

Measurement of responsiveness to inhaled histamine using FEV₁: comparison of PC₂₀ and threshold

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ABSTRACT Two methods of interpreting histamine inhalation dose-response curves were compared in 27 normal and 41 asthmatic subjects. The histamine provocation concentration producing a 20% fall (PC₂₀) in forced expiratory volume in one second (FEV₁) was calculated on the basis of the lowest FEV₁ after inhalation of saline and the lowest value after inhalation of histamine. The histamine threshold was determined as the first histamine concentration causing the FEV₁ to fall more than 2 SD below the mean of five pre-histamine (three pre-saline, two post-saline) FEV₁ determinations. The PC₂₀ was on average one doubling concentration larger than the threshold. The PC₂₀ provided better discrimination between asthmatic and normal subjects than did the histamine threshold and was significantly more reproducible. These findings suggest that the histamine threshold may prove useful for studies on populations, particularly those with a low degree of responsiveness to histamine, because of the possibility of measuring a response at a lower histamine concentration. On the other hand, the PC₂₀ is preferable for clinical use in individuals because of its better discriminating power and better reproducibility.

Bronchial provocation tests with chemical mediators such as histamine and methacholine are being used increasingly frequently in the assessment of patients with respiratory disorders.^{1,2} The need to standardise methods has been emphasised recently.^{1,3,4} One factor requiring standardisation is the method of measurement of the response. The one-second forced expiratory volume (FEV₁) is commonly used. Most often the concentration (or dose) of the bronchoconstricting agent producing a predetermined response—for example, a 20% reduction in FEV₁—is calculated and called PC₂₀⁵ or PD₂₀.³ Recently Habib *et al* have suggested the use of histamine threshold as a method of expressing the results of histamine bronchial provocation.⁶ The histamine threshold was defined as the concentration of histamine producing a fall in FEV₁ of more than 2 SD below the mean of four pre-histamine (three pre-saline and one post-saline) determinations.

In this study we have compared the histamine PC₂₀ with the histamine threshold in 41 asthmatic and 27 normal subjects. Reproducibility of both determinations was assessed in 20 of the asthmatic subjects.

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Accepted 22 February 1983

Methods

Subjects

Forty-one subjects with definite bronchial asthma⁷ were selected from the respiratory clinic at the University Hospital in Saskatoon. Twenty-seven normal non-smoking subjects with no chest disease or symptoms, no asthma, no rhinitis, and no recent respiratory infection (that is, in the last four weeks) were also studied. The study was approved by the University of Saskatchewan ethics committee and signed informed consent was obtained.

Histamine inhalation

Histamine inhalation tests were performed as previously described.^{5,8} Aerosols were generated with a Wright's nebuliser calibrated to deliver an output of 0.130–0.135 ml/min; this required an air flow of 7.5 l/min. Aerosols were inhaled for two minutes of tidal breathing through the mouth at five-minute intervals. Isotonic 0.9% saline was inhaled first, followed by doubling concentrations of histamine from 0.03 mg/ml to 8.0 mg/ml. The FEV₁ was measured three times before any inhalation, and 30 and 90 seconds after each inhalation. The test was continued until the FEV₁ had fallen by 20% or until the top concentration had been administered.

The histamine PC₂₀ and the histamine threshold were determined from all curves. The percentage fall in FEV₁ was determined from the lowest FEV₁ after saline inhalation and the lowest FEV₁ after histamine inhalation. Histamine PC₂₀ was calculated by linear interpolation between the last two data points on the dose-response curve, or was expressed as ">8 mg/ml" if there had been no response.^{5,8} The histamine threshold was determined by the method of Habib *et al.*⁶ The mean and SD of the five pre-histamine (three before saline and two after saline) FEV₁ measurements were determined. The threshold was defined as the lowest concentration first causing the FEV₁ to fall more than 2 SD below the mean pre-histamine FEV₁.

Study design

All 68 subjects attended the laboratory when symptoms (if any) were well controlled. Inhaled sympathomimetic agents were withheld for six hours, and oral theophylline products for 12 hours, while corticosteroids were continued in the same dosage. None of the subjects was using sodium cromoglycate or antihistamines. In all subjects a single histamine inhalation test was carried out and both PC₂₀ and the threshold were determined.

Reproducibility was assessed in 20 asthmatic subjects. Duplicate histamine inhalation tests were performed at the same time of day within five days. Tests were done at a time when symptoms were stable, when there had been no respiratory infection or allergen exposure for at least four weeks, and when baseline FEV₁ was reproducible to within 10%.

