

Measurement of PC₂₀ histamine with the use of two different nebulizers and measurement of FEV₁ and PEF

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Histamine challenge was performed in 19 patients using two nebulizers (PARI and Wright) and FEV₁ and PEF were measured to determine PC₂₀ histamine. FEV₁ and PEF gave identical PC₂₀ histamine values. The PARI nebulizer gave PC₂₀ histamine values that were 2.5 doubling concentrations lower than the Wright nebulizer. The reproducibility of histamine challenge with the PARI nebulizer was studied in 15 patients and the results suggested that the challenge was reproducible within one doubling concentration of histamine.

Key words: bronchial challenge; histamine.

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Histamine or metacholine challenge is widely used for measurement of bronchial reactivity. Bronchial hyperreactivity is a prominent feature of asthma and is measured for diagnostic purposes and classification (5).

Bronchial reactivity is often expressed as the concentration of histamine (PC₂₀) that causes a 20% fall in forced expiratory volume in 1 s (FEV₁) or peak expiratory flow (PEF). The various types of nebulizers that are used for aerosol generation have different output in ml/minute and different particle size distribution. Because of this, nebulizers do not give identical PC₂₀ values in histamine challenge (4, 8).

The purpose of this study was to compare two techniques for determining PC₂₀ histamine. One method is simple and inexpensive and the other more expensive and sophisticated. An experiment was also performed to assess the reproducibility of histamine challenge with the PARI nebulizer.

METHODS

Study populations

The study population for the comparison study consisted of 19 consecutive patients with symptoms suggesting asthma and/or rhinitis who were referred to our clinic for allergological evaluation. The combination of asthmatic patients with daily symptoms and patients with rhinitis only or seasonal mild asthma gave a wide range of bronchial reactivity. The patients underwent histamine challenge with the two methods on two separate days at the same time of the day within 1 week. The difference in baseline FEV₁ between the two study days was less than 10% in all subjects. Theophylline, beta agonists and anticholinergics were not allowed on the study day and sustained release preparations of theophylline and beta agonists were withheld during the 24 h prior to challenge.

To assess the reproducibility of histamine challenge with the PARI nebulizer we performed three challenges in each of 15 asthmatic patients in stable condition. Median age was 25 years (range 15–36), median PC_{20} histamine mg/ml was 0.21 (range 0.02–1.21), and median FEV_1 percent predicted was 103 (range 75–124). Challenges were performed at 1-week intervals, and baseline FEV_1 did not differ by more than 10% in all subjects. Each patient was challenged with the same nebulizer and at the same time of day. Criteria for medical treatment were the same as mentioned above.

Histamine challenges

The two methods used for histamine challenge are procedures modified from Cockcroft (2). Inhalation of aerosol was performed with tidal breathing for 2 min and a nose clip was used to ensure oral breathing. The challenge started with the inhalation of isotonic saline. FEV_1 and PEF measured 90 s after this inhalation were used as baseline in further calculations. FEV_1 and PEF were measured 30 and 90 s after each inhalation. Histamine was inhaled in doubling concentrations from 0.03 mg/ml to 8 mg/ml (method I) and 16 mg/ml (method II) or until the FEV_1 and PEF had fallen at least 20% below baseline level. Measurement of lung function was performed with a Wright peak flow meter and a dry bellow spirometer (Vitalograph 20600, Buckingham, England). PC_{20} was determined by linear interpolation between the dose that caused >20% fall in FEV_1 and PEF and the preceding dose.

Method I used a PARI nebulizer (Paul Ritzan, Pariwerk, Starnberg am See, Germany). The nebulizer was filled with 2 ml of test solution and driven by compressed air with a flow rate of 5 l/min. The mean output was 0.57 ml/min (range 0.47–0.63) for 10 tested nebulizers. Eight of the 10 nebulizers were within 10% of the mean. Repeated measurements showed that 5/10 nebulizers were within 10% of the mean for two measurements and 10/10 were within 15% of the mean for two

measurements. The flow rate was set at 5 l/min for all nebulizers and no individual calibration was attempted.

