

Effects of neostigmine and glycopyrrolate on pulmonary resistance in spinal cord injury

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Abstract—Preliminary findings in subjects with spinal cord injury (SCI) suggest that neostigmine administered intravenously increases colonic tone, increases colonic contractions, and facilitates bowel evacuation. Of concern are potential pulmonary side effects, including an increase in airway secretions and bronchospasm. The objectives of the study were to determine the effects of intravenously administered neostigmine or neostigmine combined with glycopyrrolate on forced oscillation indices in persons with SCI. Pulmonary resistances at 5 Hz (R5) and 20 Hz (R20) were measured with the use of an impulse oscillation system (IOS) in 11 subjects with SCI. Values were obtained before and after the intravenous administration of 2 mg of neostigmine alone and, on a separate day, before and after the administration of 2 mg of neostigmine combined with 0.4 mg of glycopyrrolate. Baseline R5 and R20 values before neostigmine correlated significantly with baseline values before neostigmine combined with glycopyrrolate. Following neostigmine, mean R5 values increased 25% and mean R20 values increased 18%. Following neostigmine combined with glycopyrrolate, mean R5 values fell 9% and mean R20 values fell 7%. In summary, baseline IOS values obtained on 2 different days were highly reproducible in this population. Neostigmine alone induced significant bronchoconstriction, whereas neostigmine combined with glycopyrrolate caused bronchodilation.

Key words: glycopyrrolate, impulse oscillation, neostigmine, spinal cord injury.

INTRODUCTION

Neostigmine, an acetylcholinesterase inhibitor, has been used successfully to rapidly decompress the colon in patients with acute colonic pseudo-obstruction [1]. Preliminary findings in subjects with spinal cord injury (SCI) suggest that parenteral administration of the drug increases colonic tone, increases colonic contractions, and facilitates bowel evacuation [2]. Side effects are of concern because in some individuals, the agent increases airway secretions and bronchial reactivity, which may exacerbate active bronchospasm [1]. These concerns may be particularly significant in subjects with tetraplegia, who demonstrate hyperresponsiveness to methacholine, histamine, and ultrasonically nebulized distilled water

Abbreviations: COPD = chronic obstructive pulmonary disease, IOS = impulse oscillation system, Rrs = respiratory system resistances, SCI = spinal cord injury, sGaw = specific airway conductance, VA = Department of Veterans Affairs.

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comparable to that seen in mild asthma [3–5]. Also, individuals with tetraplegia have reduced baseline airway caliber caused by unopposed parasympathetic activity, thereby suggesting that any agent that increases acetylcholine concentrations at muscarinic receptors may cause further bronchoconstriction [6]. One potential method for attenuating the effects of neostigmine on pulmonary function without reducing bowel stimulation is the simultaneous administration of the anticholinergic agent glycopyrrolate. To assess the effects of neostigmine alone and neostigmine combined with glycopyrrolate on pulmonary function in SCI, we used the impulse oscillation system (IOS) to measure total respiratory system resistances over a wide range of frequencies. Values at lower frequency (R5) estimate central and peripheral pulmonary mechanics; values at high frequency (R20) reflect more central airway dynamics.

METHODS

Subject Selection

Eleven subjects participated in the study. Three had chronic cervical cord injury (tetraplegia) and eight had thoracic or lumbar injuries (paraplegia). All were outpatients followed by the SCI Service at the Department of Veterans Affairs Medical Center, Bronx, New York (BVAMC). All participants were clinically stable and denied any history of asthma, allergies, recent respiratory tract infections, or other acute pulmonary conditions. The Institutional Review Board of the BVAMC approved the study, and we obtained informed consent prior to investigation. All subjects were being studied primarily so that we could assess the value of neostigmine in facilitating bowel evacuation. None of the subjects were using medications known to affect airway tone or responsiveness.

