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Effect of aerosol fenoterol on the severity of bronchial hyperreactivity in patients with asthma

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ABSTRACT Beta adrenergic agents given by aerosol decrease the responsiveness of the airways to histamine and methacholine in subjects with asthma, causing a shift of the dose response curve to the right. To find out whether the shift is related to the dose of beta adrenergic agent given and to determine the duration of the reduced responsiveness, eight subjects with asthma were given histamine inhalation tests after inhaled saline and after increasing doses of inhaled fenoterol on different days. The histamine inhalation tests were repeated at hourly intervals for five hours after a selected dose of fenoterol. Fenoterol caused a dose related shift to the right of the histamine dose response curve in each subject and in some the dose response relationship reached the "non-symptomatic range." The shift in the dose response curve was short lived and had returned towards the control position within three hours in all subjects. There was no change in shape of the curves at the time of maximal shift. The results show that inhaled fenoterol greatly reduces the airway responsiveness to histamine, but up to 400 μg of fenoterol every four to five hours may be needed to keep the responsiveness of the airways in the non-symptomatic range.

Dose response curves showing the response of the airways to inhaled histamine can be plotted from the results of carefully conducted bronchial provocation tests. The airway response to inhaled histamine is much greater in asthmatic than in non-asthmatic subjects. The factors responsible for this increased responsiveness are not known. It is, however, known that the position of the dose response curve, based on the dose which causes a 20% fall in the one second forced expiratory volume (PD_{20-FEV_1}), varies with the severity of the disease and is shifted to the left (increased responsiveness) by exacerbations of asthma and by allergen challenge.[1,2] We have shown that inhaled fenoterol greatly decreases the responsiveness to histamine in asthmatic subjects, shifting the dose response curve to the right.[3]

This study was undertaken to determine whether the histamine dose response curve is shifted in a dose related manner after inhaled fenoterol, how long the reduced responsiveness lasts, and whether prior inhalation of fenoterol changes the shape of the dose response curve.

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Methods

SUBJECTS

Eight subjects with asthma of varying severity, aged 20–56 years, were studied on five separate days at the same time of day within a four week period. Their age, sex, atopic state, and baseline FEV_1 values (expressed as percentages of the normal values of Morris *et al*[4]) are shown in table 1.

All subjects were having bronchodilator treatment, either regularly or when they had symptoms, and six also required sodium cromoglycate or beclomethasone or both to control symptoms. One subject was having oral steroids. No medication was taken for at least six hours before any test and no changes in medication took place during the study. Great care was taken to ensure that no exacerbation occurred to alter the degree of bronchial responsiveness during the study. Informed consent was obtained from each subject, and approval for the study was obtained from the ethics committee of the Royal Prince Alfred Hospital.

METHODS

Bronchial challenges were performed with histamine diphosphate (Sigma Chemical Co, St Louis, USA) by the method of Chai *et al*.[5] After an initial

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Table 1 *Age, sex, and atopic state of subjects with values for FEV_1 (percentage of predicted value) before challenge and the histamine PD_{20-FEV_1} (μmol) after saline and increasing doses of inhaled fenoterol*

Subject	*Sex*	*Age*	*Atopic*	*Drugs*	*Initial FEV_1*	*Saline PD_{20}*	*Fenoterol inhalation (μg) 100*		*200*		*400*	
							FEV_1	*PD_{20}*	*FEV_1*	*PD_{20}*	*FEV_1*	*PD_{20}*
1	M	56	No	B Sp	79	0·87	B 74 A 95	7·7	B 74 A 95	6·5	B 79 A 97	10·5
2	F	20	Yes	B Sp	96	1·80	100 101	4·1	96 99	8·5	96 99	11·3
3	F	20	Yes	S I	100	0·095	99 110	4·1	99 113	4·7	96 112	12·0
4	M	20	Yes	S	101	0·11	100 110	10·0	95 106	2·9	96 109	6·4
5	M	38	Yes	S, B I, St	50	0·056	70 76	0·39	48 71	1·8	53 74	1·8
6	F	23	Yes	S, B I	69	0·052	69 74	3·3	62 78	3·6	72 83	5·3
7	M	21	Yes	S B	73	0·012	50 60	0·14	41 65	0·09	81 88	2·1
8	F	54	Yes	S	88	0·013	89 108	0·54	81 104	0·46	104 121	2·3
Mean (SD)					82 (17)	0·096*	B 81 (18) A 92 (19)	1·83*	B 74 (22) A 91 (18)	1·94*	B 84 (17) A 98 (16)	5·04*

*Geometric means.
PD_{20}, PD_{20-FEV_1}: see under "Methods"; B—before, A—20 minutes after fenoterol; S—salbutamol 200 μg; B—beclomethasone 100 μg; I—sodium cromoglycate 20 mg (all three inhaled four times a day); Sp—salbutamol when required; St—oral corticosteroid treatment.

inhalation of saline histamine was administered (the first concentration being 0·03%) through a de Vilbiss No 646 nebuliser attached to a cylinder of medical air set at 20 lb/in² (138 kPa). The time of each nebulisation was controlled by a dosimeter (Rosenthal-French, USA) set at 3 seconds. Inhalations were taken during an inspiration from functional residual capacity (FRC) to total lung capacity (TLC).

