Inhibition of the bronchial response to respiratory heat exchange by increasing doses of terbutaline sulphate

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ABSTRACT Ten asthmatic patients inhaled terbutaline sulphate (250, 500, or 1000 μg) or placebo on separate days, double blind and in random order, 30 minutes before isocapnic hyperventilation induced by cold air inhaled in doses that increased in a precisely controlled manner. The respiratory heat exchange (RHE) was calculated for each level of ventilation and the results were expressed as the RHE causing a fall in FEV_1 of 10% (PD_{10} RHE). The PD_{10} RHE after placebo was highly reproducible. After terbutaline inhalation there was a highly significant shift in the RHE dose-response curves to the right and a trend towards a linear increase in PD_{10} RHE with increasing doses of terbutaline. The subjects who were most responsive to the RHE required more terbutaline to inhibit the response completely. The results indicate that RHE dose-response curves are a precise method to examine the effects of drugs on hyperventilation-induced asthma, that increasing doses of terbutaline can produce increasing protection, and that the degree of protection is dependent on the level of increased bronchial responsiveness to RHE.

Inhibition of exercise-induced asthma by premedication with an inhaled β -adrenoceptor agonist is an important strategy in the treatment of asthma. Inhaled β -agonists have been shown to be more effective than other medications in blocking the bronchoconstrictor response to exercise.¹ Previous studies, however, have generally examined the effect of a single dose of a β -agonist on the response to one exercise stimulus.^{2,3} Doctors usually advise their patients to use one dose (usually two puffs) before exercise without knowing whether a smaller dose would be sufficient or a larger dose more effective.

The elegant work of Deal and colleagues has shown that the inciting stimulus for exercise-induced bronchoconstriction is respiratory heat exchange.⁴ The bronchoconstrictor response to exercise is the same as the response to isocapnic hyperventilation causing the same amount of respiratory heat exchange.⁵ Respiratory heat exchange dose-response curves can be constructed by the use of isocapnic hyperventilation induced by subfreezing air,⁶ which should allow a more precise examination of the effects of drugs on exercise-induced asthma.

We have examined the effect of three doses of inhaled terbutaline sulphate (250, 500, and 1000 μg) on the dose-response curves for isocapnic hyperventilation induced by subfreezing air in 10 asthmatic patients.

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Methods

Ten adults with asthma and no other chest disease were selected from the staff and patients attending the Firestone Regional Chest and Allergy Unit at St Joseph's Hospital (table 1). All subjects had episodic dyspnoea and wheezing and a fall in forced expiratory volume in one second (FEV_1) of 20% or more after isocapnic hyperventilation induced by subfreezing air. Nine were atopic as indicated by wheal and flare responses to allergy prick tests with 16 common allergen extracts. At the time of the study symptoms of asthma did not disturb sleep and FEV_1 was greater than 75% of the predicted normal value. Respiratory infection or exposure to allergens to which

Table 1 Characteristics of the subjects

Subject No	Sex	Age (y)	Height (cm)	Atopic state*	Treatment
1	M	32	187.9	9	S not daily
2	F	39	163.8	0	S not daily
3	M	29	178.0	4	S 400
4	F	21	157.5	13	S 400 B 400
5	F	34	152.4	4	S not daily
6	F	38	166.4	2	S not daily
7	F	34	170.2	6	S not daily
8	M	30	177.8	3	S not daily
9	F	22	165.1	3	S not daily
10	M	24	180.3	1	S not daily

*Number of positive wheal and flare responses in prick skin tests with 16 common allergen extracts.

S—salbutamol; B—beclomethasone dipropionate (both μg daily).

the subjects were sensitised had not occurred for at least six weeks. An inhaled bronchodilator was used daily by two subjects and beclomethasone dipropionate by one of these. All other patients required inhaled bronchodilator less than once daily (table 1). The study was approved by the hospital research committee and all the subjects gave informed written consent.

Each subject attended the laboratory at the same time of day on five days within two weeks. On each day inhaled bronchodilator was withheld for at least eight hours. After arrival at the laboratory subjects rested for 30 minutes, then spirometry was performed with a Collins 9L water spirometer; three measurements of FEV₁ were made at intervals of one minute and vital capacity was measured once. Four puffs of the test medication were inhaled, three different metered-dose inhalers being used to give the appropriate dose of test medication on each study day. The inhalers were held 3 cm from the wide-open mouth, the subject exhaled to functional residual capacity, the inhaler was activated just after the onset of a five-second inspiration to total lung capacity, and then the breath was held for 10 seconds. Placebo was given on two days and terbutaline sulphate 250 µg, 500 µg, and 1000 µg on the other three days, double blind and in a balanced random order. After 30 minutes FEV₁ was measured again and isocapnic hyperventilation induced by subfreezing air was started.