Equipment

We measured total pulmonary resistances using a commercially available system (VIASYS Healthcare, Respiratory Technologies, Yorba Linda, California). While subjects were supine, measurements were obtained with the use of nose clips and a free-flow mouthpiece. Subjects were asked to slightly extend their necks and to limit abdominal motion during the study. A laboratory technician supported the subjects' cheeks during the maneuver. The forced oscillation instrument applied pressure pulses five times/second during tidal volume

breathing. We calculated resistances from the pressure/flow relationship obtained from impulses applied at the mouth during a 30 s period and analyzed them at 5 and 20 Hz (R5 and R20). We repeated 30 s recordings until three recordings fulfilled quality assurance coherence coefficient criteria. A test was accepted if the coherence coefficient was 0.7 or greater at 5 Hz and 0.9 or greater at 20 Hz for either five breaths or 30 s of recording [7]. Large and small airway mechanics were inferred from responses at high (20 Hz) and low (5 Hz) frequencies, respectively. Low frequency oscillations are transmitted to the lung periphery, while those at 20 Hz are limited to larger airways [7].

Study Protocol

On study day 1, baseline measurements at R5 and R20 were obtained. The measurements were repeated 30 minutes after the intravenous administration of 2 mg of neostigmine. On a separate day, within 2 weeks of the first study, R5 and R20 were measured before and after the intravenous administration of 2 mg of neostigmine combined with 0.4 mg of glycopyrrolate.

RESULTS

Morphometric data are listed in **Table 1**. Three subjects had tetraplegia and eight had paraplegia with levels of injury ranging from C-4 to L-3. Eight were never smokers and three were ex-smokers. Baseline R5 and R20 values before neostigmine and before neostigmine plus glycopyrrolate are shown in **Table 2**. Following administration of neostigmine mean R5 and R20 values increased by 25 and 18 percent, respectively (**Table 2** and **Figure 1**). On a separate day, following the administration of neostigmine combined with glycopyrrolate, mean R5 and R20 values decreased by 9 and 7 percent, respectively. Baseline R5 and R20 values obtained for individual subjects were found to be highly correlated on 2 separate days of testing (**Figure 2**).

DISCUSSION

We used IOS to measure total pulmonary resistance, which is the composite of chest wall, pulmonary tissue, and airway resistances. Body plethysmography would have been more sensitive and specific for assessing airway

Table 1.
Characteristics of subjects.

Subject	Age	Height	Weight	DOI	LOI	Group	Motor COL	Smoke History
1	48	70	165	14	C4	Tetraplegia	Complete	Never
2	29	65	150	5	C5–6	Tetraplegia	Complete	Never
3	49	72	156	31	C6–7	Tetraplegia	Incomplete	Former
4	52	69	200	8	T3	Paraplegia	Complete	Never
5	25	68	140	1	T3	Paraplegia	Incomplete	Never
6	39	71	205	2	T6	Paraplegia	Complete	Former
7	46	71	228	17	T7	Paraplegia	Complete	Never
8	40	69	183	15	T9–11	Paraplegia	Complete	Former
9	42	73	205	21	T11	Paraplegia	Complete	Never
10	42	74	270	16	T12	Paraplegia	Complete	Never
11	57	68	150	17	L-3	Paraplegia	Incomplete	Never
Mean	43	70	187	13	—	—	—	—
SD	9	3	40	9	—	—	—	—

COL = completeness of lesion DOI = date of injury LOI = level of injury

Table 2.
IOS results before and after neostigmine and neostigmine +glycopyrrolate.

