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Infusion of Neostigmine–Glycopyrrolate for Bowel Evacuation in Persons with Spinal Cord Injury

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Defecatory complications are common after spinal cord injury (SCI) and have been attributed, in part, to an imbalance of the autonomic nervous system between parasympathetic and sympathetic effects on the colon. Because parasympathetic (*i.e.,* cholinergic) input to the bowel may be downregulated after SCI, it was hypothesized that neostigmine, a medication that increases cholinergic tone by blocking the metabolism of acetylcholine, might promote bowel evacuation in these persons. Since neostigmine is known to cause bradycardia and bronchoconstriction, we also assessed whether these side-effects could be prevented by coadministration of neostigmine with glycopyrrolate, an anticholinergic agent that has limited activity on the muscarinic receptors of the colon. The hypothesis was tested in 13 persons with SCI in whom videofluoroscopy was carried out after instillation of a barium oatmeal paste into the rectum and descending colon. On separate days, subjects received, in a randomized, blinded design, one of three intravenous infusates (normal saline, 2 mg neostigmine, or 2 mg neostigmine + 0.4 mg glycopyrrolate). The effect of these infusates on bowel evacuation of the barium paste, heart rate, and airway resistance was determined. Both neostigmine and neostigmine + glycopyrrolate resulted in prompt bowel evacuation. The nadir heart rate was lower after neostigmine alone than with the combination. Neostigmine administration increased both total and central airway resistance, an effect that was not observed with the coadministration of glycopyrrolate. Other side-effects of neostigmine and the combination of drugs included muscle fasciculations and dry mouth, both of which were mild and short-lived. Abdominal cramping was noted in subjects with spinal cord lesions below thoracic level 10. These results indicated that neostigmine/glycopyrrolate administration is safe and well tolerated in persons with chronic SCI.

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INTRODUCTION

Spinal cord injury (SCI) prolongs transit time through the colon, resulting in constipation, impactions, and diverse anorectal problems (1–3). Prolongation of the colonic transit time has been attributed to a relative decrease in prokinetic actions of parasympathetic neurons (4). Collectively, the alterations in bowel habits that occur after SCI have been termed difficulty with evacuation (DWE). The standard approach to routine bowel care after SCI involves dietary changes, oral administration of stimulant or osmotic laxatives, enemas, suppositories, and digital manipulation of the anal orifice (5). Though effective in most individuals with SCI, these approaches are time-consuming and the outcome is often unpredictable. As a consequence, individuals with SCI continue to regard bowel problems as a major barrier to their complete reintegration into society.

Data are presented herein regarding the use of neostigmine to promote bowel evacuation in individuals with SCI. By inhibiting the enzyme acetylcholinesterase, neostigmine increases parasympathetic stimulation of the bowel. This, in turn, increases peristaltic contractions of the left colon resulting in evacuation of intestinal contents. Neostigmine has become a mainstay in the treatment of intestinal pseudoobstruction, another condition thought to result from parasympathetic–sympathetic derangement. Appreciating a possible functional similarity to pseudoobstruction, our hypothesis was that neostigmine would result in prompt evacuation of the colon in persons with SCI.

Bradycardia and bronchoconstriction are well-established adverse actions of neostigmine administration (6). These potential cardiopulmonary adverse effects have restricted the use of parenteral neostigmine to that of monitored settings. In seeking to overcome this limitation, we assessed whether the adverse cardiopulmonary effects of neostigmine could be blocked without interfering with its prokinetic properties on the colon. On the basis of previous reports, we postulated that glycopyrrolate, a selective anticholinergic agent, may antagonize the major, untoward side effects of neostigmine without interfering with its actions on the bowel.

Material in this paper was presented, in part, at the meeting of the American Gastroenterological Association held during May 2003 in Orlando, FL and published in abstract form in Gastroenterology 2003; 124(Suppl 1):A-115.