Analysis

Standard statistical tests were used.⁹ Histamine PC₂₀ and histamine threshold were compared in the 41 asthmatic patients by the method of least-squares regression. Reproducibility of the two determinations was assessed by examining the correlation obtained by least-squares linear regression of the first and second determination, and by comparing the percentage difference (100 × difference between 2 tests/mean of 2 tests) for PC₂₀ and threshold by the paired *t* test. Since PC₂₀ is a continuous variable and threshold a discontinuous variable, repro-

Anthropometric data on 41 asthmatics and 27 control subjects

| | Asthma | Control |
|---------------------------------|--------------|----------|
| Age (y; mean ± SD) | 36 ± 17 (SD) | 26 ± 7 |
| Sex (M:F) | 17:24 | 9:18 |
| Height (cm; mean ± SD) | 167 ± 8 | 172 ± 9 |
| Atopic (n) | 30 | 7 |
| FEV ₁ (%; mean ± SD) | 84 ± 21 | 106 ± 10 |

ducibility was also assessed with "clinical PC₂₀," defined as the first concentration to produce a 20% fall in FEV₁. The reproducibility of the clinical PC₂₀ was compared with the reproducibility of threshold by the paired *t* test.

Results

Anthropometric data are shown in the table. The asthmatic subjects were older and had lower FEV₁ values than the normal subjects.

The distribution of histamine PC₂₀ and histamine threshold values is shown in figure 1. All asthmatic subjects but only one normal subject had a histamine PC₂₀ below 8 mg/ml. All asthmatic subjects and eight normal subjects (30%) had a histamine threshold of 8 mg/ml or below. The threshold occurred after a fall in FEV₁ of 6.6% ± 4.6% in the asthmatic subjects compared with a 3.4% ± 1.9% fall in normal subjects (*t* = 3.96, *p* < 0.001). PC₂₀ and threshold values are compared in figure 2. The results of the linear regression were as follows: log threshold = 0.86 × log PC₂₀ - 0.03 (*r* = 0.89). On average the threshold was one concentration lower than the PC₂₀.

The reproducibility of the PC₂₀ and threshold in 20 asthmatic subjects is shown in figure 3. The PC₂₀

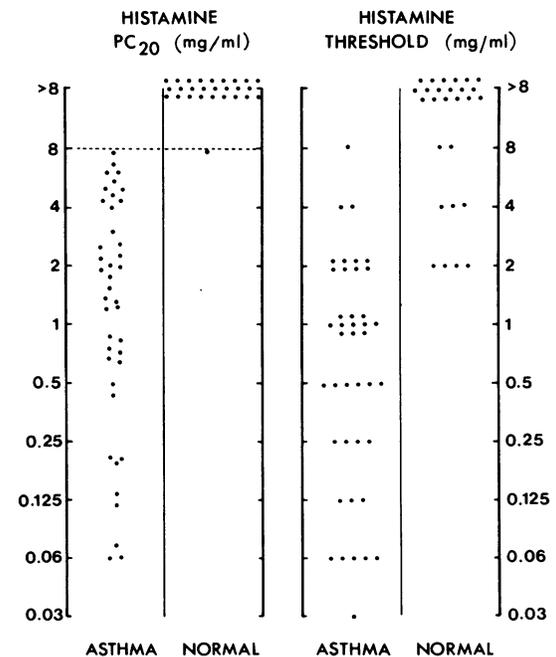


Fig 1 Distribution of histamine PC₂₀ and histamine threshold values in 41 asthmatic and 27 normal subjects.

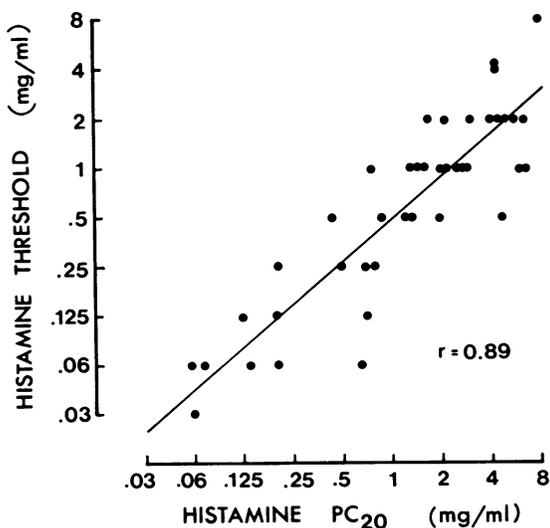


Fig 2 Comparison of histamine PC_{20} and histamine threshold in 41 asthmatic subjects.

was more reproducible, all repeat tests being within one doubling concentration. The correlation for repeat PC_{20} determinations was 0.98 and for repeat threshold determinations 0.91. The mean percentage difference between two tests was $20\% \pm 18\%$ for PC_{20} and $43\% \pm 38\%$ for the threshold (paired $t = 2.52$, $p < 0.05$). The clinical PC_{20} was identical on repeat testing in 15 of the 20 tests, and differed by one concentration in the other five. The clinical PC_{20} was more reproducible than the threshold ($t = 2.1$, $p < 0.05$).

