Is an Abbreviated Bronchial Challenge with Histamine Valid?*

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Investigators have validated an abbreviated protocol for testing nonspecific bronchial reactivity with methacholine. We performed a similar validation study with histamine, another bronchoprovocative agent known to induce airflow obstruction. Histamine is pharmacologically distinct from methacholine and, under some circumstances, may provide specific clinical and investigative advantages to methacholine. Twenty-four patients with a clinical history of asthma underwent bronchoprovocative testing using the standard histamine airway protocol recommended by the American Academy of Allergy, Committee on Standardization of Bronchoprovocation. In addition, two abbreviated histamine challenge protocols were tested using the same administration and testing equipment. The abbreviated protocols involved fewer dilutions and dosages of histamine than the standard histamine protocol but covered the same range of cumulative doses. The two abbreviated protocols differed only in the intervals for determination of FEV_1 between doses of histamine (30 s vs 3 min). The sequence of these three protocols was randomized for each study subject and each airway challenge was separated by one week. The two abbreviated protocols took significantly less time to administer than the standard protocol—18 min vs 30 min vs 44 min. Both the provocative dose to cause a 20 percent decline in the FEV_1 (PD_{20} FEV_1) and the slope of the dose-response curve were not significantly different between the standard protocol and either of the two abbreviated protocols. Moreover, a high degree of agreement was observed between the two abbreviated protocols and the standard histamine protocol for both the PD_{20} FEV_1 and the slope of the dose-response curve. These findings indicate that similar estimates of bronchial reactivity are obtained from either of the abbreviated protocols when compared with the standard histamine protocol.

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PD_{20} FEV_1 = provocative dose to cause a 20 percent decline in the FEV_1; TLC = total lung capacity

Clinicians and investigators have acknowledged that a single definition of asthma does not exist.[1] Wheezing, cough, chest tightness, spirometric evidence of airflow obstruction, response to bronchodilators, and variation in peak flow are all considered helpful in the diagnosis of asthma. In addition, assessment of bronchial reactivity is increasingly used, both clinically and epidemiologically, to objectify this diagnosis. Moreover, nonspecific bronchial reactivity has been used to estimate the degree of airway reactivity following exposure to airway irritants and sensitizers, to follow the clinical course of asthma and bronchitis, and to provide prognostic information about the airway disease.

Methods of assessing bronchial reactivity include cold air hyperventilation, exercise provocation, and exposure to aerosols of pharmacologic agents that induce reversible airflow obstruction. Methacholine and histamine, two of the most widely applied pharmacologic agents used for this purpose, cause airflow obstruction in asthmatics.[2] In fact, the diagnosis of asthma is virtually eliminated by a negative response to either of these agents.[3,4] Importantly, the airway response to methacholine is very similar to that of histamine[5] and, functionally, these agents are used interchangeably in assessing airway reactivity.

However, histamine and methacholine have different pharmacologic properties. Side effects, half-lives, and the cumulative effect, in particular, differ between these two agents.[6,7] Under some circumstances, these differences may be clinically or scientifically important. Side effects to either of these agents are dose related and are observed with increasing frequency at concentrations at or greater than 8 mg/ml.[6] Flushing and headache have been reported more frequently with histamine;[6] however, chest tightness, cough, and dyspnea occur with a similar frequency between the two agents. Importantly, the biologic half-life of inhaled histamine is markedly shorter than methacholine.[7] Although the ranges of peak action of histamine and methacholine are similar, 30 s to 2 min for histamine and 1 to 4 min for methacholine, the mean time until recovery of baseline lung function is significantly shorter for histamine than methacholine, 42.3 minutes for histamine vs 131.4 min for methacholine.[7]

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Finally, the action of histamine, unlike methacholine, is not thought to be as cumulative.[6] This permits administration of more than one histamine test within the same day. More than one methacholine challenge within the same day does not give an accurate estimation of airway reactivity presumably because of its prolonged half-life.[6-8]

Abbreviated airway challenges are particularly relevant for epidemiologic studies where overall time involvement and simplicity of administration are essential elements of a feasible field application. Standard measures of bronchial reactivity are time-consuming and involve multiple concentrations of the bronchoconstrictive agent.[3] Abbreviated methods for testing nonspecific bronchial responsiveness have been developed for methacholine[9] and histamine.[10] However, the delivery system for the abbreviated histamine challenge was a hand-operated nebulizer that is probably not an optimal or reliable method of adminstration. In addition, the abbreviated histamine challenge used a very short time interval between doses of histamine and these authors[10] did not test whether this shortened interval was justified.

