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Effects of GABA-B Agonist Baclofen on Bronchial Hyperreactivity to Inhaled Histamine in Subjects with Cervical Spinal Cord Injury

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Abstract. Bronchial provocation studies performed in our research center have consistently demonstrated airway hyperresponsiveness to both inhaled methacholine and histamine in subjects with chronic cervical spinal cord injury (SCI). More recently, we reported that the airways of such subjects maintained on chronic baclofen (γ-aminobutyric acid) therapy were not hyperreactive to inhaled methacholine. In this study we determined whether baclofen also blocks the effects of the bronchoprovocative agent histamine in subjects with cervical SCI. Twenty-four male subjects with cervical SCI participated in this study; 14 were maintained on oral baclofen, and 10 served as age-matched controls. The subjects were challenged with increasing concentrations of aerosolized histamine until either a 20% fall in forced expiratory volume in 1 s (FEV_1) from baseline (defined as PC_{20}) was observed, or a maximum of 25 mg/ml histamine was administered. We found that 11 of the 14 baclofen subjects (78.5%) and 8 of the 10 control subjects (80%) responded ($PC_{20} < 8$ mg/ml) to the histamine challenge. Mean PC_{20} values among responders in the baclofen ($PC_{20} = 2.91 \pm 2.3$) and control ($PC_{20} = 2.18 \pm 1.9$) groups did not differ significantly. Because histamine acts directly on histamine receptors and indirectly on cholinergic pathways, our findings that baclofen blocks bronchoconstriction due to inhaled methacholine, but not that due to histamine, suggests that hyperresponsiveness in subjects with cervical SCI may be secondary to nonspecific airway hyperreactivity.

Key Words: GABA-B agonist—Quadriplegia—Histamine—Airway hyperresponsiveness.

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Introduction

γ-Aminobutyric acid (GABA) is a mammalian central nervous system inhibitory neurotransmitter that has also been identified in peripheral organs, including the lungs [27]. Animal studies have revealed that GABA and the GABA-B receptor agonist baclofen attenuate neuronally induced cholinergic and peptidergic airway contraction by inhibiting the release of both acetylcholine from cholinergic neurons and tachykinins from afferent nerves [4–6, 29, 34]. Presumably, through modulation of endogenous release of tachykinins, GABA-B agonists also inhibit microvascular leakage, anaphylactic bronchospasm, and cough [7]. In guinea pig airway challenge studies, baclofen administered systemically inhibited bronchospasm induced by aerosolized histamine, ovalbumin in sensitized animals, and prostaglandin (PG) $F_{2\alpha}$ but not that caused by acetylcholine [20]. Additional animal studies have demonstrated that GABA-B agonists have no effect on bronchoconstriction responses in the lung induced by exogenous cholinergic agonists [7]. In contrast, among subjects with cervical spinal cord injury (SCI), it was demonstrated that baclofen administered chronically to treat muscle spasm blocked bronchoconstriction caused by aerosolized methacholine [11].

Bronchial challenge studies have consistently demonstrated airway hyperresponsiveness to inhaled methacholine or histamine in subjects with chronic cervical SCI [11–13]. Findings that baclofen blocked methacholine hyperresponsiveness [11] suggest that the agent may be of therapeutic value in attenuating the clinical features of nonspecific airway hyperreactivity in these subjects. Therefore, we sought to determine whether baclofen also blocks the effects of the bronchoprovocative agent histamine in subjects with cervical SCI.

Materials and Methods

The study group included 14 subjects with cervical SCI who were chronically maintained on oral baclofen (>1 year) and 10 age-matched control subjects with cervical SCI who were not prescribed this agent. Baclofen is commonly used therapeutically for the relief of muscle spasm; subjects in the baclofen study group were treated with this agent for clinical reasons and were thus assigned to this group based solely on this criterion. None of the subjects was receiving other medications known to alter airway tone or responsiveness. Subjects had no preinjury history of pulmonary disease or respiratory symptoms, and none reported recent or active pulmonary infections. The Institutional Review Board for human studies of the Bronx Veterans Affairs Medical Center granted approval for the study. Informed consent of each subject was obtained prior to the investigation.

