).

In this study, neostigmine significantly decreased colonic compliance at 12mmHg and 20mmHg, but not at 40mmHg or 44mmHg. The most logical interpretation is that, at lower and intermediate pressures, the pharmacological effect of the drug reduced compliance, whereas, at 40mmHg, the pressure imposed by the rigid piston barostat overcomes the contraction induced by neostigmine.

Our studies explored the association of baseline colonic compliance measured at 16mmHg distension and colonic transit. The statistically significant, though weak ($R_s=0.21$), correlation may be surprising on first examination, since it would imply slightly faster colonic transit in a more compliant (or less contracted) colon. However, it is relevant to note that transit is dependent on resistance to flow in addition to the contractile response of the colon. It has been demonstrated that there is a paradoxical relationship between contractility

of the colon and bowel function (28), although those earlier studies did not appraise colonic compliance, tone or the high amplitude colonic contractions. Conversely, the studies that have demonstrated the propulsive potential of high amplitude colonic contractions by simultaneously measuring colonic transit did not include measurements of compliance and tone. Clearly, further studies are needed to appraise the effects on colonic transit on all these dimensions of motor functions in the unprepared colon (29).

Our data are consistent with a small overall contribution of higher compliance (in the absence of megacolon) of the colon, facilitating colonic transit, possibly reflecting the ability of the colon to relax in response to the oncoming fecal bolus. This is also consistent with the importance of the role of inhibitory innervation in the relaxation of the receiving segment in the classical models of peristalsis in the colon (30).

One of 144 patients had a significant adverse effect to neostigmine, reinforcing the need to administer the drug cautiously. The heart rate, blood pressure, and oxygen saturation should be monitored until it returns to baseline. A physician should be by the patient's bedside for 15 minutes and, preferably, until the heart rate begins to increase. Venous access and atropine should be readily available to reverse any adverse hemodynamic effects such as bradycardia, which is symptomatic, or when the pulse declines to less than 45 beats per minute.

In a meta-analysis of four randomized, controlled trials assessing intravenous neostigmine, with a dose ranging from 2 to 5mg, for acute colonic pseudo-obstruction, abdominal pain was the most common side effect (53.1%), followed by sialorrhoea (31.1%), and vomiting (15.6%) (31). Bradycardia occurred only in about 6.5% of patients (31). In our study, bradycardia (i.e., heart rates less than 50bpm) was documented in 27/144 (18.8%) of the patients; one patient developed severe bradycardia that was reversed with atropine. The mean time to maximum heart rate drop was approximately 13.0 minutes in other patients. One study in which colonic motor activity was recorded with barium fluoroscopy suggested that glycopyrrolate attenuated neostigmine-induced bradycardia and bronchospasm, but not increased colonic contractility in patients with spinal cord injury (32). These effects of glycopyrrolate need to be confirmed with more detailed assessments of colonic motor activity and transit.

While this is the largest study to assess the colonic motor effects of neostigmine in constipated patients, there are some limitations. Colonic transit was not evaluated in all patients. Other common adverse effects of neostigmine (e.g., abdominal pain) are not reported because they were not systematically appraised in these patients. In addition, this is a retrospective evaluation; a prospective study of the same number patients would require at least 5 years, given the frequency of colonic motility testing at our institution.

Another limitation of this study is that it focused on the pharmacological effects and safety, rather than the outcomes from the results or the impact on choice of therapy. The latter would need to be addressed by future prospective studies.

In conclusion, neostigmine reduced colonic compliance in patients with chronic constipation, and our study provides quantitative data on the magnitude of the response that

is most readily appreciated at distensions up to 20mmHg, making this a feasible test of motor function that may be applied in clinical or research settings. The pharmacological effect of cholinesterase inhibition with neostigmine provides objective evidence of the colon's neuromuscular responsiveness to endogenous acetyl choline, providing a rationale for medical therapy in patients with constipation. The study also provides reassurance that, with sensible precautions, this pharmacological test can be applied in the clinical motility laboratory setting.

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KEY MESSAGES

- Neostigmine significantly decreases colonic compliance in patients with refractory chronic constipation, and symptomatic bradycardia in response to neostigmine should be promptly reversed with atropine.
- We aimed to evaluate effects of i.v. neostigmine on colonic compliance and its safety in patients with chronic constipation.
- We retrospectively reviewed medical records of a randomly selected group of 144 patients with chronic constipation who were refractory to treatment. Data abstracted included barostat balloon mean volumes with increases in pressure (4mmHg steps from 0–44mmHg) before and after i.v. neostigmine [data are mean ($\pm$ SD) or median (interquartile range, IQR) as appropriate].
- Among patients who had undergone colonic transit measurement by scintigraphy, the overall colonic transit at 24 hours [GC24 (n=115)] was 1.5 ± 0.7 (normal >1.3), and at 48 hours [GC48 (n=75)] it was 2.3 ± 0.9 (normal >1.9). Neostigmine decreased colonic compliance at lower distension pressures [e.g. 12 and 20mmHg (both $P<0.001$)], but not at 40mmHg.

Figure 1.
Selection of patients included in the appraisal of the effects of neostigmine on colonic compliance

Figure 2.
Plots of mean barostat balloon volumes at different distension pressures in the 144 patients before and after injection of neostigmine

Figure 3. Barostat balloon volumes in response to 12, 20 and 40mmHg distension pressures (corrected for volume at 4mmHg distension) at baseline and after i.v. neostigmine

Figure 4.
Spearman correlation of colonic transit and uncorrected colonic volume at 16mmHg at baseline

Table 1

Measurements of cardiovascular parameters at baseline and in response to neostigmine

Data (mean±SD)	N	Baseline	Post-neostigmine
Heart rate, bpm	144	79.1±19.1	52.0±17.1
Systolic blood pressure, mmHg	144	119.3±16.7	93.4±48.3
Diastolic blood pressure, mmHg	144	69.5±12.5	87.7±27.2
Oxygen saturation, %	144	98.2±2.2	97.5±3.2
Time to maximum heart rate drop, min	144		13.0 ± 5.8