The purpose of this investigation was to evaluate the clinical utility of an abbreviated histamine protocol. This was accomplished by administering a standard histamine protocol and two abbreviated histamine challenge protocols in a randomized crossover design to 24 nonsmoking volunteers (21 mild asthmatics). Our results indicate that the abbreviated histamine protocol adequately assesses airway reactivity in this population.

Methods

Study Population

Twenty-four nonsmoking adult volunteers were selected for this investigation. They were recruited using a local community newspaper advertisement that requested asthmatic nonsmokers 18 years or older. The study population consisted of 12 women and 12 men with an age range of 20 to 52 years. Twenty-one of these volunteers had a physician-confirmed diagnosis of asthma. Twenty (83 percent) study subjects were never-smokers and four (17 percent) subjects were former smokers (no cigarettes smoked within the last six months). Approximately two thirds (n = 16) of the study subjects were receiving long-term bronchodilator medication. Of these 16 subjects, 11 used inhaled β-agonists, four used inhaled steroids, three used a theophylline preparation, and six were receiving oral antihistamines. All subjects withheld the use of their bronchodilator medications for at least 24 h prior to each histamine challenge.

Dosimeter and Spirometric Assessment

A nebulizer (DeVilbiss 646, Somerset, PA) was used with a dosimeter (DeVilbiss). The dosimeter was powered by compressed air at 20 psi to deliver a 0.6 s dose of 0.03 ml of the aerosol. The output of the dosimeter was measured and calibrated prior to the study. The aerosol delivery was triggered by the study subject's inspiratory effort. Inhalation was made from functional residual capacity (FRC) to total lung capacity (TLC) and held for 2 s.

Following administration of the aerosol, the patient performed a forced expiratory maneuver monitored on a spirometer (Spirotech S100) according to the guidelines established by the American Thoracic Society.[11,12] The spirometer was statically and dynamically calibrated each day of the investigation. The forced expiratory maneuver was conducted with the subject in the sitting position and wearing nose clips. The average of two maximal acceptable efforts (within 5 percent) was recorded in each instance.

Histamine Challenge Protocols

Each study subject had three separate histamine airway challenge protocols. For all subjects, each test was separated by one week and was performed on the same day of the week at the same time of the day. The order of the standard and abbreviated challenge was randomized between the study subjects. The three histamine challenge protocols consisted of a standard histamine challenge[13] with spirometric assessments at 30 s and 3 min, an abbreviated histamine protocol with spirometric measurements at 30 s, and a modified, abbreviated protocol with spirometric measurements at 30 s and 3 min. The standard challenge included five inhalations each of 0.03, 0.06, 0.12, 0.25, 0.5, 1.0, 2.5, 5.0, and 10.0 mg/ml concentrations of buffered histamine at room temperature delivered according to the guidelines established by the American Academy of Allergy, Committee on Standardization of Bronchoprovocation.[13] The abbreviated and modified abbreviated histamine protocols used one breath of 0.16 mg/ml, three breaths of 0.16 mg/ml, one breath of 2.12 mg/ml, four breaths of 2.12 mg/ml, three breaths of 10.6 mg/ml, and four breaths of 10.6 mg/ml histamine. The dosing schedule of the abbreviated protocols was developed to minimize the concentrations of histamine to complete an airway challenge and still approximate the total dosing of the standard histamine challenge (Table 1). Because the peak reaction to histamine is thought to occur 30 s to 2 min following the aerosol inhalation,[7] the modified abbreviated protocol included a spirometric assessment at 30 s and 3 min after each dose of histamine. This precaution was