Spirometric measurements were obtained from subjects who were seated in their wheelchairs using a SensorMedics 2200 Automated Pulmonary Function Lab (Yorba Linda, CA). Baseline values of forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) were obtained for each subject according to the recommendations set forth by the American Thoracic Society [2]. Spirometry results were expressed as absolute values and percent predicted based upon the standards of Morris et al. [25].

Subjects performed a series of tests, each involving five slow inhalations (inspiratory time, 5 s) from functional residual capacity (FRC) to total lung capacity (TLC) of normal saline followed by increasing concentrations (0.025, 0.25, 2.5, 10, and 25 mg/ml) of histamine diphosphate (Freeman Industries, Tuckahoe, NY) or methacholine (Provocholine, Roche Laboratories, Nutley, NJ). All subjects were instructed not to hold their breath at TLC and to exhale slowly; the time between each inhalation was

approximately 10 s. The aerosols were administered by a Salter 8900 nebulizer (Asthmakit, Diemolding Healthcare Division, Canastota, NY) containing 4 ml of solution and driven by air at a flow rate of 8 liters/min with an output of 0.35 ml/min. Upon initiation of each breath, nebulization was performed by manual occlusion of a thumbport. Spirometry was measured 2–3 min after each set of five inhalations (saline and incremental concentrations of histamine), or sooner if the subject complained of dyspnea or chest tightness. The bronchial challenge test was terminated when either the FEV_1 decreased 20% or more from baseline (PC_{20}), or the maximal concentration (25 mg/ml) was administered. A PC_{20} of less than 8 mg/ml was considered diagnostic for airway hyperresponsiveness [19]. The PC_{20} was calculated using a Sensor-Medics computer program, which generated the value by interpolation from a logarithmic dose-response curve. Subjects with significant responses to histamine immediately inhaled a β_2-agonist. For those subjects not responding to the maximal concentration of histamine (25 mg/ml), a PC_{20} value of 25 was used in the calculation of mean PC_{20}. The total cumulative units for each logarithmic concentration (mg/ml) of histamine were calculated as the cumulative sum of number of breaths multiplied by concentration administered: 0.125, 1.375, 13.88, 63.88, or 188.88.

To compare the logarithmic method characterized above with the doubling dose protocol described by Juniper et al. [19], six subjects initially responding to the inhaled histamine returned on a later date to undergo additional bronchial challenge testing. The two tests were performed on separate days: the logarithmic method on one visit and a doubling dose protocol on the second. The doubling protocol involved five slow inhalations from FRC to TLC while inhaling normal saline or increasing concentrations (0.075, 0.15, 0.31, 0.625, 1.25, 2.5, 5, 10, and 20 mg/ml) of histamine administered by a Salter 8900 nebulizer driven by air at a flow rate of 8 liters/min with an output of 0.35 ml/min. The remaining aspects of this second bronchial challenge were identical to those applied in the logarithmic method.

Finally, to confirm and support our previous findings that baclofen inhibits methacholine-associated bronchial hyperresponsiveness [11], five of the control subjects and four of the subjects in the baclofen group who had been challenged with histamine returned on a separate day and underwent a methacholine challenge using the logarithmic method as described previously.

All data were expressed as mean ± S.D. A natural logarithmic transformation was performed on PC_{20} values for all subjects, and a geometric mean was calculated. An unpaired Student's *t*-test was conducted to measure differences between the baclofen and control group, and a paired *t*-test was applied to the different concentration protocols and the provocative agents (histamine and methacholine). A Pearson correlation coefficient (r) was calculated to determine whether a linear association exists between PC_{20} and either duration or dosage of baclofen therapy. The level of significance was set at $p < 0.05$.

Results

Age and duration of injury did not differ significantly between the baclofen and control groups (Table 1). Both groups contained subjects with primarily cervical 5, 6, or 7 lesions, and subjects included nine who never smoked, ten ex-smokers, and five active smokers (Table 1).

Subjects in the baclofen group had been receiving between 30 and 160 mg of the medication per day for 1–15 years. Baseline FEV_1, FVC, and percent predicted were reduced comparably in both groups (Tables 2 and 3). FEV_1/FVC ratios were reduced in baclofen subject 11 and in control subjects 8 and 10. Mean FEV_1/FVC ratios did not differ significantly between the two groups. Eleven of the 14 subjects receiving baclofen (78.5%) and eight of ten subjects in the control group (80%) had a significant bronchoconstrictor response to aerosolized histamine ($PC_{20} < 8$mg/ml) (Tables 2 and 3). No significant differences were found in either the arithmetic mean (Ar) or the geometric mean (Geo) PC_{20} values among responders in the baclofen (2.91 ± 2.3 Ar, 0.79 ± 0.80 Geo) and control (2.18 ± 1.9 Ar, 0.25 ± 1.29 Geo) groups (Tables 2 and

Table 1. Subject characteristics and profile.