METHODOLOGY

Subjects

Thirteen subjects with SCI (5 with quadriplegia and 8 with paraplegia) were entered into this study after being informed of the risks and benefits of participation. The informed consent had previously been reviewed and approved by the Institutional Review Board of the VA Medical Center, Bronx, NY. Individuals with the following conditions were excluded from participating in the study: A history of cardiac or renal disease, arrhythmias, bronchial asthma, and autonomic dysreflexia. The usual bowel care of the subjects required 1–2 h but was otherwise uncomplicated at the time of the study.

Methods

Subjects were studied after having performed their usual bowel care regimen during the evening and morning prior to the investigation. Bowel care consisted of ingestion of a laxative the night before (cascara or senna) and administration of enemas and suppositories on the morning of the study. Digital rectal stimulation was also employed by some of the participants. At the time of the studies (early afternoon), intravenous access was established and subjects were placed on a padded fluoroscopic table in the left lateral position. Subjects remained in this position for the entire study. Under fluoroscopic guidance, approximately 200 ml of an oatmeal barium paste having the consistency of soft stool was instilled into the rectum and descending colon. After a 20 min equilibration period, subjects were administered intravenously one of the following on three different days: 2 mg neostigmine, 2 mg neostigmine + 0.4 mg glycopyrrolate, or normal saline. These infusates were administered in a random order and the subjects were blinded as to the nature of the infusate. Over the next 30 min, the following parameters were measured: bowel evacuation, blood pressure, and pulse (Vital Check 4400, Alaris Medical Systems, San Diego, CA), and total and central airway resistances (Viasys Healthcare, Respiratory Technologies, Yorba Linda, CA). The latter were measured using the forced oscillation technique. Oscillations produced by a loudspeaker were "forced" into the airway during normal tidal breathing for 30 s at two frequencies (5 Hz for total and 20 Hz for central airway resistance). Airway resistance was calculated from the pressure–flow relationship obtained on the reflected waves (7).

Bowel Evacuation

The amount of oatmeal-barium paste evacuated after the various infusates was semiquantitively assessed by an investigator, who was blinded to the nature of the infusate. A baseline radiograph (obtained after the 20 min equilibration period) was compared to the one obtained 30 min after administration of the infusate. Evacuation was graded from 0 (no evacuation) to 4 (complete evacuation) (a–d in Fig. 1). A non-parametric analogue of the ANOVA for repeated measurements (Friedman's test) and Student–Neuman–Keuls tests were employed to assess the significance of the observed differences. Interobserver agreement regarding scores was greater than 95%.

Heart Rate and Blood Pressure

The mean heart rate (over 5 min) and lowest observed heart rate (over 15 s) were recorded. Mean blood pressure was derived from values obtained at 5-min intervals. The Student's paired *t*-test was used to compare the differences for significance.

Airway Resistance

Maximum percent change in total or central airway resistance was measured at lower frequencies (R5) and higher frequencies (R20), respectively. The significance of the differences between the various conditions was determined by the Student's paired *t*-test.

Other Side Effects

Subjects were monitored every 5 min for the following symptoms and signs: salivation, diaphoresis, xerostomia, muscle fasciculations, and abdominal cramps. The investigators who monitored these side effects were blinded as to the type of infusion delivered.

RESULTS

Subject Demographics

The mean age of the subjects was 46 yr (range 25–69). The mean duration of their injuries was 14 yr (range 1–31). The level of injury and the type of injury (complete (C) or incomplete (I)) for each subject is as follows:

Subject	Age	Duration of Injury (yr)	Level of Injury	Motor	Sensory
1	43	24	C5	C	I
2	48	31	C–7	C	I
3	49	31	C–7	C	C
4	51	8	T3	I	I
5	41	21	T11	C	I
6	49	15	T–11	C	C
7	69	6	T6	C	I
8	25	1	T3	C	I
9	28	4	C–6	C	I
10	48	13	C–4	C	C
11	46	16	T7	C	C
12	39	1	T6	C	C
13	42	15	T12	C	I

Effect of Neostigmine and Combined Neostigmine–Glycopyrrolate on Bowel Evacuation

Neostigmine and the combination of neostigmine and glycopyrrolate both caused a similar expulsion of simulated