Table 1—*Dosing and Cumulative Breath Units for the Standard Histamine Protocol and the Abbreviated Histamine Protocol*

Standard Histamine Protocol			Abbreviated Histamine Protocol		
Concentration, mg/ml	Inhalations	Cumulative Breath Units, mg/ml	Concentration, mg/ml	Inhalations	Cumulative Breath Units, mg/ml
0.3	5	0.15	.16	1	0.16
0.6	5	0.45	.16	3	0.64
0.12	5	1.05	2.12	1	2.76
0.25	5	2.3	2.12	4	11.24
0.5	5	4.8	10.6	3	43.04
1.0	5	9.8	10.6	4	85.44
2.5	5	22.3			
5.0	5	47.3			
10.0	5	97.3			

Table 2—*Demographic and Clinical Characteristics* of the 24 Study Subjects*

Characteristics	
Age, y	29.3 ± 9.5
Sex	
Male	12 (50%)
Female	12 (50%)
Smoking status	
Never	20 (83%)
Former	4 (17%)
Current	0
Pack-years (former smokers only)	8.2 ± 14.5
Physician diagnosis of asthma	21 (88%)
Long-term bronchodilator medication	16 (67%)

*Expressed as either mean ± standard deviation for continuous variables or N (percent) for categorical variables.

taken so that the peak of the reaction to histamine was not inadvertently missed by the abbreviated protocol.

Statistical Analysis

The baseline FEV_1 was chosen as the best of two reproducible (within 5 percent) trials before and after inhalation of the diluent (sterile isotonic saline solution). At each subsequent dosage level, the average of two reproducible FEV_1s was recorded until the patient either reached a 20 percent decline in FEV_1 from baseline or completed the protocol. The provocative dose that caused a 20 percent decline in an individual FEV_1 (PD_{20} FEV_1) was calculated by linear interpolation.[14] Dose-response curves were calculated as the slope of the decline in FEV_1 divided by the cumulative dose of histamine (ΔFEV_1/cumulative dose of histamine).

To assess the validity of the abbreviated histamine challenge protocols, we compared the airway response to both of the abbreviated protocols with the airway response to the standard histamine protocol. A goodness of fit test[15] was performed to assess the normality of distribution of the PD_{20} FEV_1 and the slope of the dose-response curve. These findings allowed us to use parametric statistical tests for the PD_{20} FEV_1 and the slope of the dose-response curve to histamine following logarithmic (base 10) transformation of the data. Paired *t* tests[15] were used to directly compare individual responses with the different protocols. The calculated PD_{20} FEV_1 and the slope of the dose-response curve for the different protocols were compared using correlation coefficients. The validity of the abbreviated protocols was further assessed using intraclass correlation coefficients[16] to compare these protocols with the standard histamine challenge. The intraclass correlation coefficient is a measure of agreement that accounts for the chance probability of agreement between two individual observations. Values of 0.75 or greater are considered excellent agreement, values from 0.40 to 0.75 are considered fair to good agreement, and values below 0.40 are considered poor agreement.[17]

Results

The demographic and clinical characteristics of the study subjects are displayed in Table 2. An equal number of men and women were studied. Although the average age of subjects was 29 years, the ages ranged from 20 to 52 years. Four patients were former smokers with at least one month since their last cigarette and these former smokers had a minimal overall history of cigarette smoking (mean pack-years = 8.2). The majority of patients (n = 16) were receiving long-term bronchodilator medication for the treatment of airflow obstruction.

