

Effect of aerosol and oral fenoterol on histamine and methacholine challenge in asthmatic subjects

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ABSTRACT In order to determine the effect of drugs on bronchial hyperreactivity in subjects with asthma, 12 atopic asthmatic volunteers underwent bronchial challenge with either histamine or methacholine on three separate days. Before the challenges no medication was given on the first day, on the second 400 μ g of aerosol fenoterol and on the third 5 mg of oral fenoterol were administered. The aerosol fenoterol caused the dose response curves to both histamine and methacholine to be shifted to the right in all subjects. The oral dose produced no significant change from the control values. The slope of the dose response curves was not altered by either the oral or the aerosol drug. It is concluded that aerosol but not oral fenoterol in the clinical dosage, causes a change in the sensitivity but not in the reactivity of the airways of patients with atopic asthma.

Fenoterol, a β_2 -adrenergic agonist has been shown in both oral and aerosol forms to be an effective bronchodilator.¹⁻³ The aerosol form has been shown to protect against exercise-induced asthma (EIA)² and to prevent early reactions to allergen challenge.³ Oral sympathomimetics appear to be less effective than aerosols in preventing EIA.^{2,4} Cockcroft *et al*⁵ have shown that both inhaled and oral salbutamol will protect against histamine-induced bronchoconstriction, although the aerosol gives greater protection than the oral drug. This difference between oral and aerosol forms may reflect different tissue concentrations of the drug or may indicate that the mechanisms of bronchodilatation and of the prevention of induced bronchoconstriction are different. Orehek *et al*⁶ have distinguished two factors in the asthmatic reaction to bronchial challenge. Firstly, sensitivity which is the amount of a provoking agent required to produce a bronchoconstrictor response, and secondly reactivity, the way in which the airways respond to successive doses of the provoking agent. Their data suggest that it is the reactivity which best distinguishes asthmatic from non-asthmatic subjects. The cause of the heightened reactivity in asthma is unknown.

In order to study the factors which alter the degree of bronchial reactivity, a β_2 -adrenergic agonist (fenoterol) was administered by aerosol and by

mouth on different days, and the changes induced in sensitivity and reactivity to methacholine and histamine challenge were measured.

Methods

Twelve previously diagnosed atopic asthmatic volunteers, seven men and five women, aged between 19 and 38 years (mean 24 years) underwent bronchial challenge with either histamine diphosphate (Sigma Chemical Co, St Louis) or methacholine chloride (JT Baker Chemicals, NJ) on three separate days, at the same time of day. Eight were studied after both histamine and methacholine challenge. All medications were withheld for at least six hours before any challenge. Informed consent was obtained from each volunteer.

On the first day a bronchial challenge with methacholine or histamine was performed using the standardised procedure described by Chai *et al*.⁷ Methacholine, in doubling concentrations from 0.075 mg/ml to 50 mg/ml, or histamine in doubling concentrations from 0.03 mg/ml to 10 mg/ml, was delivered through a De Vilbiss No 646 nebuliser attached to a cylinder of medical air set at 20 psi. The time of each nebulisation was controlled by a Dosimeter (Rosenthal-French, USA) set at 0.6 seconds. The subjects inhaled slowly from functional residual capacity (FRC) to total lung capacity (TLC) through a mouthpiece with the nose clamped.

Lung function was measured using a Vitalograph

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dry spirometer from which forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were recorded. For each subject, values were recorded initially and 90 seconds after each dose. The challenge began with five breaths of a saline control and continued with five breaths of each successive concentration of the provoking agent. The challenge was stopped when a 20% or greater fall in FEV₁ was reached and maintained over three minutes. Spirometric function was measured at five, seven, 10, and 15 minutes after completion of the challenge. All measurements were performed in duplicate or until reproducible values were obtained. Fenoterol aerosol was administered at the end of the test to ensure complete recovery from bronchoconstriction.

On the second day 400 µg of aerosol fenoterol was administered by metred dose inhaler and 15 minutes later a challenge with histamine or methacholine was carried out. One and a half hours before challenge on the third day 5 mg of oral fenoterol was administered.