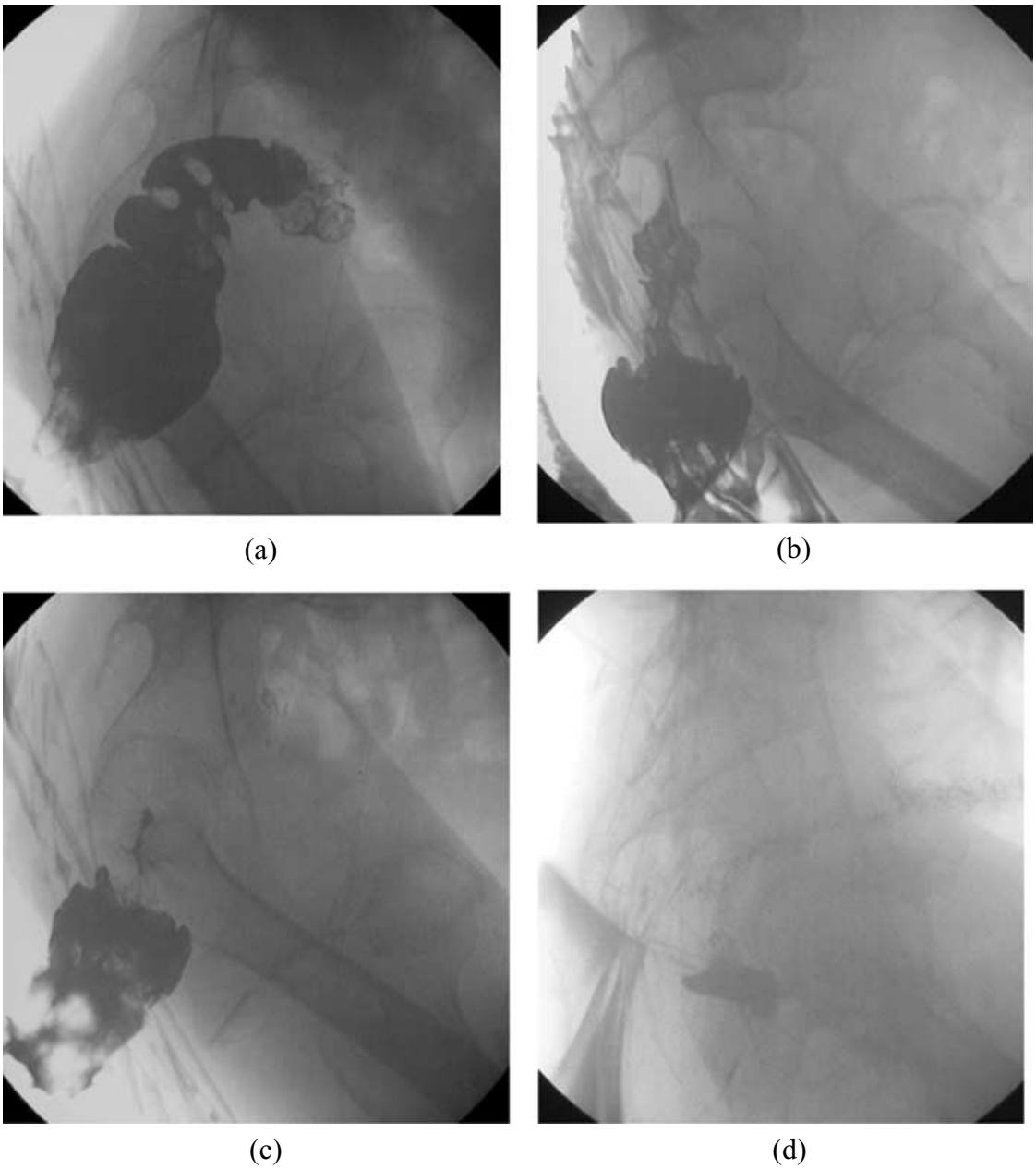

Figure 1. Semi-quantitative measure of bowel emptying using barium-oatmeal paste. A blinded investigator assigned a score ranging from 0 to 4 by comparing the baseline radiograph before an infusate with that obtained 30 min after normal saline, neostigmine, or neostigmine (glycopyrrolate. Evacuation score: a = 1, b = 2, c = 3, and d = 4.