Subject	R5 Neostigmine			R20 Neostigmine			R5 Neostigmine +Glycopyrrolate			R20 Neostigmine +Glycopyrrolate		
	Before (kPa/L/s)	After (kPa/L/s)	% Change	Before (kPa/L/s)	After (kPa/L/s)	% Change	Before (kPa/L/s)	After (kPa/L/s)	% Change	Before (kPa/L/s)	After (kPa/L/s)	% Change
1	0.339	0.558	65	0.303	0.407	34	0.363	0.379	4	0.321	0.330	3
2	0.387	0.398	3	0.271	0.330	22	0.359	0.311	-13	0.278	0.222	-20
3	0.559	0.616	10	0.397	0.375	-6	0.503	0.428	-15	0.349	0.375	7
4	0.715	0.893	25	0.573	0.681	19	0.850	0.820	-4	0.644	0.648	1
5	0.279	0.287	3	0.226	0.235	4	0.275	0.275	0	0.235	0.227	-3
6	0.376	0.637	69	0.271	0.459	69	0.411	0.361	-12	0.318	0.279	-12
7	0.540	0.629	16	0.308	0.327	6	0.631	0.441	-30	0.356	0.328	-8
8	0.364	0.407	12	0.261	0.280	7	0.364	0.333	-9	0.259	0.228	-12
9	0.461	0.604	31	0.329	0.378	15	0.465	0.417	-10	0.399	0.342	-14
10	0.692	0.865	25	0.509	0.540	6	0.672	0.612	-9	0.509	0.446	-12
11	0.732	0.864	18	0.543	0.679	25	0.678	0.653	-4	0.514	0.505	-2
Mean	0.495	0.614	25	0.363	0.426	18	0.506	0.457	-9	0.380	0.357	-7
SD	0.163	0.201	23	0.124	0.150	20	0.178	0.168	9	0.126	0.132	8

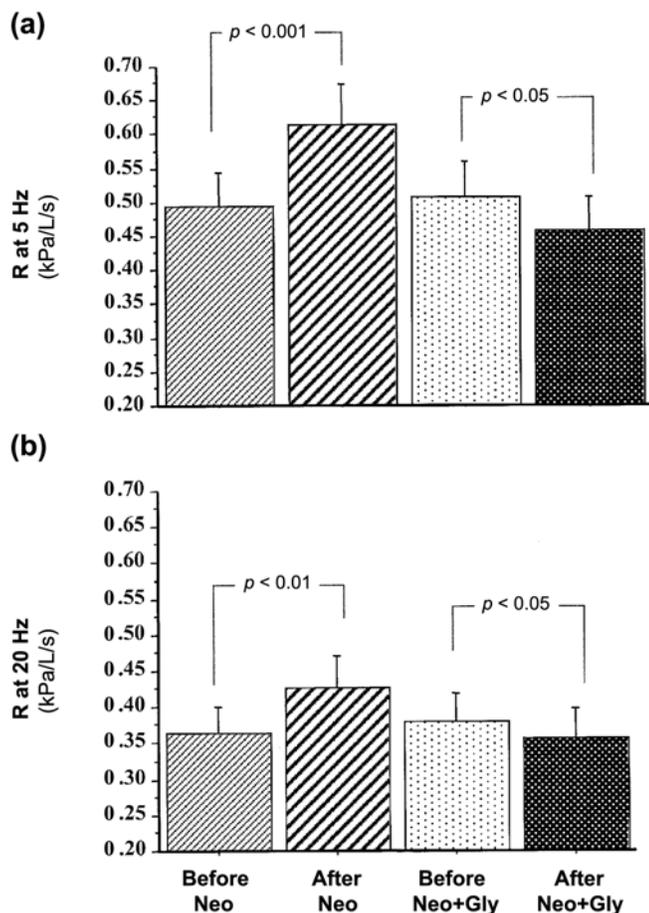


Figure 1.

(a) R5 and (b) R20 values before and after administration of neostigmine (neo) alone or before and after neostigmine combined with glycopyrrolate (gly). Data are expressed as mean \pm SD. An unpaired Student's t-test was applied to determine differences for R5 and R20 for neostigmine alone and for neostigmine combined with glycopyrrolate.

resistance, but this modality was not practical in the current study. The IOS has significant advantages, in that the equipment is portable and tests can be performed at the bedside during normal tidal breathing with minimal patient effort. Because of low reproducibility and wide range of normal values, IOS has been suggested to have limited utility [8]. However, in the current study, although baseline values varied widely among the different subjects, baseline R5 ($r^2 = 0.89$) and R20 ($r^2 = 0.91$) had significant reproducibility in individual subjects studied on two separate days spanning a several-week period. This high reproducibility suggests that many of the variables, which may affect oscillation measurements, including