Doses were recorded in inhalation units, as described by Chai *et al*⁷ where one unit equals one inhalation of a 1 mg/ml solution of either methacholine or histamine. Response was measured as the percent fall in FEV₁ from the pre-challenge value by the formula:

$$\text{Percent fall FEV}_1 = \frac{\text{post saline FEV}_1 - \text{post challenge FEV}_1}{\text{post-saline FEV}_1} \times 100$$

Individual log dose response curves were plotted and the dose required to produce a 20% fall in FEV₁ (PD₂₀FEV₁) was recorded. In addition, dose-response regression equations were calculated for the individual subjects from at least three points between the dose which initiated a consistent fall in FEV₁ and the final dose. Correlation coefficients were calculated, and the regression equations were rejected when a significant correlation was not found. The coefficient "a" from the formula, percent fall FEV₁ = a log dose + b, was recorded as a measure of the slope of the dose response curve.

Bronchodilator effect was recorded as percent rise in FEV₁ from the formula:

$$\text{Percent rise FEV}_1 = \frac{\text{post dilator FEV}_1 - \text{pre-dilator FEV}_1}{\text{pre-dilator FEV}_1} \times 100$$

Predicted values for FVC and FEV₁ were taken from the data of Morris *et al*.⁸ Statistical comparison of the results was made using Student's *t* tests of paired observations. Significance was taken at the 5% level.

Rate of recovery from challenge was analysed by performing regression analysis on the pooled data

from all subjects at 1.5, 3, 5, 7, 10, and 15 minutes after challenge. Analysis of covariance was used to determine any differences between the three regimens in each study.

Results

Typical dose-response curves for one subject (NB) are shown in fig 1. These were plotted for all subjects and the data obtained from them are presented in table 1 for histamine challenge and in table 2 for methacholine challenge. Both tables show the FEV₁ results before the challenges, after no drug (C), after 5 mg of oral fenoterol (O), and after 400 µg of aerosol fenoterol (A) together with the PD₂₀ and values for the slope of the curves. The mean values for PD₂₀ are the geometric mean. It can be seen from the initial values for FEV₁, which are expressed as a percentage of predicted values, that none of the subjects had severe airways obstruction before the challenge even on the control day, six hours after the last medication. The baseline FEV₁, before challenge, was not different after the two forms of administration of the drug.

After aerosol fenoterol, the PD₂₀ for both histamine and methacholine was significantly higher than the

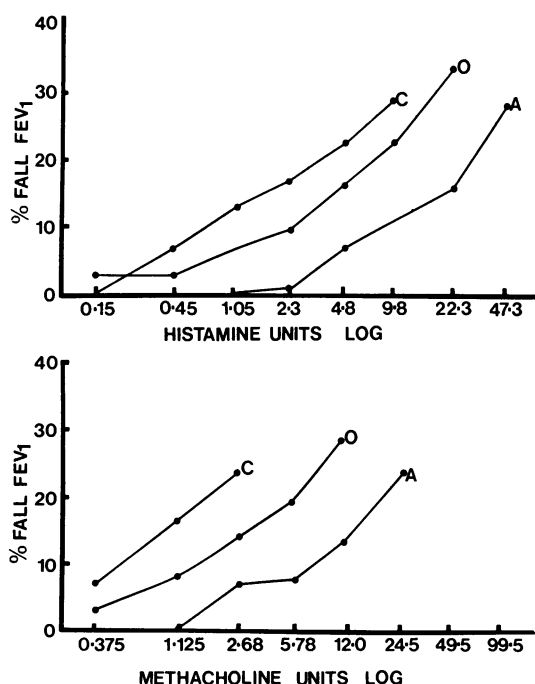


Fig 1 Dose-response curves to histamine and methacholine challenge in one subject. C = challenge alone; O = challenge after 5 mg oral fenoterol; A = challenge after 400 µg aerosol fenoterol.