Lung function was measured with a Vitalograph dry spirometer. Forced expirations were repeated until reproducible values for FEV_1 were recorded. The FEV_1 was recorded at the beginning, after the saline inhalation, and 90 seconds after each histamine inhalation. Histamine was inhaled in doubling concentrations until a 30% fall in FEV_1 was observed.

PROTOCOL

On the first day a standard challenge, as described above, was performed. On the second day, after spirometry, 100 μg fenoterol was inhaled from the nebuliser. This was given as four inhalations from FRC to TLC taking five to six seconds, with the breath held for 20 seconds at TLC. FEV_1 was measured 20 minutes later, after which a histamine challenge was given as on day 1. This procedure was repeated on the third and fourth days after 200 and 400 μg fenoterol respectively.

On the fifth day 400 μg fenoterol was given to five subjects, 200 μg to one, and 100 μg to the other two. The histamine challenge was repeated hourly for five hours. In all subjects the dose of fenoterol selected was the dose that moved the response curve to a range not usually associated with symptoms of asthma.[6] The aim of this part of the study was to determine the effective duration of a dose necessary to make each subject symptom free.

The dose of histamine, recorded in terms of micromoles delivered by the nebuliser to the mouth of the subject, was plotted on a log scale against percentage fall in FEV_1 from the post-saline (day 1) or post-fenoterol (days 2–5) values. The dose causing a 20% fall in FEV_1 (PD_{20-FEV_1}) was recorded. A sigmoid function $\log, (Y/1-Y) = \alpha + \beta \log x$, where Y is the percent fall in FEV_1 and x is dose of histamine) was fitted to the curves by the method of least squares. Values for α (position constant) and β (slope constant) were calculated.[7] Student's t test was used to test the significance of differences between paired observations.

Results

Table 1 presents individual values for initial FEV_1 and PD_{20-FEV_1} after histamine challenge that followed saline and 100, 200, and 400 μg nebulised fenoterol. After fenoterol the dose response curve shifted to the right in all subjects. Geometric mean PD_{20-FEV_1} values were higher after each dose of fenoterol than after saline (100 μg, $p < 0·05$; 200 μg, $p < 0·01$; 400 μg, $p < 0·01$). There was no

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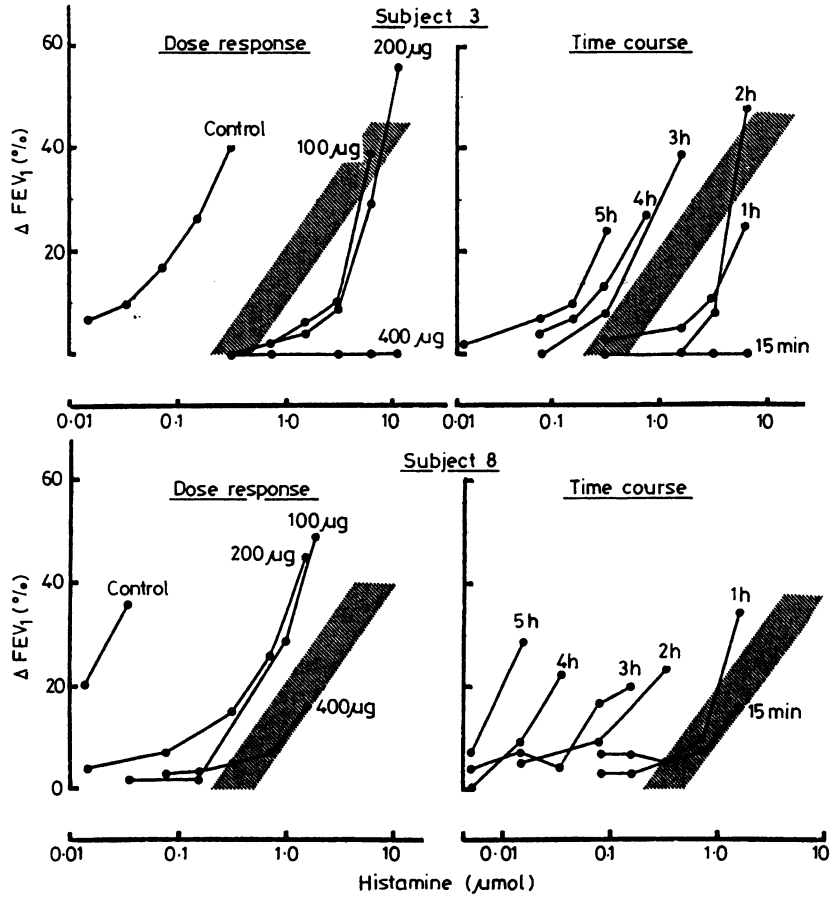