Method II used a standard Wright nebulizer driven with compressed air at a pressure of 0.5–0.7 bar. The nebulizers were individually calibrated to the pressure that gave an output of 0.13–0.15 ml/min when filled with 2 ml of test solution. A flow regulator was used which ensured a constant pressure to the nebulizer. Repeated measurements showed that the output was 0.13–0.15 ml/min for all nebulizers.

Statistics

For statistical evaluation all PC_{20} values were transformed to logarithms of base two so that a difference between PC_{20} values would be expressed in doubling units. Pearson correlation and linear regression methods were used for statistical analysis. For graphical presentation the absolute differences of PC_{20} histamine were used. This emphasizes the differences between measurements contrary to the traditional x-y diagram of absolute values (1).

RESULTS

With method I all patients had bronchial hyperreactivity, but six did not have a 20% decrease in FEV_1 and PEF with method II. Three of the six had a decrease in FEV_1 and PEF approaching 20% so that a PC_{20} histamine could be extrapolated, but three patients had no decrease in FEV_1 and PEF with method II.

Importance of measuring FEV_1 or PEF

The PC_{20} histamine values obtained by measuring FEV_1 and PEF were identical with method I and method II. Method I gave a close correlation between the two PC_{20} values ($r = 0.95$, $P = 0.00$). Regression analysis showed that the slope of the regression line ($b = 0.97$, $SE = 0.05$) did not differ significantly from 1.0 and the intercept did not differ

Difference in doubling concentrations
PARI, FEV₁ versus PEF

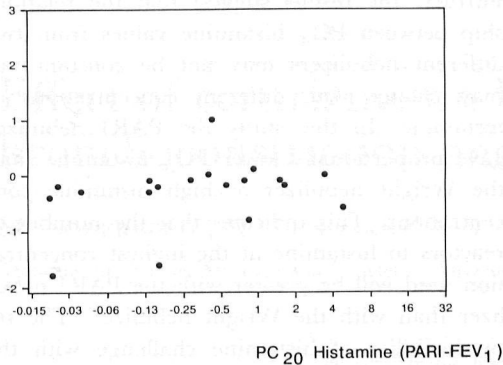


Fig.1. Absolute difference in doubling concentrations of PC₂₀ histamine with PARI nebulizer (FEV₁-PEF).

significantly from zero ($a = -0.25$, $SE = 0.14$). In 17 of 19 challenges the difference between PC₂₀ histamine obtained by FEV₁ and PEF was less than one doubling concentration of histamine (Fig.1). Method II also showed a close correlation between the two PC₂₀ values ($r = 0.95$, $P = 0.00$). Regression analysis showed that the slope of the regression line ($b = 0.91$, $SE = 0.08$) was not significantly different from 1.0 and that the intercept ($a = 0.00$, $SE = 0.2$) was not significantly different from zero. In 14 of 16 challenges the difference between the PC₂₀ histamine values

Difference in doubling concentrations
PEF, Wright versus PARI

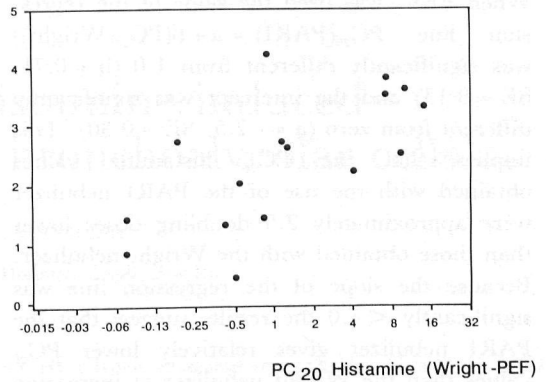


Fig.3. Absolute difference in doubling concentrations of PC₂₀ histamine with measurement of PEF (Wright-PARI).

obtained with FEV₁ and PEF measurement was less than one doubling concentration of histamine (Fig.2). The results thus showed that there was no significant mean difference in PC₂₀ histamine values obtained by the measurement of FEV₁ and PEF in histamine challenge with the two nebulizers.