Table 3—*Duration of Administration of Histamine Challenge by Protocol*

Protocol	Mean (Range) min
Abbreviated	17.5 (12-27)
Modified abbreviated	30.4 (14-42)
Standard	43.8 (11-64)

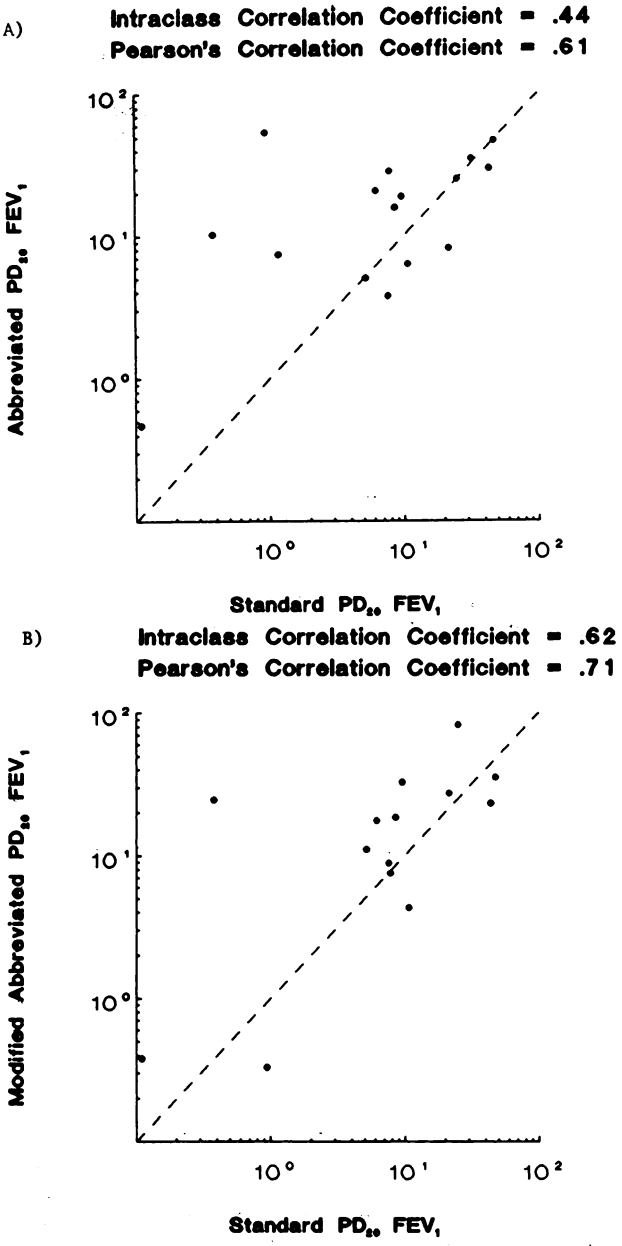

FIGURE 1A (*top*). Reproducibility of airway responses to inhaled histamine between the standard and the abbreviated protocol. PD_{20} FEV_1 is the provocative dose of histamine causing a 20 percent fall in FEV_1. B (*bottom*). A comparison of PD_{20} FEV_1 results from the standard vs the modified abbreviated histamine challenge protocol. The intraclass and Pearson's correlation coefficients are indicated above each graph. The dashed line represents perfect agreement between tests.

