

Histamine inhalation tests: inhalation of aerosol via a facemask versus a valve box with mouthpiece

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Inhalation tests with histamine or methacholine are useful in clinical practice and research to determine the level of bronchial responsiveness. The factors which influence the dose deposited in the lung must, however, be regulated so that the results can be accurately interpreted. In the method introduced by DeVries *et al*¹ and modified by Cockcroft and coworkers² the aerosol is generated continuously and inhaled by tidal breathing. The dose deposited in the lung may be influenced by nebuliser output, particle size, the nature of apparatus between the nebuliser and the mouth, the variability of tidal breathing, and the duration of inhalation. The effect of each of these, with the exception of the apparatus between the nebuliser and mouth, has been systematically investigated.³⁻⁵ In the method described by Cockcroft² the aerosol passes through a facemask, which is held loosely over the mouth and clipped nose. It is possible that this might lead to more variation in the dose inhaled than if the aerosol is delivered directly into the mouth via a valve box and mouthpiece. In the present study we have compared responses and reliability with these two methods of aerosol delivery.

Methods and results

Ten adults with asthma, who were selected to give a range of bronchial responsiveness, participated in the study. Each subject's symptoms were under control and the FEV₁ was over 90% of predicted (table). None had had recent exposure to an allergen to which they were sensitised or symptoms of a respiratory infection, which could have made their bronchial responsiveness unstable. Medications known to acutely influence the results were withheld for their duration of action. Each subject had one histamine test on four separate days, at the same time of day and within one week. The tests were carried out by the method described by Cockcroft *et al*² with a Wright nebuliser operated to give an output of 0.13 ml/min. In two tests the nebuliser was connected directly to a facemask held loosely over the mouth (fig, a), while in two it was connected directly into the central chamber of a Hans Rudolph inspiratory-expiratory valve box and a mouthpiece (fig, b). The order of the test was randomised. In each test a nose clip was worn and the aerosol was inhaled through the

mouth by tidal breathing for two minutes. Phosphate buffered saline was inhaled first, followed at intervals of five minutes by twofold increasing concentrations of histamine acid phosphate from 0.125 to 16 mg/ml. The response was measured by FEV₁, at the start of the test and at 30 and 90 seconds after each inhalation. The inhalations were continued until there was a fall in FEV₁ of 20% or more below the lowest post saline value. The results were expressed as the concentration required to cause a fall in FEV₁ of 20% (PC₂₀). This was obtained from the log dose-response curve by linear interpolation between the last two points. At the end of the study each subject was asked which method of aerosol delivery he or she preferred.



(a)



(b)

Aerosol delivery with (a) facemask and (b) valve box with mouthpiece. A nose clip is worn with both methods.

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Results of inhalation tests

Subject No	FEV ₁ (% pred ¹¹)	PC ₂₀ (mg/ml)		Valve and mouth-piece	
		Facemask			
		1	2	1	2
1	97	2.55	3.15	3.65	2.90
2	114	2.55	2.85	3.85	2.75
3	91	2.45	3.20	4.05	3.10
4	92	8.00	8.60	7.00	7.00
5	90	1.62	2.30	2.30	1.48
6	112	0.62	0.54	0.65	0.50
7	95	0.57	0.73	0.46	0.87
8	112	1.15	2.00	2.20	2.45
9	92	11.70	8.10	9.50	8.95
10	96	3.28	3.29	4.80	3.04

PC₂₀ values were transformed to logarithms before analysis. The reliability of each method was examined by calculating the within subject standard deviation from a one way analysis of variance. For the facemask the log₁₀ PC₂₀ SD was 0.084 mg/ml (equivalent to 21% on the untransformed scale) and for the mouthpiece it was 0.105 mg/ml (27%). The intraclass correlation coefficient is the ratio of this within subject variance and the between subject variance.⁶ For the facemask the intraclass correlation coefficient was 0.958, indicating that 95.8% of the total variation in PC₂₀ was due to differences between subjects (signal) and only the remaining 4.2% was due to the imprecision of the method (noise). The intraclass correlation coefficient for the mouthpiece was 0.931. This modest difference in the intraclass correlation between the two methods was due mainly to the slightly higher within subject variability for the mouthpiece method. Formal comparison of within subject variability, however, indicated there was little evidence of a difference between the methods ($p > 0.10$). Thus these methods should be considered of high and equivalent reliability. Constant variances over the ranges tested for the two methods was shown by poor correlations between the absolute differences and the means.⁷ For the facemask $r = 0.388$ and for the mouthpiece $r = 0.629$; neither of these value reached conventional significance ($p > 0.05$). The PC₂₀ pairs obtained for each method were averaged and compared by linear regression analysis (table). The slope of 1.005 was not different from 1.000 ($p > 0.5$) and the intercept of 0.039 was not different from zero ($p > 0.15$); the overall significance was $p > 0.001$. Paired t analysis showed a lack of bias between the methods ($p > 0.10$); there was little evidence of any difference in variance over the range tested ($r = 0.006$). Six subjects preferred inhalation via a facemask.

Discussion

The results of this study show that, when histamine aerosol is generated continuously and inhaled by tidal breathing, there is no difference in PC₂₀ or its reliability whether the aerosol is inhaled through the mouth from a facemask or from a mouthpiece connected to a valve box.

The most important technical factors which may influence aerosol deposition are nebuliser output and the duration of inhalation.³ Nebuliser output at several flow

rates must be measured with each nebuliser. The flow-output calibration curve allows the correct flow to be selected for a specific output. These characteristics should probably be checked at least annually. Inhalation by tidal breathing gives greater reproducibility of results over two minutes than over 30 seconds,⁴ but more careful regulation of tidal breathing is not important.⁵ In contrast, particle size, at least from 1.3 to 3.6 μm aerodynamic mass median diameter, does not influence the response.³ We have shown that whether the aerosol is delivered via a facemask or a mouthpiece also does not influence the response.

Standardisation of technical factors is important for the accurate interpretation of results. In the method used in this study nebuliser output was regulated at 0.13 ml/min and the duration of tidal breathing was two minutes. When the response is measured by FEV₁ and when the preinhalation FEV₁ is normal, a PC₂₀ of less than 8 mg/ml is considered to indicate an increase in bronchial responsiveness. Values of PC₂₀ above 8 mg/ml are found mainly in non-asthmatic people,^{8,9} whereas patients with current symptoms of asthma usually show PC₂₀ values below 8 mg/ml.¹⁰

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