stool, which was greater than with normal saline (median score 3 *vs* 4 *vs* 0, respectively; $p < 0.01$) (Fig. 2). The mean time to expulsion was 11.5 min (range 5–20 min) after neostigmine and 13.5 min (range 4–23 min) after the combination. After neostigmine alone, 57% of subjects had an evacuation score of 3 or greater as compared to 64% of subjects after the combination (non-significant difference), whereas, after normal saline, none of the subjects scored 2 or greater. There was no correlation between the level of SCI and the likelihood of bowel evacuation with any of the infusates.

Effects of Neostigmine and Combined Neostigmine–Glycopyrrolate on Heart Rate and Airway Resistances

HEART RATE AND BLOOD PRESSURE. The mean heart rate response to each of the infusions is shown (Fig. 3). Both infusions caused a comparable decrease in mean heart rate. However, the lowest heart rates for any 15 s interval were recorded when subjects were given neostigmine alone. Nadir heart rate below 40 were seen in 23.1% and 7.7% of the neostigmine and neostigmine–glycopyrrolate infusions, respectively. Nadir heart rate below 50 were seen in 53.8% and

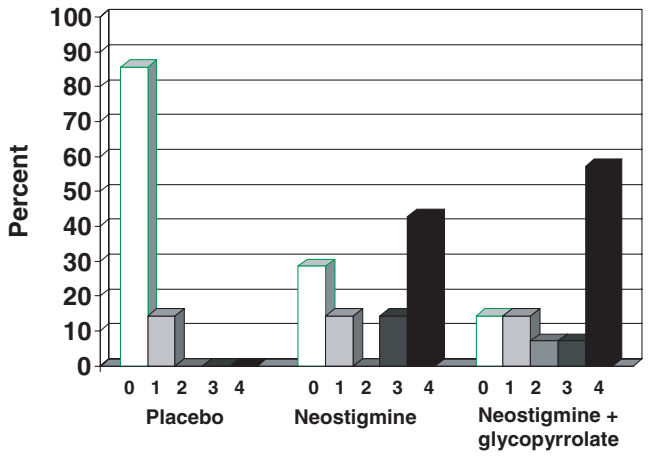

Figure 2. Histogram showing the effect of normal saline (control), IV neostigmine (2 mg), and IV neostigmine (2 mg) (glycopyrrolate (0.4 mg) on evacuation of an oatmeal-barium paste from the rectum and descending colon. Bowel emptying was assigned a score of 0–4, as described in Methods. Neostigmine and neostigmine + glycopyrrolate produced similar degrees of emptying; evacuation was significantly greater than after normal saline ($p < 0.01$). Emptying of the oatmeal-barium paste was determined by comparing spot films before and 30 min after each infusate.

38.5% of the neostigmine and neostigmine–glycopyrrolate infusions, respectively. Blood pressure was unaltered by either treatment. Normal saline infusion had no effect on heart rate or blood pressure.

AIRWAY RESISTANCE. Neostigmine alone increased total and central airway resistance by 27% and 17%, respectively, relative to normal saline ($p < 0.01$). In contrast, the combination of neostigmine and glycopyrrolate had a bronchodilating effect on these parameters [−10% ($p < 0.05$) and −8% ($p < 0.05$), respectively, relative to normal saline]. Normal saline infusion had no effect on airway resistance compared to baseline values.