Table 1 Dose-response curves to histamine challenge

Subject	Age (yr)	Sex	Pre-challenge FEV ₁ (% predicted)			PD ₅₀ FEV ₁ (Inhalation dose units)			Slope		
			C	O	A	C	O	A	C	O	A
CE	29	F	113	117	126	6.1	26.0	> 97.3	12.2	18.5	—
LM	21	F	104	109	112	3.4	29.0	7.0	15.6	18.9	18.8
JE	18	F	103	106	97	1.2	3.5	14.3	26.1	14.0	26.0
IJ	20	M	89	83	89	9.8	10.0	> 97.3	28.9	33.2	—
DW	19	M	90	109	116	2.5	6.8	38.0	21.6	42.9	34.5
JM	22	M	63	92	99	12.6	11.0	97.3	24.0	10.4	27.4
NL	21	F	76	83	83	2.4	1.7	24.0	32.4	11.3	40.1
CB	38	M	100	105	107	7.9	4.4	65.0	14.7	17.2	44.6
DA	30	F	80	79	104	5.6	2.7	35.5	45.4	17.5	22.2
AT	28	M	104	106	103	37.0	30.0	> 97.3	37.8	22.1	—
Mean	24.6		92.2	98.9	103.6	†5.6	8.1	29.7	25.9	20.6	30.5
SEM	2.0		4.9	4.2	4.0	1.4	1.4	1.4	3.4	3.2	3.6

†Geometric mean.

C = challenge alone, O = challenge after 5 mg oral fenoterol, A = challenge after 400 µg aerosol fenoterol.

Table 2 Dose-response curves to methacholine challenge

Subject	Age (yr)	Sex	Pre-challenge FEV ₁ (% predicted)			PD ₅₀ FEV ₁ (Inhalation dose units)			Slope		
			C	O	A	C	O	A	C	O	A
CE	29	F	110	123	121	2.6	33.0	> 475.0	24.6	11.2	—
LM	21	F	100	115	115	1.65	3.8	17.5	19.7	16.8	12.9
JE	18	F	97	103	105	0.65	1.8	40.0	35.7	42.5*	87.2*
IJ	20	M	89	91	95	3.6	18.0	110.0	21.3	12.7	23.3
DW	19	M	107	113	114	2.4	16.0	16.5	28.7	28.1	19.0
JM	22	M	80	93	100	10.0	11.0	50.0	16.0	16.1	34.5
NL	21	F	78	79	83	1.7	2.2	30.0	36.3*	19.9	37.5*
CB	38	M	84	96	113	3.4	4.0	32.0	42.5*	24.9	25.6
RC	20	M	70	79	83	40.0	39.0	260.0	9.6	13.2	8.2
DM	19	M	103	108	107	1.9	9.2	> 475.0	20.9	15.2	—
Mean	22.7		91.8	100.1	102.6	†3.2	9.0	44.7	25.5	20.1	31.1
SEM	2.0		4.3	4.8	4.0	1.4	1.4	1.4	3.2	3.0	8.7

Footnotes as in table 1.

*Correlation coefficient not significant.

PD₂₀ for both the control study and the study after oral fenoterol ($p < 0.001$, in all cases). After oral fenoterol the PD₂₀ was not significantly different from the control values for both challenges.

In some subjects aerosol fenoterol reduced the response to methacholine and histamine challenge so that the maximum challenge dose produced less than a 20% fall in FEV₁. In these subjects, PD₂₀ was calculated as greater than the maximum doses (methacholine: 475 units, histamine: 97 units). No value for the slope of the dose-response curves could be calculated for these subjects. The correlation coefficients for the slope of the dose-response curves were significant in all subjects for histamine but for only seven subjects for methacholine (see table 2). For the three subjects without significant correlation coefficients estimated values for slope

have been included in table 2, but have not been included in the analysis.

In all instances where the correlation coefficients were significant, neither aerosol or oral fenoterol altered the slopes of the dose-response curves. In order to show the mean values for the change in position of the curves, the inhalational units causing 10% and 20% changes in FEV₁ for the histamine and methacholine challenges have been plotted in fig 2.

Figure 3 shows the individual dose-response curves for histamine on the control day and after the aerosol form of the drug. The hatched area indicates the position on the dose-response curve which, in our laboratory, separates people with current or recent clinical asthma from normal people.