Isocapnic hyperventilation was carried out by the method described by O'Byrne *et al.*⁶ Cold dry air (−18°C, 0% relative humidity) was generated by a heat exchanger and was inhaled in amounts that doubled with each increment (7.5, 15, 30, and 60 l/min and at maximum voluntary ventilation) for three minutes at intervals of five minutes. Carbon dioxide was added to the inhaled air to keep the subject eucapnic during each period of hyperventilation. The response was measured by change in FEV₁ from the lowest baseline value at 0.5 and 1.5 minutes after each inhalation. If there was a fall in FEV₁ the measurement was repeated at 3 minutes, and subsequently at 2-minute intervals if necessary, until the lowest value was recorded. Once the FEV₁ started to improve the subject received the next inhalation of cold air. Inhalations were discontinued once the FEV₁ had fallen by 20% or after the maximum voluntary ventilation. The respiratory heat exchange (RHE) in kilocalories/minute (kcal/min) was calculated for each level of ventilation by the formula $RHE = VE(HC[Ti - Te] + HV[WCi - WCe])$, where VE = minute ventilation (l/min), HC = heat capacity of air (0.000304 kcal/min), Ti = inspired air temperature (°C), Te = expired air temperature (°C), HV = latent heat of vapourisation of water (0.00058 kcal/mg), WCi = water content of inspired air (mg/l), and WCe = water content of expired air (mg/l). The inspired air was dry. Expired air was assumed to be fully saturated⁷ at the expired temperature and the water content was obtained from standard

saturation temperature relationships.⁸ The response was expressed of the provocation dose of RHE to cause a fall in FEV₁ of 10% (PD₁₀RHE) and was obtained from the log dose-response curve by linear interpolation of the last two points.⁶

ANALYSIS

A randomised block design was used in this experiment. Each subject in the study represented a homogeneous block within which each of the five treatments (two placebo, and three active doses) are contrasted. The appropriate analytical approach was a two-way analysis of variance.

In the analysis⁷ of the data three questions were considered: (1) What was the reproducibility of PD₁₀RHE? (2) Did terbutaline decrease responsiveness to hyperventilation and did the effects show a dose-response relationship? (3) Did those subjects most responsive to the stimulus require a higher dose of terbutaline to inhibit the response than the less responsive subjects?

Reproducibility was determined from within-subject and between-subject variance in the two PD₁₀RHE determinations after placebo inhalation and was quantified in terms of the intraclass correlation.⁹ The effect of the drug on PD₁₀RHE was examined initially to detect any difference between the five treatments, and then linear contrast¹⁰ was used to compare placebo with active preparations and a second contrast to assess whether the dose-response relationship was linear. Analysis of covariance¹¹ was used to adjust the observed treatment effect for differences in baseline FEV₁. The proportion of subjects protected by terbutaline in the groups showing high and low initial responsiveness was compared with Fisher's exact test.

Results

The mean baseline FEV₁ was greater than 90% of predicted normal and did not differ significantly on the five study days (table 2). The mean increases in FEV₁ after placebo on the two occasions were similar (table 2). The mean increases in FEV₁ after terbutaline and placebo inhalation were significantly different ($F_{1,36} = 14.97$, $p < 0.001$) (table 3). There was, however, no evidence of bronchodilator dose-response relationship with increasing doses of terbutaline ($F_{1,36} = 0.56$, $p > 0.1$) (table 3). These results were unchanged after covariance adjustment for the baseline FEV₁ level.

The response to isocapnic hyperventilation induced by subfreezing air on the two placebo days was the same. The within-subject standard deviation of PD₁₀RHE was 0.2 on the log_e scale and the between-subject standard deviation was 0.78. The intraclass correlation was 0.93, thus 93% of the total variation in PD₁₀RHE reflected real differences between subjects (signal) as opposed to inherent imprecision of the measurement (noise). Terbuta-