Group	Age (years)	Level of lesion	Duration of injury (years)	Smoking status[a]	Medication	Baclofen duration (years)	Therapy dose (mg/day)
Baclofen							
1	32	C-5	12	Never	None	5	30
2	48	C-6	29	Ex (10 years)	Prazosin hydrochloride	15	160
3	23	C-6	2	Ex (2 years)	Oxybutyn chloride, Docusate sodium	2	80
4	65	C-5	4	Ex (4 years)	Butalbital, diazepam	4	40
5	60	C-6	30	Ex (20 years)	Diazepam, docusate sodium	10	70
6	38	C-6	8	Ex (7 years)	Phenytoin sodium	6	60
7	33	C-6	9	Active (10 py)	Diazepam	8	40
8	47	C-7	4	Never	None	4	40
9	24	C-6	3	Ex (3 years)	Diazepam, docusate sodium	4	120
10	41	C-5	16	Ex (3 years)	None	1	60
11	46	C-6	20	Active (15 py)	Diazepam	5	40
12	39	C-4	9	Never	None	9	60
13	41	C-6	9	Never	Diazepam	5	40
14	24	C-5	5	Never	None	5	80
Mean ± S.D.	40 ± 13		11 ± 9			5.9 ± 3.6	65.7 ± 36
Control							
1	31	C-7	8	Never	None		
2	34	C-7	8	Never	None		
3	40	C-5	16	Ex (10 years)	None		
4	27	C-6	3	Active (5 py)	None		
5	47	C-6	11	Never	Diazepam		
6	49	C-6	28	Active (30 py)	None		
7	35	C-7	12	Ex (10 years)	Diazepam		
8	54	C-5	19	Active (40 py)	Captopril, docusate sodium		
9	42	C-5	20	Never	None		
10	64	C-7	19	Ex (15 years)	None		
Mean ± S.D.	42 ± 11		14 ± 7				

[a] ex, stopped smoking for more than 1 year; never, never smoked; active, current smoker; py, pack years.

3). The PC_{20} values of combined responders and nonresponders also did not differ for either the arithmetic mean or the geometric mean between the two groups (baclofen group = 6.69 ± 7.8 Ar, 1.26 ± 1.18 Geo; control = 6.74 ± 9.8 Ar, 0.84 ± 1.69 Geo). There were no significant differences in spirometry parameters, level of lesion, duration of injury, or smoking status between responders and nonresponders in either group. No significant correlations were observed between PC_{20} values and either dosage or duration of baclofen therapy.

The mean histamine PC_{20} value obtained by the doubling dose method (2.10 ± 1.34 Ar and 0.42 ± 1.16 Geo) did not differ significantly from that achieved using the logarithmic protocol (3.49 ± 2.69 Ar and 0.77 ± 1.34 Geo). The mean methacholine PC_{20} value of 1.35 ± 0.97 mg/ml among control subjects 1, 4, 6, 7, and 8

Table 2. Individual baseline pulmonary function and PC_{20} results for the baclofen group. All lung function parameters are expressed in liters and percentage predicted.

Subject	FEV_1		FVC		FEV_1/FVC	PC_{20} (mg/ml)
	L	% pred.	L	% pred.		
Responders						
1	1.70	39	1.83	30	98	1.41
2	3.10	80	4.22	77	76	6.73
3	3.10	74	3.45	63	90	3.72
4	1.47	50	1.83	44	80	1.99
5	2.00	58	2.37	48	84	1.88
6	1.91	47	2.19	41	87	1.74
7	3.31	72	4.05	69	82	7.35
8	3.42	83	4.68	82	73	2.71
9	1.75	41	2.03	38	86	3.11
10	2.35	61	2.95	58	80	0.80
11	1.74	48	2.54	53	69	0.52
Nonresponders						
12	2.38	62	2.91	58	82	18.25
13	2.96	80	3.19	66	93	19.10
14	2.23	45	2.36	37	95	23.70
Mean ± S.D.	2.4 ± 67	60 ± 15.5	2.9 ± .91	55 ± 15.7	83.9 ± 8.3	6.7 ± 7.8

Table 3. Individual baseline pulmonary function and PC_{20} results for the control group. All lung function parameters are expressed in liters and percentage predicted.

