MEASUREMENT AND CLINICAL SIGNIFICANCE OF BRONCHIAL RESPONSIVENESS TO HISTAMINE

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SYNOPSIS

A study was conducted on normal subjects and asthmatic patients to determine their $PC_{20}FEV_1$ (provocation concentration causing a fall of 20% in the forced expiratory volume in one second) using histamine by inhalation in gradually increasing concentrations. The twenty normal subjects showed no significant bronchoconstriction on spirometry at the maximum dose of histamine used whereas all the fourteen asthmatic patients had $PC_{20}FEV_1$ within the dose range of histamine inhaled. There was a clear separation between the two groups in the test results. Further, it appeared that patients with a longer remission from acute asthma tended to have a higher $PC_{20}FEV_1$.

INTRODUCTION

Asthma is difficult to define but most would accept that "asthma is a disease characterised by wide variations over short periods of time in resistance to flow in intrapulmonary airways." (1). One of the characteristic features of asthma is the extreme sensitivity of the airways to physical, chemical and pharmacologic stimuli. Bronchial responsiveness describes this tendency of the airways to bronchoconstrict to specific or nonspecific stimuli. Nonallergic or nonspecific airway responsiveness to histamine and methacholine is increased in virtually all, if not all, subjects with current symptoms of asthma (2). The degree of increase is related to the severity of symptoms (3, 4) and the ease with which asthma is induced by nonallergic (5-7), and allergic (8) stimuli.

Nonspecific responsiveness can be quantitated by inhalation tests with histamine or methacholine, by exercise or by isocapnic hyperventilation of cold air. The exercise test is less sensitive than the histamine or methacholine inhalation test as a measure of nonspecific bronchial responsiveness (5, 6, 9). Responsiveness to methacholine is similar to responsiveness to histamine (within one two-fold concentration difference) when compared under carefully controlled conditions (4, 10, 11). Solutions of histamine are renewed every three months while those of methacholine every two weeks.

On the above considerations it was decided to use histamine to provoke bronchoconstriction in the laboratory.

METHOD

Subjects: These comprised 20 normal subjects and 14 asthmatics. The 20 normal subjects were all young healthy adults (medical students aged 22 to 23 years) with no past or family history of asthma and no past or current history of chest disease or any other illness. All were non-smokers. The 14 asthmatic patients were symptom-free at the time of investigation. Their clinical details are shown in Table 1. All were suffering from uncomplicated clinical asthma, and were considered atopic after responding positively to more than two allergens on skin-prick testing. The allergens used were from Bencard and comprised house dust, house dust mite, mixed feathers, cat fur, dog hair, human hair, kapok, cotton flock, Group B 3 and B 5 pollens, alternaria and Group M 2 moulds. None of the asthmatics smoked cigarettes. All were below 40 years old.

Histamine inhalation and spirometry: Medications which influenced the response to histamine inhalation were withheld before the test for their duration of action. The beta 2 adrenoceptor agonists were withheld for 8 hours, short-acting axanthines for 24 hours and long-acting xanthines and antihistamines for 48 hours. Cromoglycate and corticosteroids were continued in the same dose. The test was not performed if the FEV, was reduced to 1.5 L or less.

Histamine solutions using histamine diphosphate (Sigma) were prepared by the pharmacist locally to give concentrations of 50 mg/ml(5%), 25 mg/ml(2.5%), 6.25 mg/ml(0.625%), and 3.13 mg/ml(0.31%). Standard spirometric measurements of the forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC) were made initially, and one minute after saline, and each dose of histamine given by the De Vilbiss Number 40 nebuliser. The dose schedule is as shown in Table 2.

The mouth piece of the nebuliser was placed between the subject's teeth. The subject exhaled to just below functional residual capacity and then inspired slowly and completely. At the beginning of the inspiration, the operator gave the bulb of the nebuliser one firm squeeze. When the subject had inspired completely he held his breath for 5 seconds. When more than one puff was required for a given dose, they were given in consecutive breaths.

The challenge was stopped when the FEV_1 had fallen by at least 20% from the postsaline value or dose 9 had been given. Results were expressed as the $PC_{20}FEV_1$ (provocation concentration of histamine required to elicit a 20% fall in the FEV_1) which is obtained from the log dose-response curve by linear interpolation of the last two points and expressed as micromoles of histamine inhaled. The response to bronchodilator (two inhalations of salbutamol) was measured ten minutes after it was given. The whole procedure took less than 30 minutes.

Statistics. Statistical analysis was done using the Wilcoxon's sum of ranks test and the Mann-Whitney statistic. Only p values less than 0.05 were considered statistically significant.