Discussion

The results show that the histamine PC_{20} provides better discrimination between asthmatic and normal subjects than does the histamine threshold, and that it is also more reproducible. The threshold is on average one concentration less than the PC_{20} and thus, unlike the PC_{20} , can be determined in many normal subjects.

Since the PC_{20} and the threshold were calculated from the same curves, the greater degree of overlap between asthmatic and normal subjects for the threshold was initially surprising. The explanation is that the threshold in normal subjects occurs at a lower percentage fall in FEV_1 than in the asthmatic subject, 3.4% compared with 6.6%. There are three possible reasons for this. Firstly, asthmatic patients are known to have a greater variability in flow rates than normal subjects.¹⁰ Secondly, a response to diluent that may be seen in asthma¹¹ would be reflected by increased variability of the baseline FEV_1 by the technique used to calculate the histamine threshold. Thirdly, since asthmatic subjects had lower baseline FEV_1 values a similar absolute value for the standard deviation would represent a larger percentage of the mean FEV_1 . All three factors were probably relevant in this study and explain why the histamine threshold often reflects a smaller change in FEV_1 in normal subjects than in asthmatic subjects, leading to the observed greater overlap.

Reproducibility of results is important in standardisation of inhalation provocation tests. The histamine PC_{20} calculated by this method has been shown to be reproducible to within one doubling

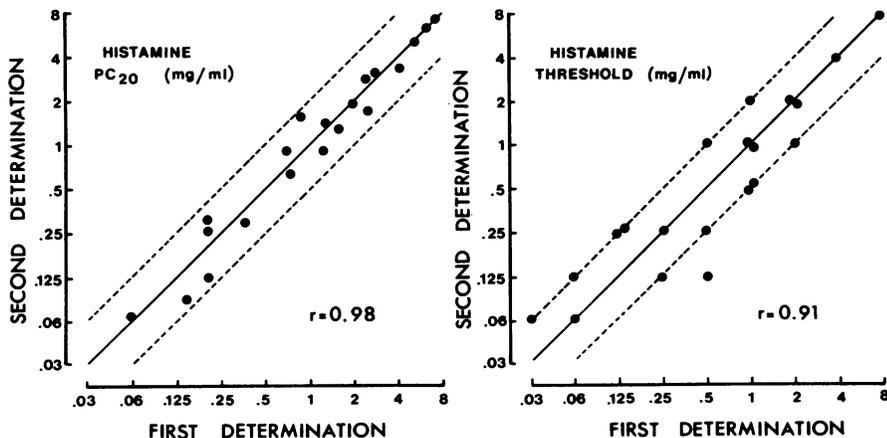


Fig 3 Reproducibility of histamine PC_{20} (left) and histamine threshold (right) in 20 asthmatic subjects. The first determination is plotted against the second determination. The solid lines are the lines of identity and the dotted lines represent ± 1 doubling dilution difference.

concentration.⁸ This was confirmed in the present study. The reproducibility of PC_{20} was better than that of the threshold. Statistical comparison of the PC_{20} and threshold values may not be entirely valid because PC_{20} is a continuous variable and threshold is a stepwise non-continuous doubling variable (that is, 1-2-4-8). From a practical point of view, the histamine PC_{20} is reported clinically as a non-continuous variable. Thus the reproducibility data were reanalysed with the "clinical PC_{20} " defined as the histamine concentration producing a fall in FEV_1 of 20% or more. This comparison also showed PC_{20} to be more reproducible than threshold values. Nevertheless, the threshold was fairly reproducible, showing a difference of one concentration or less in 19 of 20 asthmatics.

There are at least two theoretical reasons for discouraging the use of the histamine threshold, as calculated by this method, in individual subjects. The standard deviation obtained from only five measurements may not be an accurate enough assessment of the true standard deviation, in which case a change of more than 2 SD below the mean would be required to represent a significant change in FEV_1 . In our normal subjects 2 SD represented a 3.3% fall in FEV_1 ; thus the threshold, on average, was equivalent to a " $PC_{3.3}$ " only. More than 2 SD might be more appropriate when only five pre-histamine measurements are used. Furthermore, deriving the threshold in this manner excluded consideration of response to diluent, a feature considered important in analysing response to bronchoconstricting agents.^{3,5,8} On these two theoretical grounds histamine threshold probably has little clinical application to individual subjects performing inhalation provocation tests.

Methods used to perform and interpret the results of bronchial provocation tests may vary, depending on the purpose of the test. The data presented here show that histamine PC_{20} is preferable to histamine threshold for clinical use because of better discrimination and better reproducibility. Histamine threshold, however, might be useful for research studies applied to populations. It has been particularly valuable in studying groups of subjects who are normal or near normal, where the increased sensitivity can be put to advantage and histamine responses can be measured in many normal subjects.^{6,13,14}

We wish to thank Miss KA Storey and Mr JT Mink for help in preparing the manuscript. This work was supported by grant MA5071 from the Medical Research Council of Canada.

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