Importance of type of nebulizer

A significant linear relationship between PC₂₀ histamine obtained by the two nebulizers was

Difference in doubling concentrations
Wright, FEV₁ versus PEF

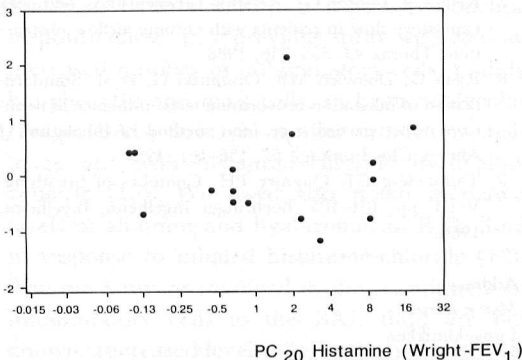


Fig.2. Absolute difference in doubling concentrations of PC₂₀ histamine with Wright nebulizer (FEV₁-PEF).

Difference in doubling concentrations
FEV₁, Wright versus PARI

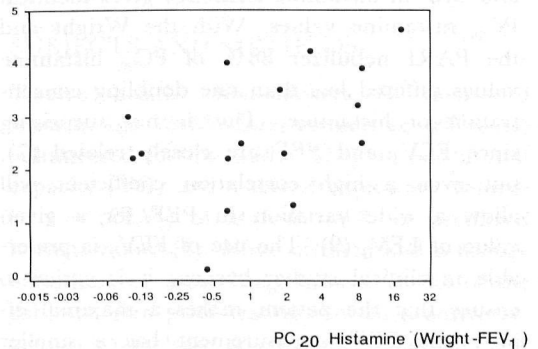


Fig.4. Absolute difference in doubling concentrations of PC₂₀ histamine with measurement of FEV₁ (Wright-PARI).

found when FEV_1 and PEF were used to assess lung function; the results were identical. When FEV_1 was used the slope of the regression line $PC_{20}(PARI) = a + b(PC_{20}(Wright))$ was significantly different from 1.0 ($b = 0.71$, $SE = 0.13$) and the intercept was significantly different from zero ($a = -2.5$, $SE = 0.30$). This implies that the PC_{20} histamine values obtained with the use of the PARI nebulizer were approximately 2.5 doubling doses lower than those obtained with the Wright nebulizer. Because the slope of the regression line was significantly < 1.0 the results suggest that the PARI nebulizer gives relatively lower PC_{20} values than the Wright nebulizer at increasing concentrations of histamine. The large differences were emphasized when the absolute differences of PC_{20} histamine were depicted, (Figs. 3 and 4).

Reproducibility of challenge with the PARI nebulizer

Eight of 15 sets of three challenges differed in PC_{20} histamine values by less than 25 %, six by 25–50 %, and one set, the greatest difference, by 63 %. Fifty percent difference represents one doubling concentration on the low side and 0.56 doubling concentration on the high side. The results suggest that the challenges are reproducible within one doubling concentration of histamine.

DISCUSSION

This study demonstrates that the use of FEV_1 and PEF in histamine challenge gives identical PC_{20} histamine values. With the Wright and the PARI nebulizer 88 % of PC_{20} histamine values differed less than one doubling concentration of histamine. This is not surprising since FEV_1 and PEF are closely related (7), but even a high correlation coefficient will allow a wide variation in PEF for a given value of FEV_1 (9). The use of FEV_1 is preferable in clinical studies because it is easier to ensure that the patient makes a maximal effort, and FEV_1 measurement has a smaller coefficient of variation than PEF (3). The well-known fact that different nebulizers have dif-

ferent output and characteristics and give different PC_{20} histamine values was confirmed. Further, the results suggest that the relationship between PC_{20} histamine values from two different nebulizers may not be constant but may change with different concentrations of histamine. In this study the PARI nebulizer gave proportionally lower PC_{20} histamine than the Wright nebulizer at high histamine concentrations. This indicates that the number of reactors to histamine at the highest concentration used will be greater with the PARI nebulizer than with the Wright nebulizer. The reproducibility of histamine challenge with the PARI and Wright nebulizers was of the same order (one doubling concentration) (8).

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