Table 2 Results of inhalation tests

Subject	Placebo 1			Placebo 2			Terbutaline 250 µg			Terbutaline 500 µg			Terbutaline 1000 µg		
	Baseline FEV ₁ * FEV ₁ † PD ₁₀ RHE‡	FEV ₁ †	FEV ₁ †	Baseline FEV ₁ †	FEV ₁ †	FEV ₁ †	Baseline FEV ₁ †	FEV ₁ †	FEV ₁ †	Baseline FEV ₁ †	FEV ₁ †	FEV ₁ †	Baseline FEV ₁ †	FEV ₁ †	FEV ₁ †
1	91	0	0.12	86	0	0.19	94	0	1.36	91	0	1.79	81	21	1.98
2	77	3.6	0.43	84	3.5	0.51	76	18	1.26	79	13	1.65	75	23	1.88
3	88	0	0.48	91	0	0.86	83	0	1.02	83	10.4	1.05	85	20	1.35
4	75	20	0.50	75	0	0.40	85	0	0.81	81	10	0.92	83	7	0.96
5	101	0	0.60	95	0	0.95	94	15	1.24	99	5.3	1.54	99	0	1.50
6	105	0	1.24	107	0	1.48	108	13.5	>2.0	109	16.3	>2.0	115	3	>2.1
7	98	7.4	1.33	94	4.3	1.38	95	18	2.21	94	13	>2.25	90	17	>2.5
8	86	3	1.42	89	3	1.45	89	2.5	>3.0	90	4	>3.2	84	8	>3.2
9	85	0	1.50	81	0	1.66	86	0	1.70	86	0	2.02	87	4	2.08
10	107	0	2.00	108	0	1.93	112	0	2.76	114	3	>3.0	111	3.4	>3.1
Mean	91.3	3.4	0.96	91.0	1.1	1.08	92.2	6.7	1.74	92.6	7.5	1.94	91.0	10.6	2.1
SD	11.2	6.3	0.61	10.6	1.7	0.59	11.1	8.3	0.74	11.7	5.8	0.74	13.17	8.7	0.72

*Baseline FEV₁ expressed as percentage of predicted normal.¹²

†Percentage increase in FEV₁ 30 minutes after premedication.

‡See under "Methods".

Table 3 Analysis of variance for bronchodilator effect

Source	df	SS	MS	F	p
Between subjects	9	663.52	73.72		
Between treatments	4	556.32	139.08	3.92	0.010
Placebo v active	1	509.60	509.60	14.37	<0.001
Placebo 1 v placebo 2	1	26.45	26.45	0.75	NS
Linear dose-response relationship	1	20.00	20.00	0.56	NS
Quadratic dose-response relationship	1	0.27	0.27	0.01	NS
Residual	36	1276.88	35.47		
Total	49	2496.72			

Table 4 Analysis of variance for log PD₁₀RHE

Source	df	SS	MS	F	p
Between subjects	9	6.108	0.679		
Between treatments	4	6.961	1.740	10.63	<0.001
Placebo v active	1	6.775	6.775	41.39	<0.001
Placebo 1 v placebo 2	1	0.097	0.097	0.60	NS
Linear dose-response relationship	1	0.373	0.373	2.28	0.053
Quadratic dose-response relationship	1	0.025	0.025	0.15	NS
Residual	26	4.256	0.164		
Total	39	17.325

Log dose-response curves constructed after inhalation of cold air in subject 2, showing a progressive shift to the right with increasing doses of inhaled terbutaline.

Conversion: traditional to SI units—1 kcal ≈ 4.18 kJ.

line caused an appreciable shift to the right of the dose-response curves ($F_{1,29} = 41.39$, $p < 0.001$) (fig, table 4). In two subjects the response was abolished after 250 µg terbutaline and in two others it was abolished after 500 µg. The remaining six subjects had at least a 10% fall in FEV₁ after terbutaline inhalation (1000 µg) and hyperventilation induced by cold air. In these subjects 1000 µg of terbutaline provided more protection than 500 µg, which in turn provided more protection than 250 µg (table 2). As a PD₁₀ RHE value could not be obtained from four subjects at one or more drug dose levels, the values at these levels were treated as unknown for the purpose of analysis and a multivariate linear regression approach to an unbalanced two-way analysis of variance was used. There was a trend towards linear dose-response relationship with increasing doses of terbutaline but this did not reach significance ($F_{1,29} = 2.28$, $p = 0.053$) (table 4).

The relationship between the bronchial responsiveness to RHE after placebo and the effect of terbutaline was examined. Complete inhibition of the response to RHE could not be achieved in any of the five most responsive subjects (initial PD₁₀ RHE less than 1 kcal/min (4.18 kJ)) at any dose of terbutaline, while the response in four of the five less responsive subjects (initial PD₁₀ RHE greater than 1 kcal/min) was completely inhibited. This difference was significant ($p = 0.024$).