RESULTS

Both groups of subjects had similar baseline FEV_1 and FVC values ($p > 0.05$). In the normal subjects, all tolerated the maximum amount of inhalational histamine without wheezing. The average change in the post-histamine FEV_1 and FVC compared to the baseline was minimal. However for the individual normal subject, the maximum fall in FEV_1 was 16.6% and in FVC 10.5% (in the same subject). In contrast, asthmatic patients on varying doses of inhalational histamine dropped both their FEV_1 and FVC on the average, 26.5% and 21.3% respectively (Table 3). And this occurred over the whole range of histamine doses. As shown in Table 1, the $PC_{20}FEV_1$ with histamine ranged from exquisite sensitivity of 0.16 micromoles up to 7.80 micromoles, a fifty-fold difference. There appears to be a suggestion from the data in Table 1 of a correlation of a greater $PC_{20}FEV_1$ with decreasing need for asthma medication and frequency of asthma attacks although the numbers are small.

Therefore no normal subject dropped his FEV_1 greater than 20% even with the maximum dose of histamine while all the 14 asthmatic subjects did so and four of them though only just, at the ninth dose of histamine. Following bronchodilator aerosol, the acutely induced airways obstruction was completely reversed. No systemic symptoms were noted and no patient complained of more than moderate transient dyspnoea and throat irritation with coughing.

DISCUSSION

As early as 1947, Curry (12) showed that asthmatic patients were more sensitive to histamine and methacholine than were patients with hay fever or no allergic disorders. Since then others have confirmed these findings using various methods of administration, dosages and parameters for measuring airways obstruction (3, 13-16). The method used in this study is from a protocol of the Respiratory Disease Committee, International Union Against Tuberculosis. Bronchial reactivity by this method has been determined for normal subjects and asthmatics in Australia (17). Non-technical factors influencing the method of measurement of bronchial responsiveness to histamine include medications (18), baseline airway calibre (19), respiratory infection (20) and allergen exposure (21). All these were considered and both groups of subjects had similar FEV_1 and FVC before bronchial histamine challenge. Technical factors requiring standardisation are aerosol generation and inhalation, volume and speed of inspiration, method of measurement of response, preparation and handling of histamine solutions, pH, temperature and stability (22). The De Vilbiss nebulizer No. 40 delivers a standard dose of solution per puff with each firm squeeze. Proper coordination is required to ensure that the histamine is completely inhaled especially when consecutive puffs are required.

Although changes in airway calibre can be measured by several techniques, standard spirometric indices especially the FEV_1 suffice for this test and in a cooperative subject, an acute fall of as little as 5% in the FEV_1 can be statistically significant. (23). The subjects selected for this study were either normal or asthmatic; hence the clear separation between them in their bronchial response to histamine. This will doubtless become blurred when the intermediate responses of some non-asthmatic relatives of asthmatic patients and atopic subjects are taken into account. Further some patients with chronic bronchitis, allergic rhinitis and even normal subjects during and after a respiratory tract infection will show bronchial reactivity in the asthmatic range (12, 16, 20, 24-27).

Thus although it has been shown that more than 90% of all patients with asthma and 99 to 100% of patients with current symptomatic asthma have responses outside the normal range, bronchial hyperreactivity is not unique to asthma. A low level of nonspecific bronchial reactivity therefore virtually excludes but a high level does not establish a diagnosis of asthma.

Even among asthmatics, there might be a relationship between the degree of bronchial reactivity and the duration and severity of asthma (2,3, 28), and recently the level of airway responsiveness to histamine has been correlated with the minimum medications required to control asthma, a high responsiveness requiring greater amount of medication (4). The small number of asthmatics in this study appears to support this relationship although there is an overlap in the $PC_{20}FEV_1$ of patients whose attacks are infrequent. Those on daily medication had lower $PC_{20}FEV_1$

than those taking medication only when attacks of asthma occurred.

There is evidence that in established asthma the level of hyperresponsiveness remains stable over long periods of time (29). Townley and coworkers (30) showed that although 100% of current asthmatics had bronchial hyperreactivity, only 82% of former asthmatics (free from asthma symptoms for 1 to 20 years) showed this characteristic. Of the eight patients in this study with asthma taking medication only when required, they were free of asthma for three weeks to 12 years and still showed bronchial hyperreactivity. But four of them showed this at the maximum dose of histamine inhaled.