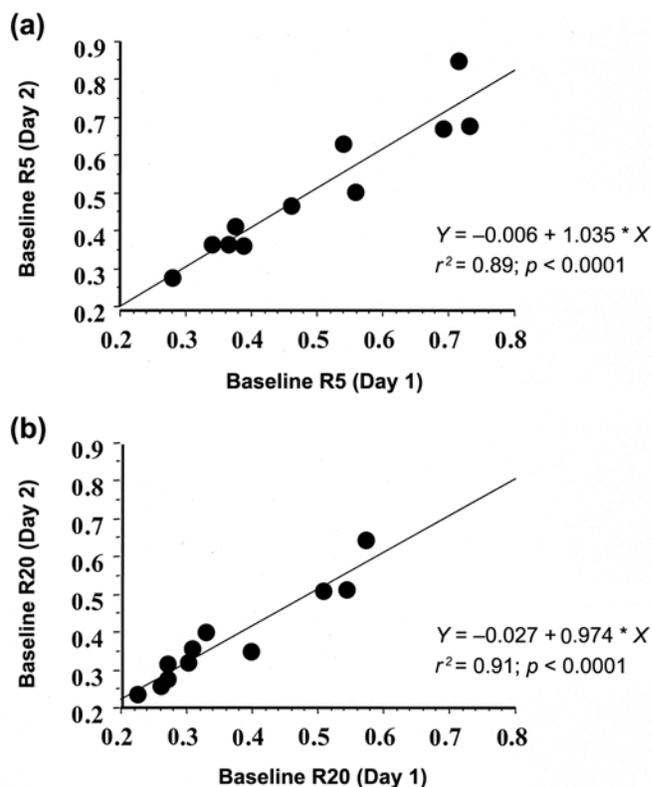


Figure 2.

Correlation of baseline (a) R5 values on days 1 and 2 and (b) R20 values on days 1 and 2. Simple regression analysis was used to assess the relationships between (a) days 1 and 2 of baseline R5 values and (b) days 1 and 2 of R20 values.

state of relaxation, position of arms, and tongue position, are better controlled when measurements are obtained in the supine position.

In the current study, the intravenous instillation of neostigmine was followed by a significant increase in R5 (25%) and R20 (18%). Comparable increases in both parameters indicate that the agent induced significant constriction of both small and large airways. Although subjects with tetraplegia and paraplegia had similar responses to neostigmine, only three subjects with tetraplegia were studied. Previous observations showing that subjects with tetraplegia, but not those with paraplegia, were hyperresponsive to aerosolized methacholine and that they had reduced baseline specific airway conductance (sGaw) suggest that individuals with higher-level lesions would be more susceptible to the bronchoconstrictive effects of neostigmine [3,6]. A significant increase in airway resistance has been reported in able-bodied individuals following neostigmine [9]. Bronchospasm and

tracheobronchial hypersecretion have been observed in patients undergoing reversal of neuromuscular blockade with neostigmine combined with an anticholinergic agent [10,11].

We found that administering neostigmine combined with glycopyrrolate was followed by significant bronchodilation as measured by decreases in R5 (9%) and R20 (7%). These findings demonstrate that bronchoconstriction associated with neostigmine is prevented by the simultaneous administration of an anticholinergic agent, without decreasing the effectiveness of neostigmine on bowel evacuation [2]. We did not evaluate the effect of glycopyrrolate alone on IOS parameters. By using neostigmine and atropine combined to reverse neuromuscular blockade in patients with or without chronic obstructive pulmonary disease (COPD), Bourgain et al. found that total respiratory resistance was not altered significantly and that changes were similar in COPD compared with normals [12]. Other investigators, by use of spirometry or body plethymography, have shown that intravenously administered or nebulized glycopyrrolate caused significant bronchodilation in normal subjects and among patients with COPD or asthma [13–17].

CONCLUSION

In summary, in subjects with SCI, the intravenous infusion of neostigmine was associated with a significant increase in total pulmonary resistance. The combination of neostigmine with glycopyrrolate was associated with a significant decrease in resistances, demonstrating that cholinergically mediated bronchoconstriction is prevented by the addition of glycopyrrolate.

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