Bronchodilatory effects of ipratropium bromide in patients with tetraplegia

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Airway hyperresponsiveness was recently described in patients with chronic cervical spinal cord injury (tetraplegia). The response was attributed to unopposed cholinergic bronchoconstrictor activity due to loss of sympathetic innervation of the airway. To determine if the administration of a cholinergic antagonist alters resting airway tone in these patients, ipratropium bromide (72 µg) was administered by aerosol to 25 tetraplegic patients. We found that 12 of 25 patients (48%) had significant improvement (defined as $\geq 12\%$) in forced expired volume in 1 s (FEV₁) and/or forced vital capacity (FVC). A significant correlation between airway responsiveness and complaints of dyspnea at rest, completeness of injury (sensory), or smoking history was not found. These findings of improved airflow after the use of an anticholinergic bronchodilator agent provides further evidence that transection of the cervical cord results in unopposed parasympathetic activity and a resultant increase in resting airway tone.

Keywords: bronchial obstruction; pulmonary; lungs; spinal cord injury; tetraplegia; anti-cholinergic agents; ipratropium

Introduction

It was recently reported that approximately 40% of otherwise healthy patients with tetraplegia undergoing routine pulmonary function testing had a significant bronchodilator response ($> 12\%$) following inhalation of a beta₂ agonist.¹ This finding suggested that many patients with cervical spinal cord injury have an obstructive ventilatory impairment, characterized by an increase in resting airway tone, in addition to the well described restrictive ventilatory defect.^{2–8} Further evidence of ventilatory impairment comes from methacholine challenge testing, which demonstrated marked airway hyperresponsiveness in all patients with tetraplegia, a response which was completely blocked by pretreatment with the cholinergic antagonist ipratropium bromide.⁹

Based upon these findings, it was postulated that airway hyperresponsiveness in patients with tetraplegia represents a loss of modulatory sympathetic fibers, which originate in the upper six thoracic segments of the spinal cord; thus, broncho-constrictive cholinergic innervation, which arises in the vagal nuclei of the brainstem and passes down the vagus nerves to synapse in ganglia that are located in the walls of airway, would remain intact.¹⁰

To further evaluate the apparent cholinergic hyperresponsiveness in patients with tetraplegia we assessed pulmonary function parameters before and after the administration of ipratropium bromide to determine if the agent caused bronchodilation in this population.

Methods

Twenty-five male patients with tetraplegia were recruited from the Spinal Cord Injury Service at the Veterans Affairs Medical Center, Bronx, New York. The study group consisted of 10 current smokers and 15 non-smokers (defined as those who are ex-smokers with no cigarette use for 1 year or more, or a lifetime never smoker). Six patients had complete motor and sensory loss, 17 had complete motor and incomplete sensory loss, and two had incomplete motor and sensory loss. At the time of study, no subject displayed evidence of respiratory tract infections or other acute pulmonary symptoms, and none gave a history of asthma or allergies.

Pulmonary function testing was performed with the patients seated upright in their wheelchairs using a SensorMedics dry rolling seal spirometer (Yorba Linda, CA). Spirometry was performed before and 45 min after inhalation via a spacer (Inspirease, Schering, Kenilworth, NJ) of four puffs (72 µg) of ipratropium bromide (Boehringer Ingelheim, Ridgefield, CT). American Thoracic Society (ATS) guidelines for spirometry were followed with reproducibility for FVC, FEV₁, volume of extrapolation, and end of test criteria (no flow for 2 s and exhalation for ≥ 6 s) being achieved.¹¹ Those patients classified as 'responders' achieved a bronchodilator response as described by the ATS ($\geq 12\%$ increase post bronchodilator for FVC and/or FEV₁).¹² Those with less than a 12% improvement were classified as 'non-responders'. All patients

were able to complete pre- and post-bronchodilator testing. The spirometric standards of Morris were used.¹³ This study was approved by the institutional review board of the Veterans Affairs Medical Center.

The results are reported as mean $\pm$ SEM. A paired *t* test was performed between the pre- and post-spirometry values for the study group as a whole. χ^2 analysis was used to determine differences in the frequency of responders *versus* non-responders for dyspnea (yes, no), completeness of injury (incomplete sensory, complete sensory), and smoking history (current smokers, non-smokers).