Bronchodilator therapy before the challenge did not affect the rate of recovery in the 15 minutes after

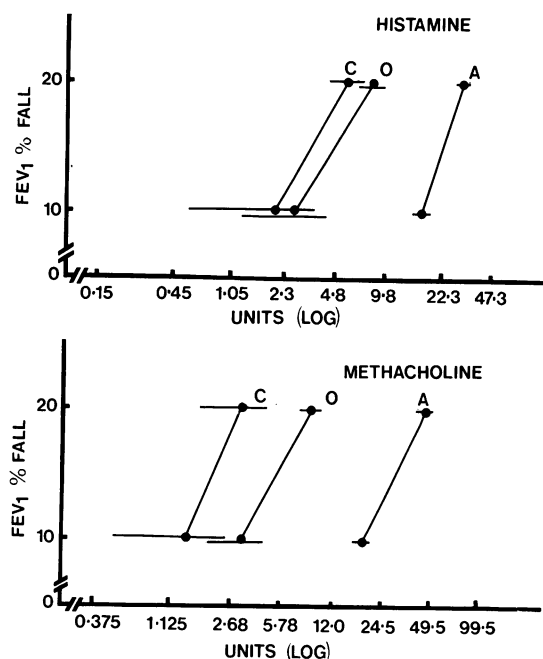


Fig 2 Geometric means for $PD_{10}FEV_1$ and $PD_{20}FEV_1$ (\pm standard error) for all subjects after histamine and methacholine challenge. C = challenge alone ($n = 10$ histamine and methacholine); O = challenge after 5 mg oral fenoterol ($n = 10$ histamine and methacholine); A = challenge after 400 μ g aerosol fenoterol ($n = 7$ histamine and 8 methacholine).

the challenges. After histamine most subjects were within 13% and after methacholine within 21% of their initial values.

Discussion

This study shows that fenoterol administered by aerosol but not by mouth in normal clinical dosage, changes the position of the dose-response curve (reduces the sensitivity) of asthmatic subjects to histamine and methacholine. In these subjects, neither aerosol nor oral fenoterol had an effect on the slope of the dose-response curve (that is the reactivity) to histamine or methacholine.

The design of the study was kept simple and was not done in a double-blind manner because, during previous studies, we have found that subjects invariably know when the active drug has been given. Each subject was simply told that the study was to determine the effect of the drug on his response to bronchial provocation. It was never suggested that one form of administration might have a different effect from the other form.

Juniper *et al*⁹ have shown that sensitivity to both histamine and methacholine is highly reproducible in asthmatic subjects. Reactivity is a more variable measurement and is difficult to determine accurately using the present method since several points on the linear part of the curve must be documented. A significant correlation coefficient for the dose response in all subjects given methacholine would probably have been achieved if the doses had been

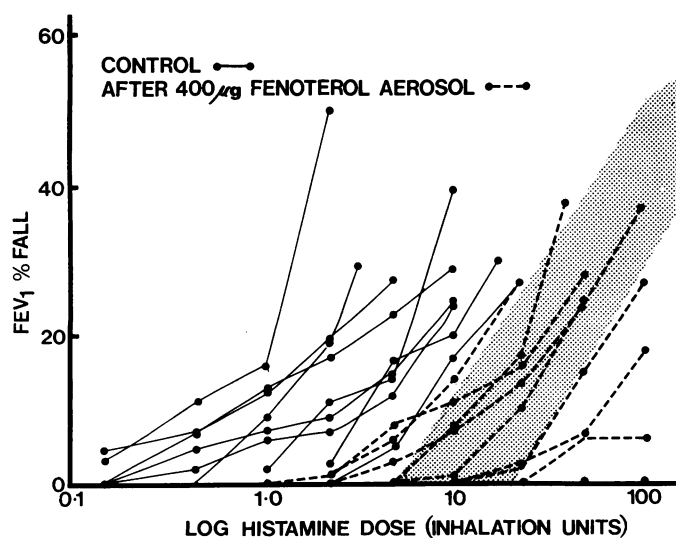


Fig 3 Individual dose-response curves to histamine challenge alone and after 400 μ g aerosol fenoterol. For an explanation of the hatched area, see text.

increased more gradually. However, even in these three subjects, the slope was obviously not changed by the drugs.