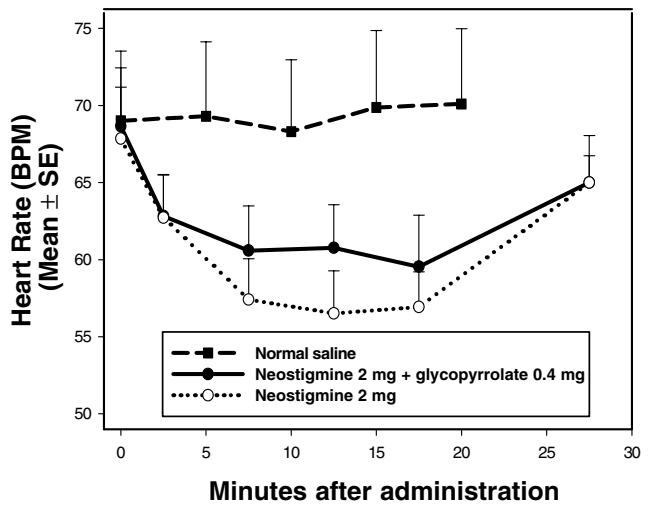

Figure 3. Comparison of the effect of normal saline, neostigmine, and neostigmine (glycopyrrolate on mean heart rate at 5 min intervals. There was no significant difference in mean heart rate at any of these time points. Infusion of normal saline (4 ml) had no effect on the heart rate.

OTHER SIDE EFFECTS. Facial and tongue fasciculations were noted by 92% of subjects who received neostigmine alone. Addition of glycopyrrolate did not change the likelihood of this reaction (89%). This was also the case for other symptoms, such as diaphoresis and salivation. The majority of subjects whose injuries were below thoracic level 10 (T10) experienced abdominal cramps. This was not different for neostigmine alone or the combination of drugs. Subjects with lesions higher than T10 did not report cramps as a side effect. Subjects considered all of these symptoms to be mild. When the side-effects occurred, they persisted less than 30 min post-infusion. No episodes of autonomic dysreflexia were observed.

DISCUSSION

Neostigmine can be administered safely to subjects with SCI and it results in relatively prompt and predictable evacuation of simulated stool from the rectum. Not unexpectedly, bradycardia and increased airway resistance occurred *parri passu* with bowel evacuation. However, the present report indicates that these cardiopulmonary actions of neostigmine can be attenuated by the concurrent administration of the anticholinergic agent, glycopyrrolate. Most importantly, glycopyrrolate counteracts the cardiopulmonary effects of neostigmine without blunting it actions on bowel emptying. Finally, no serious side effects, including autonomic dysreflexia, occurred in any subject. Muscle fasciculation and dry mouth were noted by most subjects but were mild, short lived, and required no therapeutic intervention.

Difficulty with evacuation is a common clinical sequela after SCI (4, 8, 9). The type of bowel dysfunction that occurs after SCI is a function of the level of spinal cord damage. Lesions above the conus medullaris have upper motor neuron effects on the bowel, while those below this level have lower motor neuron consequences (5). The former is characterized by constipation with a spastic anal sphincter; the latter also results in constipation but is more likely to be associated with incontinence because of flaccidity of the anal sphincter mechanism. Therefore, regardless of the level of injury, constipation is common after SCI. The pathogenesis of constipation after SCI has been studied using a variety of methods including radioopaque markers (10, 11), scintigraphy (12), and manometry. Colonic transit time is reproducibly prolonged in these persons. This likely arises as a result of a relative decrease in parasympathetic stimulation of the colon (4). Parasympathetic input stimulates peristalsis while sympathetic effects are anti-peristaltic; it is considered likely that prolonged colonic transit time results from either an absolute or relative lack of parasympathetic colonic stimulation (3).

Bowel care is an important component of rehabilitation after SCI and generally involves introduction of high fiber diets, stool softeners, and regular use of laxatives (stimulant and/or osmotic), digital rectal stimulation, enemas, and suppositories with each individual empirically determining the most efficacious and practical approach (5). Despite these measures, bowel care remains an unpleasant, time-consuming, and, at times, unpredictable experience. Since the underlying pathophysiology in SCI is suggestive of downregulation of parasympathetic activity (13, 14), it seemed that it might be useful to pharmacologically increase parasympathetic tone. The present study is the first step in assessing the potential efficacy and safety of such an approach.