Fig 1 *Dose response curves after each dose of fenoterol and at hourly intervals after 400 µg fenoterol in subjects 3 and 8.*

Table 2 *Values for FEV_1 (% predicted) and PD_{20-FEV_1} (µmol histamine) at hourly intervals in eight subjects after a single dose of inhaled fenoterol*

Subject	*Fenoterol dose (µg)*	*Time after fenoterol inhalation*									
		1 h		*2 h*		*3 h*		*4 h*		*5 h*	
		FEV_1 (% pred)	*PD_{20}*	*FEV_1 (% pred)*	*PD_{20}*	*FEV_1 (% pred)*	*PD_{20}*	*FEV_1 (% pred)*	*PD_{20}*	*FEV_1 (% pred)*	*PD_{20}*
1	100	95	5	98	4	95	3·0	95	1·0	84	0·56
2	100	98	3·2	94	2·2	88	3·2	89	3·1	92	3·2
3	400	116	4·8	113	3·7	110	0·6	113	0·46	109	0·26
4	200	111	10	109	5	108	2·1	107	0·48	102	1·9
5	400	75	1·5	81	0·83	82	0·78	81	0·17	80	0·14
6	400	79	3·6	78	0·75	76	0·23	77	0·18	71	0·19
7	400	99	0·47	97	0·2	95	0·1	94	0·12	88	0·086
8	400	119	1·05	114	0·21	108	0·15	92	0·029	85	0·0095
	Mean	99	2·59*	98	1·20*	95	0·65*	93	0·30*	89	0·26*
	SD	16·2		13·7		12·8		12·0		12·1	

*Geometric mean.

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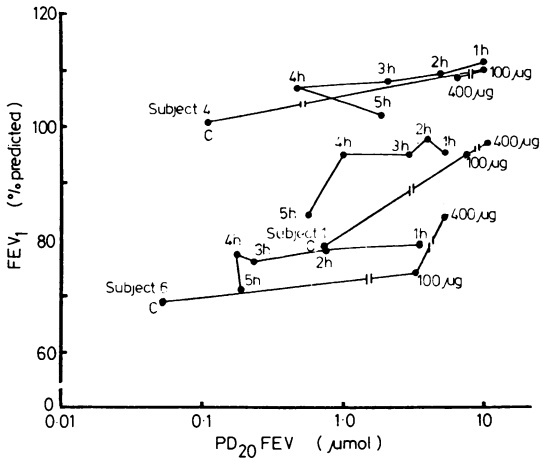

Fig 2 *Relationship between PD_{20-FEV_1} and FEV_1 (% predicted) before histamine challenge after saline (C) and 100 and 400 μg inhaled fenoterol and during the time course study in subjects 1, 4, and 6.*

significant difference between PD_{20-FEV_1} values after 100 and 200 μg fenoterol; after 400 μg fenoterol values were significantly higher than after 200 μg ($p < 0.01$).

Each dose of fenoterol resulted in a significant increase in FEV_1 ($p < 0.001$), though the mean percentage increase was not significantly different after 100, 200, and 400 μg fenoterol. Mean FEV_1 after 400 μg was 98% of the predicted value, a 14% increase, compared with 92% after 100 μg, an 11% increase.

Figure 1 shows the dose response curves after each dose of fenoterol and at hourly intervals after 400 μg in two representative subjects. In both subjects 400 μg fenoterol increased PD_{20-FEV_1} roughly 100 fold.

Table 2 shows the effect of time on the response to fenoterol. The FEV_1 (% predicted) before each hourly challenge and PD_{20-FEV_1} values for each challenge are shown. After fenoterol, mean FEV_1 increased from 82% (SD 18%) to 97% (16%) ($p < 0.001$). At 15 minutes the PD_{20-FEV_1} had increased to more than 1·0 μmol in all subjects and to more than 4·0 μmol in four. Values remained above the baseline for five hours in six subjects and for four hours in two, although the dose response curve showed roughly a 10 fold change for only two to three hours. The PD_{20-FEV_1} returned towards control values much more rapidly than the FEV_1, which was well maintained at four hours in most subjects. This can be seen in figure 2, which shows the relationship between PD_{20-FEV_1} and the FEV_1 at the time of challenge for three typical subjects.