Side effects such as tremulousness and palpitations were not reported by any subject at any dose level of terbutaline.

Discussion

The results indicate that the dose of a β -adrenoceptor agonist required to inhibit the response to isocapnic hyperventilation induced by cold air, and presumably exercise, varies between asthmatic patients. In this study the response in two subjects was completely inhibited by one puff (250 μg) of terbutaline and in two others by two puffs (500 μg); in the remainder it was incompletely inhibited by four puffs (1000 μg). Thus in clinical practice consideration should be given to adjusting the dose according to its effect and the severity of exercise.

Previous studies of exercise-induced asthma have usually examined the effect of a single dose of medication on a single period of exercise. In this type of study the result cannot be interpreted as accurately as when both drug and stimulus are delivered in precisely increasing amounts; this may account for some of the differences observed between the effect of the same drug in different subjects or of different drugs in the same subject.^{3,13-19} In the present study both terbutaline and hyperventilation were progressively increased. In addition, the response to hyperventilation was highly reproducible, with an intraclass correlation of 0.93, indicating that only 7% of the differences in an individual subject on different days was due to inherent imprecision in the measurement. This precision is not found with exercise challenge, where the minute ventilation or conditioning of the inspired air has usually not been controlled; indeed, most studies of the effect of drugs on exercise induced asthma have not reported on the precision of the method.^{3,14,15,17,19}

The response to cold air was expressed as the dose inducing a 10% reduction in FEV_1 (PD_{10}) for two reasons. Firstly, in most previous studies of exercise-induced bronchoconstriction induced by exercise and by cold air a 10% fall in FEV_1 or peak flow rates has been taken as indicating a response to the stimulus.^{1,5,20,21} Secondly, in this study the fall in FEV_1 after inhalation of cold air did not reach 20% but it did reach 10% after administration of terbutaline in some subjects. In this study, as in a previous one,⁶ in those subjects in whom PD_{10} and PD_{20} values could be directly obtained the PD_{10} was about half the PD_{20} , indicating that the log dose-response curves over this range of response are parallel.

The inhibition produced by terbutaline on the response to hyperventilation was associated with slight but significant bronchodilatation (table 3). This suggests that part of the protective effect of terbutaline was non-specific and related to change in airway calibre. There was no evidence of a linear bronchodilator dose-response relationship with increasing doses of terbutaline; there was, however, a trend to a linear increase in protection,

reflected in a progressive shift of hyperventilation dose-response curves to the right. This suggests that some of the protection was specific to the pharmacological effects of the drug.

Terbutaline was effective in shifting the dose-response curves after inhalation of cold air in all subjects studied. The mean PD_{10} RHE in the group on the two placebo days was 0.96 and 1.08 kcal/min; this equals a minute ventilation of about 30 l/min, a challenge equivalent to walking briskly on a cold day. After inhalation of terbutaline 1000 μg the mean PD_{10} RHE was 2.1 kcal/min, which equals a minute ventilation of about 60 l/min, equivalent to running rapidly on a cold day. The mean PD_{10} RHE after inhalation of terbutaline 250 and 500 μg was 1.74 and 1.94 kcal/min, which would allow exercise with a minute ventilation of 40–50 l/min before appreciable bronchoconstriction occurred.

The completeness of inhibition produced by terbutaline was related to the degree of responsiveness to hyperventilation and respiratory heat exchange. The less the responsiveness the more complete the inhibition. The subjects were selected to give a range of increased responsiveness to hyperventilation. The most responsive developed bronchoconstriction after 7.5 l/min ventilation of cold air (0.25 kcal/min RHE) and the least responsive developed bronchoconstriction after 60 l/min ventilation (2.0 kcal/min RHE). The subjects also had relatively mild asthma in the sense that symptoms in all but one were controlled by salbutamol alone and FEV_1 was greater than 75% of predicted. Evidently therefore terbutaline (1000 μg) will not completely inhibit the response to hyperventilation in more severely affected patients with a greater increase in non-specific bronchial responsiveness. Further work needs to be directed to more effectively inhibiting the response in such patients.

The trend to a linear increase in protection with increasing doses of terbutaline suggests that even higher doses might produce greater inhibition. In clinical practice higher doses might be contraindicated because of side effects. A more practical method might be to combine two drugs such as a β -adrenoreceptor agonist and sodium cromoglycate; this, however, requires further study. While such studies are required in research, they may also be useful in certain patients in clinical practice—for example, in competitive athletes to determine the most effect drug combinations for inhibiting exercise-induced asthma.

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