Subject	FEV_1		FVC		FEV_1/FVC	PC_{20} (mg/ml)
	L	% pred.	L	% pred.		
Responders						
1	2.81	66	3.00	55	94	3.54
2	3.35	77	3.95	69	85	0.47
3	2.30	59	2.72	53	85	3.97
4	2.39	63	2.74	60	87	1.76
5	1.83	56	2.29	51	80	5.58
6	2.00	53	2.78	52	72	0.98
7	2.34	60	3.20	66	73	0.11
8	2.18	59	3.25	66	67	1.04
Nonresponders						
9	2.11	59	2.58	56	82	25
10	2.15	67	3.29	66	65	25
Mean ± S.D.	2.3 ± 0.47	61 ± 8.8	2.9 ± .50	57 ± 8.5	79.7 ± 9.0	6.74 ± 9.8

was nearly identical to the mean PC_{20} value obtained from the histamine challenge 1.49 ± 1.29 mg/ml (Table 4). In contrast, the response from three of four baclofen subjects to methacholine was significantly different than their response to histamine (Table 4).

Table 4. Comparison of baseline pulmonary function and PC_{20} in control and baclofen subjects challenged with histamine and methacholine. Results are expressed as mean ± SD. All lung parameters are expressed in liters and percentage predicted. Histamine and methacholine bronchoprovocations were performed on separate days. No statistical differences were found between tests for control group. Mean PC_{20} values were significantly different for baclofen group ($p < 0.05$).

Subjects	Histamine challenge						Methacholine challenge					
	FEV_1	%	FVC	%	FEV_1/FVC	PC_{20}	FEV_1	%	FVC	%	FEV_1/FVC	PC_{20}
Control												
1	2.81	66	3.00	55	94	3.54	2.87	68	3.08	56	93	1.18
4	2.39	63	2.74	60	87	1.76	2.27	61	2.69	59	85	2.19
6	2.00	53	2.78	52	72	0.98	1.87	51	2.59	50	72	0.24
7	2.34	60	3.20	66	73	0.11	2.38	62	3.24	67	74	2.50
8	2.18	59	3.25	66	67	1.04	2.42	66	3.46	70	70	0.65
Mean ±	2.34	60.20	2.99	59.80	78.60	1.49	2.36	61.60	3.01	60.40	78.80	1.35
S.D.	0.30	4.87	0.23	6.34	11.37	1.29	0.36	6.58	0.37	8.14	9.83	0.97
Baclofen												
1	1.79	39	1.83	30	98	1.41	2.10	44	2.33	37	91	18.00
2	3.10	80	4.22	77	76	6.73	3.06	78	3.97	72	77	25.00
3	3.10	74	3.45	63	90	3.72	3.01	72	3.24	60	93	25.00
4	1.47	50	1.83	44	80	1.99	1.54	51	1.90	46	81	2.26
Mean ±	2.37	60.75	2.83	53.50	86.00	3.46	2.43	61.25	2.86	53.75	85.50	17.57
S.D.	0.86	19.45	1.20	20.70	9.93	2.39	0.74	16.32	0.93	15.41	7.72	10.72

Discussion

We found that the bronchoconstrictor response to aerosolized histamine in subjects with chronic cervical SCI who were receiving baclofen was comparable to that found in subjects not undergoing baclofen therapy. These findings contrast with those obtained by Luzzi et al. [20] who demonstrated that baclofen protected guinea pigs from histamine-induced bronchospasm. The difference in findings may be explained by species variability or, possibly, acute baclofen treatment of the animals vs chronic treatment of the human subjects. An additional consideration is that the underlying airway responsiveness in guinea pigs was presumably normal, whereas most human subjects with cervical SCI demonstrate marked hyperresponsiveness to inhaled histamine.