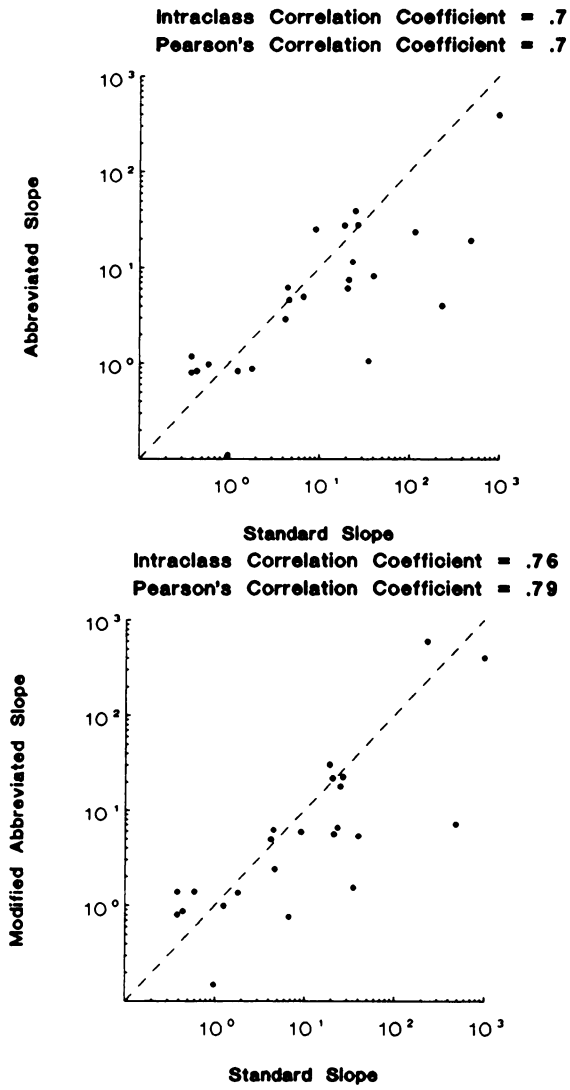

FIGURE 2A (*top*). The relationship between the slope of the dose-response curve between the standard and abbreviated histamine challenge protocols. B (*bottom*). The relationship between the slope of the dose-response curve between the standard and modified abbreviated histamine challenge protocols. The intraclass and Pearson's correlation coefficients are indicated above each graph. The dashed line represents perfect agreement between tests.

All subjects participated in all three tests except for one subject who completed only the standard protocol and the abbreviated protocol. All patients withheld use of their bronchodilator medication at least 24 h prior to the bronchial challenges. The abbreviated protocol took less than half the time of the standard test, 17.5 min vs 43.8 min (Table 3). Our modified abbreviated protocol was intermediate in length at 30.4 min.

The abbreviated and modified abbreviated histamine protocols closely approximated the airway response of the standard histamine protocol (Fig 1 and 2). Figure 1A depicts the relationship between the PD_{20} FEV_1 from the standard histamine protocol vs the abbreviated histamine challenge. The corresponding correlation coefficient is 0.61 ($p=0.013$) and the intraclass correlation is 0.44. Figure 1B characterizes the relationship between the PD_{20} FEV_1 from the standard protocol and modified abbreviated histamine protocol. Again, close correlation between the abbreviated test and the standard protocol is confirmed by both the correlation coefficient of 0.71 ($p=0.005$) and the intraclass correlation coefficient of 0.62. Figure 2A depicts the relationship between the slope of the dose-response curve from the standard vs the abbreviated histamine protocol. The correlation coefficient of 0.78 ($p=0.0001$) and the intraclass correlation of 0.70 demonstrates good to excellent agreement between the two protocols. Figure 2B shows the standard vs the modified abbreviated protocol for the slope of the dose-response curve to histamine inhalation. The correlation coefficient of 0.79 ($p=0.0001$) and the intraclass correlation of 0.76 again demonstrate excellent agreement.

DISCUSSION

Our results indicate that an abbreviated airway challenge with histamine results in similar estimates of airway reactivity when compared with the standard histamine protocol. This was valid for those subjects who had a 20 percent decline in their FEV_1 (PD_{20} FEV_1) and for estimates of airway reactivity (dose-response slope) in all of our study subjects, regardless of the response to histamine. Moreover, our findings indicate that a 3-min waiting period between subsequent concentrations of histamine does not appear to be needed. Our findings indicate that an abbreviated protocol may be used to estimate airway reactivity to histamine.

The choice of performing methacholine or histamine bronchoprovocation tests should take into consideration the unique properties of these agents. Importantly, the 70 percent shorter biologic half-life for histamine is a feature that is particularly relevant for research studies. Subjects are found to recover much more quickly from histamine-induced bronchoconstriction than from methacholine-induced bronchoconstriction.[7] Moreover, the shorter half-life may result in improved safety when these studies are performed outside the medical center. Tachyphylaxis (or diminution of response to repeated tests of nonspecific bronchial reactivity) varies with patient population and dose administered, but also should vary with the type of bronchoprovocative medication. To date, clinically significant tachyphylaxis has only been demonstrated with methacholine[8] and does not appear to be a problem with histamine.[7] Thus, repeated administration of histamine could be used to reliably and safely assess bronchial reactivity.

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