Results

Characteristics of the study population including age, duration of injury, and smoking history are shown (Table 1). Overall, 12 of 25 patients (48%) had a positive bronchodilator response. For the study group as a whole, the average FEV₁ and FVC were significantly ($P = 0.0036$ and $P = 0.0084$, respectively) higher post-bronchodilator than pre-bronchodilator. Spirometry parameters for the responder and non-responder groups before and after administration of ipratropium bromide for current smokers and non-smokers are shown (Table 2). In the smoking history subgroups, a significant bronchodilator response was seen in six of 10 (60%) current smokers and six of 15 (40%) non-smokers. χ^2 analyses revealed no significant differences between the number of patients with dyspnea at rest, smoking history, or completeness of cord lesion, and the bronchodilator response to ipratropium bromide (Table 3).

Discussion

In this study, we found that approximately 50% of patients with tetraplegia had a positive bronchodilator response to 72 μ g of inhaled ipratropium bromide. The

number of responders far exceeds that found in studies of normal patients, which demonstrated no change in parameters of static lung volumes when 240 μ g were inhaled.¹⁴ Our current findings, when viewed in the context of our previous observation that 14 of 34 (41%) tetraplegic patients had significant bronchodilatation following inhalation of nebulized metaproterenol sulfate (15 mg),¹ provide additional support that resting airway tone is increased in patients with tetraplegia. Although the results of the two studies were essentially the same, one difference was that the beta₂ agonist (metaproterenol) was given by a powered nebulizer (50 psi), whereas the anticholinergic (ipratropium bromide) was given via a spacer device. In addition, the previous finding that eight of eight non-smoking patients with tetraplegia were hyperresponsive to inhaled methacholine⁹ demonstrated that airway hyper-reactivity is also present.

A likely explanation for our previous findings^{1,9} is that transection of the cervical spinal cord disrupts sympathetic innervation of the lung, which originates in the upper six thoracic segments, thereby leaving intact parasympathetic (cholinergic) nerves, which arise in vagal nuclei in the brainstem and pass down the vagus nerve to synapse in ganglia situated in airway walls.^{10,15} As a result, cholinergic bronchoconstrictor activity is unopposed by bronchodilatory sympathetic fibers, which presumably interact with parasympathetic ganglia cells in the peribronchial plexa to modulate transmission of post-ganglionic parasympathetic fibers.¹⁵ Support comes from studies involving dogs and guinea pigs, which have shown that stimulation of thoracic sympathetic nerves causes bronchodilation that is abolished by beta-antagonist and unaffected by adrenalectomy.^{16,17} Also, of more direct relevance to spinal cord injury, in guinea pigs it has been observed that electrical stimulation of structures within the rostral region of the dorsal medulla activates a sympathetic inhibitory pathway.^{18,19} Injection of lidocaine into the spinal cord at the level of C₁–C₂ to eliminate bulbospinal sympathetic neurotransmission, or surgical section of the cord at this location, potentiated CNS-induced bronchospasm.^{18,19}

The use of anticholinergic agents to treat diseases of the airway is based on their ability to compete with acetylcholine at muscarinic receptor sites.²⁰ These receptors have been demonstrated on airway smooth muscle cells and mucous cells, especially in submucosal glands. In human airways, different muscarinic subtypes have been identified, which include M₁ receptors on sympathetic nerves and parasympathetic ganglia, M₂ receptors on cholinergic nerves (these receptors function as feedback inhibitory receptors), and M₃ receptors on airway smooth muscle. Since acetylcholine released from post-ganglionic parasympathetic nerve endings has been shown to contract smooth muscle,¹⁵ antimuscarinic drugs act to reduce vagally mediated increases in bronchomotor tone.