It appears that the effect of aerosol fenoterol is to shift the dose-response curve to the right, without altering its shape. This confirms the finding of Cockcroft *et al*⁵ who showed that the effect of β_2 aerosols was to change the position of the dose-response curve of asthmatic patients to bronchial challenge with histamine, although they did not measure the slope. This study has shown that the effect is produced by simply increasing the threshold of the asthmatic response without changing the slope. Figure 3 shows the individual results for the histamine challenge. In our experience, subjects whose dose-response curves fall in the shaded area have very mild asthma with infrequent attacks and require little therapy. The dose-response curves of all but two subjects were shifted into this range and two were clearly in the normal range in which it would be unlikely for a spontaneous attack of asthma to occur. Further studies are needed to determine if larger doses of fenoterol shift the dose-response curve even further to the right and for how long the drug is effective in maintaining the shift.

The inability of the oral β_2 agonists to protect against induced bronchoconstriction has been noted by other workers^{3,5} and is confirmed by this study for this particular dose. This difference between aerosol and oral forms of the drug may simply reflect differences in local concentration but it is possible that β_2 agonists act on more than one site in the airway. Their action on the β_2 adreno-receptors of the smooth muscle is well known. In addition, they may act on a number of structures in the mucosa including mast cells, the irritant nerve endings, or epithelial tight junctions. Since the mechanisms by which histamine and methacholine cause airway narrowing in asthmatic subjects are not understood, it is not possible to determine which of these structures may be affected by the drug.

For purposes of treatment, the greater ability of the aerosol fenoterol to protect against induced bronchoconstriction suggests that β_2 agonists in small dosage on or near the surface of the airways can decrease sensitivity and perhaps protect against a number of provoking stimuli occurring in everyday

life. In other words, it appears to shift the response of the airways temporarily from the asthmatic into the non-asthmatic range. Perhaps future drugs being investigated for the treatment of asthma could be studied both for their bronchodilating effect and their ability to protect against provoked attacks. As yet no drug has been shown to alter reactivity as opposed to sensitivity in asthmatic subjects. Further studies of the effect of increasing doses of the aerosol and of the duration of its "protective" action are needed. Tailor-made therapy, to find the dose and frequency of bronchodilator aerosol administration which keeps asthmatic subjects in the non-asthmatic range, might be a logical method of treatment, particularly for subjects with severe disease.

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References

- 1 Van Ardsel PP Jr, Schaffrin RM, Rosenblatt J, Sprenkle AC, Alfman LC. Evaluation of oral fenoterol in chronic asthmatic patients. *Chest* 1978;73:997-8.
- 2 Anderson SD, Rozea PJ, Dolton R, Lindsay DA. Inhaled and oral bronchodilator therapy in exercise induced asthma. *Aust N Z J Med* 1975;5:544-50.
- 3 Booij-Noord H, Quanjer PH, de Vries K. Protective effect of Berotec in provocation tests using inhalation of specific allergens and histamine. *Int J Clin Pharmacol Ther Toxicol*, (Suppl) 1972;4:69-72.
- 4 Anderson SD, Seale JP, Rozea P, Bandler L, Theobald G, Lindsay DA. Inhaled and oral salbutamol in exercise induced asthma. *Am Rev Respir Dis* 1976;114:493-500.
- 5 Cockcroft DW, Killian DN, Mellon JJA, Hargreave FE. Protective effects of drugs on histamine-induced asthma. *Thorax* 1977;32:429-37.
- 6 Orehek J, Gayraud P, Smith AP, Grimaud C, Charpin J. Airway response to carbachol in normal and asthmatic subjects. Distinction between bronchial sensitivity and reactivity. *Am Rev Respir Dis* 1977;115:937-43.
- 7 Chai H, Farr RS, Froelich LA *et al*. Standardisation of bronchial inhalation challenge procedures. *J Allergy Clin Immunol* 1975;56:323-7.
- 8 Morris JF, Koski A, Johnson LC. Spirometric standards for healthy non-smoking adults. *Am Rev Respir Dis* 1971;103:57-67.
- 9 Juniper EF, Frith PA, Dunnett C, Cockcroft DW, Hargreave FE. Reproducibility and comparison of responses to inhaled histamine and methacholine. *Thorax* 1978;33:705-10.