In lung, baclofen is thought to act as a neuromodulator of the autonomic nervous system by inhibiting release of both acetylcholine from cholinergic fibers and tachykinins from sensory C-fibers [7]. Histamine causes bronchial constriction directly through interaction with histamine receptors and indirectly through parasympathetic reflex release of acetylcholine and neuropeptides [36]. Our findings suggest that hyperresponsiveness to histamine in subjects with chronic cervical SCI who are receiving baclofen is mediated primarily through histamine receptors. In general, the role of vagal reflexes in histamine responsiveness in humans remains controversial. Although several investigators have found no effect of atropine or ipratropium bromide on histamine provocations in asthmatic adults [16, 35, 37], others have shown that these

anticholinergic agents attenuate histamine-induced bronchoconstriction in asthmatic and atopic subjects [4, 8, 15, 30].

Our findings demonstrated that baclofen did not affect histamine responsiveness in subjects with cervical SCI. Previously, we postulated that methacholine-associated airway hyperreactivity in subjects with cervical SCI is the result of loss of sympathetic nervous innervation of the lung (which originates from thoracic vertebrae 1–6), leaving intact unopposed parasympathetic bronchoconstrictor activity [12]. Our present finding of similar responsiveness to histamine in subjects with SCI who were receiving baclofen and those not receiving the agent, with the apparent effect presumably mediated directly through histamine receptors, suggests that hyperresponsiveness in these subjects may actually be secondary to nonspecific airway hyperreactivity similar to that observed in asthmatic subjects [18, 36]. Although the basic underlying process responsible for nonspecific airway hyperreactivity in asthmatic subjects has not been elucidated, a proposed mechanism is chronic bronchial inflammation [32], which leads to thickening of epithelial, smooth muscle, and advential layers [17] and to associated inadequate stretch of airway smooth muscle with deep breathing [31]. It is not known whether a similar process may explain airway hyperreactivity in subjects with cervical SCI. Since lung volumes are reduced, and deep inhalation is not possible in such subjects because of respiratory muscle paralysis, it is conceivable that resting airway tone is increased. Previously we found that approximately 45% of subjects with cervical SCI demonstrated a significant bronchodilatory response following inhalation of metaproterenol or ipratropium bromide [1, 33].

Circulating catecholamines also potentially contribute to the regulation of human airway tone. Epinephrine is a potent bronchodilator in normal subjects and has been used in the treatment of status asthmaticus. There is some evidence to suggest that in patients with asthma, the secretion of epinephrine may be reduced and/or not increase appropriately in response to stress [21, 24]. Administration of β-blockers produces bronchoconstriction in patients with asthma, but not in normal subjects [3, 24]. Additionally, human [28] and animal [9] studies have shown a significant increase in airway resistance to intravenous histamine in subjects pretreated with the β-blocker propranolol and in felines that received adrenalectomy. In the absence of stimulation from below the spinal lesion, decreased levels of circulating catecholamines are found in subjects with SCI at basal conditions and during orthostatic maneuvers [14, 22, 23], reflecting absent tonic supraspinal sympathetic impulses and diminished peripheral sympathetic activity [10, 26]. Thus, airway hyperresponsiveness in subjects with cervical SCI may be related, in part, to decreased levels of plasma epinephrine and norepinephrine.

In this study, we demonstrated similar PC_{20} values using two different protocols for administering the provocative agent: the logarithmic and doubling dose. The design of this study was based on clinical criteria; the baclofen study group was treated for severe muscle spasms, and, therefore, it was not feasible to implement a crossover design. In addition, baclofen can produce unpleasant side effects and should not be prescribed unless clinically warranted. Thus, we felt that randomly prescribing baclofen had the potential to cause significant consequences that outweighed the possibility of biased results due to our preselection of subjects.

GABA-B receptor agonists inhibit neuronally induced cholinergic- and tachyki-

nin-mediated airway smooth muscle contraction, airway microvascular leakage, and anaphylactic reactions in animal airways. It has, therefore, been proposed that a selective GABA-B agonist may have therapeutic potential for the treatment of asthma [7]. Our current findings, along with previous work [11] that baclofen blocks methacholine but not histamine-associated airway hyperresponsiveness in subjects with cervical SCI, suggest that this agent will be of limited effectiveness in reducing symptoms related to airway hyperreactivity. A definitive answer to the efficacy of oral baclofen therapy in subjects with airway hyperreactivity will require a prospective study of pulmonary function parameters and respiratory symptoms.

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