An analogy can be drawn between the histamine inhalation test and the glucose tolerance test. Heightened bronchial reactivity may be considered to bronchial asthma what abnormal glucose metabolism is to diabetes mellitus (31). Bronchial reactivity is not stable and has been shown in normal subjects and asthmatics to be increased by exposure to respiratory infection (32), exposure to allergens (21) or to volatile chemicals (33, 34) and by exposure to atmospheric pollutants like oxides of nitrogen (35) and ozone (36). That asthmatic subjects with long-term remissions have a lower level of bronchial reactivity, with a decrease toward normal indicates that bronchial hyperreactivity may not be a fixed, permanent abnormality (37). On the other hand, hyperreactivity associated with occupational asthma may be acquired and decreases only very slowly with prolonged absences from the work place (34) suggesting that repeated or chronic exposures to irritating materials might lead to a sustained increase in reactivity. This has led Dolovich and Hargreave (38) to ask if asthma can be acquired as a result of exposure to inducers, many as yet unknown?

Based on these concepts then, the measurement of nonspecific bronchial responsiveness as by the histamine inhalation test, would lead to the following inferences:

1. in patients with a history suggestive of bronchial asthma supported by spirometric evidence of reversible airways obstruction, almost all would show non-allergic bronchial hyperreactivity.

2. in patients with a past history of asthma now in clinical remission, the longer the remission the more likely it is that bronchial hyperreactivity may approach normal levels. In this group of patients therefore, the presence of bronchial responsiveness at the doses of histamine used in this study, would support a diagnosis of previous asthma but a negative test would not exclude the diagnosis.

ACKNOWLEDGEMENT

The author is indebted to Professor A.J. Woolcock of the Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia for supplying the protocol used in the histamine inhalation test and to Dr. Poh Soo Chuan, Senior Physician and Head, Department of Medicine III, Tan Tock Seng Hospital, Singapore, for his unfailing encouragement and advice in this study.

TABLE 1: Clinical details of asthmatic patients and their $PC_{20}FEV_1$ (arranged in ascending value)

Patient	Age (yrs)	Sex	Race	Medication (last attack)	$PC_{20}FEV_1$ μmoles
1	31	M	Ch	daily BC	0.16
2	21	M	Ind	daily BC	0.28
3	25	F	Mal	daily BC	0.32
4	17	M	Ind	daily BC	0.47
5	22	F	Ch	prn B (4 months)	0.66
6	22	M	Ch	prn B (3 weeks)	0.98
7	21	F	Mal	daily B	1.10
8	19	F	Mal	daily B	3.40
9	22	M	Ch	prn B (10 years)	5.20
10	36	M	Ch	prn B (3 months)	6.50
11	24	M	Ch	prn B (10 months)	7.80
12	22	M	Ch	prn B (8 years)	7.80
13	22	F	Ch	prn B (12 years)	7.80
14	22	F	Ch	prn B (12 years)	7.80

B — bronchodilators C — corticosteroids prn — when necessary

$PC_{20}FEV_1$ is the provocation dose of histamine to elicit a 20% fall in the forced expiratory volume in one second.

TABLE 2: dosage schedule for histamine challenge

	DOSE NO.								
A. ASTHMA SUBJECT	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Histamine soln	0.31%	0.31%	0.625%	0.625%	2.5%	2.5%	2.5%	5%	
No. of puffs	1	1	1	2	1	2	4	4	
Dose (mg)	0.009	0.019	0.037	0.075	0.15	0.30	0.6	1.2	
Dose (μmoles)	0.029	0.061	0.122	0.244	0.488	0.977	1.954	3.91	
B. NORMAL SUBJECT									
Histamine soln		0.625%		0.625%		2.5%		5%	5%
No. of puffs		1*		3*		3*		6	8
Dose (mg)		0.019		0.075		0.30		1.2	2.4
Dose (μmoles)		0.061		0.255		0.977		3.91	7.8

* If FEV_1 falls by 10% or more, transfer to Schedule A.
The De Vilbiss No. 40 nebulizer delivers 0.003 ± 0.0007 mls per puff.
The doses of histamine are considered to be cumulative.

TABLE 3: Baseline and post-histamine inhalation values of FEV_1 and FVC in normal subjects and asthmatic patients

Spirometry (Litres)	Normal subjects n = 20		Asthmatic subjects n = 14	
	Baseline	**Post-histamine***	**Baseline**	**Post-histamine****
FEV_1 mean (range)	2.73 (1.8-4.1)	2.72 (1.5.-3.9)	2.44 (1.9-3.7)	1.80 (1.0-3.0)
mean % fall of FEV_1	0%		26.5%	
FVC mean (range)	2.88 (1.9-4.2)	2.84 (1.7-4.0)	2.72 (1.8-3.8)	2.14 (1.7-3.1)
mean % fall of FVC	1.5%		21.3%	

* after 9th dose of histamine
** after varying doses of histamine sufficient to give a greater than 20% fall in FEV_1
Comparison of baseline FEV_1 and FVC values of normal subjects and asthmatic patients $p > 0.05$.

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