Our findings suggest that patients with tetraplegia may demonstrate physiological improvement in pulmonary function with the use of a beta₂ agonist or an

Table 1 Characteristics of the patients

Age (y)	43 $\pm$ 3
Height (cm)	69.7 $\pm$ 0.6
DOI (y)	11 $\pm$ 2
Incomplete	19 (76%)
Complete	6 (24%)
Dyspnea at rest	
Yes	7 (28%)
No	18 (72%)
Smoking history	
Non-smoker	15 (60%)
Current smoker	10 (40%)

Results are reported in mean $\pm$ SEM where DOI = duration of injury in years (y); non-smoker = lifetime never-smokers or ex-smoker who has quit smoking > 1 year; current smoker = those who currently smoke or have quit for $\leq$ 1 year

Table 2 Results of pre- and post-bronchodilator response

Parameter	Pre		Post			
	R (n = 6)	NR (n = 4)	R (n = 6)	R % Ch	NR (n = 4)	NR % Ch
Current smokers						
FVC (l)	2.30 ± 0.15	2.68 ± 0.19	2.54 ± 0.08		2.60 ± 0.18	
FVC (%)	48 ± 2	57 ± 7	54 ± 3	12 ± 5	55 ± 5	-2 ± 6
FEV ₁ (l)	1.72 ± 0.25	2.36 ± 0.19	2.00 ± 0.28		2.29 ± 0.18	
FEV ₁ (%)	46 ± 5	64 ± 8	54 ± 6	17 ± 2	63 ± 6	-2 ± 6
FEV ₁ /FVC	74 ± 8	89 ± 5	82 ± 6		88 ± 3	
FEF ₂₅₋₇₅ (l s ⁻¹)	1.62 ± 0.43	3.08 ± 0.51	2.44 ± 0.63		2.96 ± 0.41	
FEF ₂₅₋₇₅ (%)	40 ± 10	77 ± 12	40 ± 10	54 ± 7	76 ± 7	< 1 ± 12
Non-smokers						
FVC (l)	2.23 ± 0.10	2.64 ± 0.26	2.57 ± 0.12		2.69 ± 0.25	
FVC (%)	46 ± 2	50 ± 5	53 ± 3	16 ± 4	51 ± 5	2 ± 1
FEV ₁ (l)	1.85 ± 0.19	2.31 ± 0.18	2.11 ± 0.20		2.33 ± 0.18	
FEV ₁ (%)	50 ± 5	59 ± 5	58 ± 5	15 ± 3	60 ± 5	1 ± 1
FEV ₁ /FVC	82 ± 5	89 ± 3	82 ± 6		88 ± 3	
FEF ₂₅₋₇₅ (l s ⁻¹)	2.23 ± 0.51	3.07 ± 0.27	2.42 ± 0.57		3.20 ± 0.32	
FEF ₂₅₋₇₅ (%)	59 ± 14	82 ± 11	63 ± 15	12 ± 14	85 ± 11	6 ± 7

The results are reported as mean ± SEM where FVC = forced vital capacity, FEV₁ = forced expired volume in 1 s, FEF₂₅₋₇₅ = forced expiratory flow rate (l per s) between 25 and 75% of the exhaled volume and R = responders ≥ 12% post-bronchodilator, NR = non-responders. Pre = pre bronchodilator, post = post bronchodilator, %Ch = percent change post-bronchodilator spirometry results.

Table 3 Observed frequency of dyspnea, cord lesion completeness, and smoking history for responders (≥ 12% post bronchodilator) and non-responders

	Responders	Non-responders
Dyspnea		
Yes	3 (43%)	4
No	9 (50%)	9
Cord Lesion		
Incomplete	10 (53%)	9
Complete	2 (33%)	4
Smoker		
Yes	6 (40%)	4
No	6 (60%)	9

anticholinergic agent. Although no detailed studies have been performed which evaluate the respiratory symptoms among patients with high spinal cord injury, in one survey, it was reported that 18% (seven of 39) with complete lesions complained of chronic cough, 18% (seven of 39) of chronic sputum production, 24% (nine of 37) of persistent wheeze, and 50% (19 of 38) of any wheeze.²¹ Also, since atelectasis and pneumonia are the major causes of morbidity and mortality in patients with spinal cord injury,²²⁻²⁵ it is conceivable that chronic inhalation of a beta₂ agonist or anticholinergic agent may decrease the incidence of mucus retention and respiratory complications. A long term study would be required to determine if chronic use of bronchodilators benefits patients with spinal cord injury.

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