Neostigmine is a cholinergic agonist that is known to nonspecifically stimulate muscarinic receptors throughout the body. In the GI tract, heart, and lungs, stimulation of these receptors (M1–M3) increases motility (15), slows the heart rate (16), and increases airway tone (16). The prokinetic effect of neostigmine on the bowel is the basis for its use in the treatment of acute intestinal pseudoobstruction (AIP), a condition characterized by non-obstructive colonic dilatation, and neostigmine administration is highly effective in decompressing the bowel (17, 18). However, its use in AIP may be associated with the development of a bradycardia. For this reason, it is standard clinical practice to administer neostigmine in a monitored setting.

Neostigmine is also routinely employed to reverse the neuromuscular blockage of curare-like drugs in the operating room. Although effective in restoring neuromuscular activity, the GI prokinetic effects and the cardiodepressive actions of neostigmine can be troublesome. Anticholinergics, including atropine and glycopyrrolate, are typically administered to counter these potentially adverse effects of neostigmine. In general, however, glycopyrrolate is the preferred agent in this setting because rebound tachycardia is rare. Although the cardiodepressive actions of neostigmine are promptly reversed by both atropine and glycopyrrolate, neither anticholinergic was noted to inhibit the stimulatory effects of neostigmine on the colon (19, 20). A more recent report using a neostigmine–glycopyrrolate combination in patients with pseudoobstruction also showed that bradycardia can be completely prevented while maintaining the efficacy of neostigmine on bowel decompression (21). Thus, both in patients with intact spinal columns as well as individuals with SCI, coadministration of glycopyrrolate improves the safety profile of neostigmine without altering the efficacy of neostigmine on bowel evacuation.

Previous work from our unit supports the use of an anticholinergic to protect the airway in persons receiving neostigmine. It is appreciated that persons with SCI above the sympathetic outflow (thoracic level 6) probably have increased cholinergic tone of the airway (22) and have hyperreactive airways to methacholine, a cholinergic agent (23). Inhaled ipratroprium bromide, an anticholinergic agent, has been shown to completely block the effect of methacholine (24). In another study, ipratroprium bromide produced a bronchodilatory response to the resting airway (25). As such, it would not be unreasonable to speculate that the airway of persons with higher spinal cord lesions may be hyperresponsive to cholinergic stimulation, such as with the parenteral administration of neostigmine. Although it was not demonstrated in our subjects with high paraplegia or tetraplegia, the risk of bronchoconstriction to neostigmine may exist, and this potential side effect would likely be prevented with the simultaneous administration of glycopyrrolate. Acetylcholinesterase inhibitors, either intrathecal neostigmine (neostigmine does not cross the blood–brain barrier) or parenterally administered physostigmine, have been used to cause erections and ejaculations in persons with SCI who were impotent and infertile. Although this approach was effective in achieving its objective on the reproductive system, undesirable side effects have included orthostatic hypotension, nausea, vomiting, and autonomic hyperreflexia due to bladder distension and/or violent contractions of the ejaculatory organs (26, 27). However, these adverse events did not occur after either intravenous infusion of neostigmine alone or the combination of neostigmine and glycopyrrolate.

The apparent safety of the neostigmine–glycopyrrolate combination suggests that it may play a role in facilitating long-term bowel care, as opposed to acute administration in conditions such as acute colonic pseudoobstruction. We have recently conducted a pilot study in which the neostigmine–glycopyrrolate combination was given as an adjunct to usual bowel care regimens of subjects; preliminary findings suggest that this approach is effective in reducing bowel care time (28).

In conclusion, an acute bolus infusion of neostigmine and glycopyrrolate appears efficacious in inducing prompt colonic evacuation without adverse effects on heart rate or airway tone. The intravenous route of administration was employed in the present study as a "proof of principle" and it should be stressed that routine (or unmonitored) intravenous infusion of these agents is not advocated. However, these agents may have a role in routine bowel care if other routes of administration (*e.g.,* intramuscular or subcutaneous injection) prove as efficacious and as safe as the intravenous approach. In this respect, studies are now underway to establish whether prolonged administration by these alternate routes will be safe, predictable, effective, and potentially facilitate long-term bowel care.

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