Values for α, β, and r (correlation coefficient) are shown for the histamine dose response curves after saline and the 100 and 400 μg doses of fenoterol in table 3. There was a consistent increase in α but not in β, indicating that the position but not the slope of the dose response curve had changed in response to fenoterol (fig 1).

Table 3 *Values for α (position constant), β (slope constant), and r (correlation coefficient) calculated from the sigmoid equation after saline (C) and 100 μg and 400 μg of fenoterol aerosol*

Subject		*α*	*β*	*r*
1	C	−0·484	0·955	0·981
	100	−1·71	1·196	0·999
	400	−2·527	1·717	0·971
2	C	−0·652	0·522	0·977
	100	−1·346	1·24	0·993
	400	−2·088	1·389	0·998
3	C	0·141	0·716	0·994
	100	−1·516	1·497	0·978
	400	*		
4	C	1·034	1·915	0·957
	100	−2·291	1·973	0·995
	400	−2·264	2·01	0·997
5	C	2·619	3·002	0·936
	100	0·158	1·926	0·9995
	400	−1·023	2·030	0·995
6	C	1·047	1·34	0·980
	100	−1·619	1·92	0·998
	400	−2·354	2·41	0·977
7	C	0·854	0·767	1·00
	100	0·390	1·201	0·985
	400	−1·168	1·514	0·992
8	C			
	100	−0·408	1·582	0·9995
	400	−0·921	0·754	0·979

*FEV_1 fall < 20% after 12·0 μmol.

Discussion

We have shown previously that aerosol fenoterol alters bronchial responsiveness to histamine and methacholine, even in patients with severe asthma.[2] Similar results were found by Bandouvakis *et al*.[8] Experience with histamine inhalation tests has shown that a PD_{20-FEV_1} value greater than 4·0 μmol is almost never found in subjects who have wheezed in recent years. A value of less than 1·0 μmol is usually associated with symptoms of wheezing while values of between 1·0 and 4·0 μmol occur in subjects who may or may not have had recent symptoms.[5] This study shows that there is a dose related shift in the position of the histamine dose response curve after inhaled fenoterol without any consistent change in its shape, and that the curve can be shifted into the "non-symptomatic position." The shift in the dose response curve is shortlived compared with the effect of fenoterol on the FEV_1.

The subjects chosen for this study were known to

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have varying degrees of bronchial hyperresponsiveness with resting values of PD_{20-FEV_1} ranging from those found in patients with severe asthma (0·01 μmol) to those found in very mild asthma (1·8 μmol). All the subjects were familiar with the tests and reliable dose response curves were obtained. Three subjects had abnormal values for FEV_1 initially and this, especially in subject 5 (FEV_1 50% predicted), may have been responsible for the low PD_{20}; some of the shift in the dose response curve may have been due to the increase in FEV_1 (to 74% predicted from the baseline in subject 5) after 400 μg fenoterol. In the other subjects it seems unlikely that the change in FEV_1 was responsible for the change in the position of the dose response curve since wide variations in PD_{20-FEV_1} occurred with relatively small changes in FEV_1 (fig 2). The bronchodilating and protective effects of fenoterol do not seem to be closely linked. The FEV_1 was no greater after 400 than 100 μg fenoterol, whereas the PD_{20-FEV_1} was much higher after the 400 μg dose in all subjects. Thus 100 μg caused near maximum bronchodilatation but much less protection against histamine than 400 μg. Since 200 μg was no better than 100 μg in its protective effect, a considerably larger dose appears to be needed for protection. It was not possible to give 800 μg fenoterol because of side effects such as tremor. The bronchodilating effect of fenoterol persisted for longer than the protective effect. By four hours, mean FEV_1 had fallen from 99% to 93% of predicted values while mean PD_{20-FEV_1} had fallen from 3·87 to 0·30 μmol, having been 0·096 on the control day (fig 2).

The reason for this difference between bronchodilating and protective effects is not apparent. Possibly fenoterol stops histamine getting in to the submucosa or has two different actions at the smooth muscle level. It is known that inhaled $beta_2$ agonist drugs protect against methacholine, exercise, and allergen challenges. This suggests that the asthmatic subject is dependent on the $beta_2$ receptor for protection against various sources of provocation.

The degree to which the dose response curve was shifted was not related to the position of the curve on the control day. Subjects 2 and 3, who had very different control values for PD_{20-FEV_1} (0·095 and 1·8 μmol), both shifted to more than 11 μmol—well within the "non-symptomatic" range.

There are practical implications for treatment suggested by this study. Firstly, if the dose response curve is to be kept in the non-symptomatic range it may well be necessary to give fenoterol every four hours. Secondly some people will be relatively free from symptoms while taking fenoterol, regardless of the current FEV_1, whereas others, like subjects 5, 6, 7, and 8, will not. In these subjects the PD_{20-FEV_1} was back in the symptomatic range within two hours of inhaling fenoterol.

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