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β-adrenoceptor responses to high doses of inhaled salbutamol in patients with bronchial asthma

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1 Fourteen asthmatics (mean ± s.e. mean baseline FEV_1 62 ± 6% of predicted) were given cumulative doubling doses of salbutamol by metered-dose inhaler as follows: 100 μg, 200 μg, 500 μg, 1000 μg, 2000 μg, 4000 μg.

2 Airways, tremor, haemodynamic and cyclic AMP responses were measured at each dose increment (made every 20 min).

3 There was a linear log dose-response relationship for each airways parameter (FEV_1, VC, sGaw, FEF 50%). The plateau in the dose-response curve was not reached within our dose range. These changes were also mirrored in cyclic AMP responses.

4 There was a wide range in maximum airways response expressed in terms of absolute increase over baseline (95% confidence intervals: ΔFEV_1 667–1483 ml; Δ VC 689–1695 ml; Δ sGaw 0.92–4.50 s^{-1} kPa^{-1}; Δ FEF 50% 0.94–2.15 l s^{-1}). Patients with a lower baseline showed a greater response in terms of percent increase in FEV_1 ($r = -0.83$, $P < 0.001$). There was however, no correlation between baseline airway calibre and the dose required for maximum bronchodilatation.

5 There were objective increases (mean ± s.e. mean) in both heart rate (maximum Δ HR of 14 ± 5 beats min^{-1} at 4000 μg) and tremor power (maximum Δ Tr of 115 ± 44% at 2000 μg). These were not dose limiting side-effects as subjective symptoms were infrequent at higher doses.

6 Higher than conventional doses of salbutamol given by metered-dose inhaler may produce a distinct improvement in airways response without significant side-effects. There is a wide individual variation in airways response to inhaled salbutamol, although most patients required higher doses to achieve maximal bronchodilatation. The severity of asthma does not however predict the dose required for maximum airways response.

Keywords β-adrenoceptor salbutamol asthma tremor

Introduction

Few studies have investigated the airways response to high doses of salbutamol given by metered-dose inhaler to patients with asthma. Larsson & Svedmyr (1977) showed a dose range for maximal bronchodilatation of 0.9–9.3 mg of inhaled salbutamol, whilst Prior & Cochrane (1982) using terbutaline found that 2–5 mg was needed for optimum airways response. The wide variation in dose range appeared to be independent of the severity of asthmatics in each study.

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In addition, similar dose-related increases in heart rate (Spector & Gomez, 1977; Finch, 1981) and tremor (Larsson & Svedmyr 1977) occur with higher than conventional doses of inhaled salbutamol. However, the relationship between different β-adrenoceptor responses remains unknown.

The aim of the present study was to investigate airways responses to higher than conventional doses of salbutamol given by metered-dose inhaler, to quantify objective side-effects (both haemodynamic and tremor) and to correlate these β-adrenoceptor responses with one another.

Methods

Patients

We studied 14 stable asthmatic patients: six females, mean age of 38 ± 5 years (range 18 to 67 years). Approval of the local hospital ethics committee was obtained and all patients gave their written informed consent for this study. Mean ± s.e. mean baseline FEV_1 was 2012 ± 281 ml, 62 ± 6% of predicted value (Cotes) with a range of 581–3900 ml, 29–92% of predicted value. Patients taking oral therapy with corticosteroids, theophyllines or β-adrenoceptor agonists were excluded as these drugs may affect β-adrenoceptor responsiveness. Thirteen patients were maintained on inhaled corticosteroids (nine with low-dose beclomethasone dipropionate 400 μg daily and four with high dose beclomethasone 2000 μg daily). Three patients were also taking inhaled sodium cromoglycate. Eleven patients were taking regular inhaled salbutamol (daily dose greater than 600 μg) and three occasional salbutamol for exercise or allergen induced bronchospasm.

Study protocol

Patients attended the laboratory between 09.00 and 10.00 h, having withheld all bronchodilators for 8 h previously. After the patient had rested supine for 10 min, a run-in period of at least 30 min was used to establish a baseline. The heart rate, blood pressure and tremor were measured at 1 min intervals until they had settled to their lowest level. The mean of four consistent readings were then used as a baseline. Following this, the best of five consistent readings of FEV_1, FEF 50% and VC, and the mean of the best five sGaw measurements were taken as a baseline. Cumulative doubling doses of salbutamol from a metered-dose inhaler were then given as follows: 100 μg, 200 μg, 500 μg, 1000 μg, 2000 μg, 4000 μg. Patients had previously been checked for correct use of a metered-dose inhaler using the method described by Newman *et al.* (1980). To arrive at the desired cumulative dose of salbutamol, specially prepared inhaler canisters were used containing 100 μg or 500 μg of salbutamol per actuation (prepared by Glaxo Group Research Ltd, Greenford, Middlesex). Dose increments were made every 20 min. Tremor power (Tr), heart rate (HR) and blood pressure (BP) were measured 8 min after each dose increment with the patient lying supine. At each dose increment, the mean of four readings were used (each made at 1 min intervals). Tremor was measured by placing an accelerometer transducer (Etran Limited, Ealing, London) on the distal phalanx of the middle finger. The results were stored on computer disc and tremor power (> 2 Hz) was calculated by spectral analysis using autocovariance (Dr R. Marshall, Department of Pharmacology and Therapeutics, University of Wales College of Medicine, Cardiff). HR, SBP and DBP were all recorded with a semi-automatic sphygmomanometer (Dinamap vital signs monitor, Critikon, USA). Airway parameters were documented 12 min after each dose increment. Specific airways conductance (sGaw) was measured using the method described by DuBois *et al.* (1956a, b) using a constant volume body plethysmograph (sGaw is the reciprocal of airways resistance corrected for lung volume). A Bodystar FG90 plethysmograph (Fenyves and Gut, Basle, Switzerland) was used with on-line computer assisted determination of sGaw. The mean of five readings of sGaw were taken at each dose increment. The best of three readings of FEV_1 (forced expiratory volume in 1 s), VC (slow vital capacity) and FEF 50% (maximum forced expiratory flow rate at 50% of VC) were performed using the pneumotachograph head of the body box with on-line computer assisted analysis. Patients were also asked to grade any side effects (tremor, palpitations and headache) as mild, moderate or severe in nature.

In addition 10 ml of heparinised blood was taken from an indwelling i.v. cannula in the antecubital fossa, 12 min after each dose increment. The blood was immediately centrifuged at 3 500 rev min^{-1} for 15 min and stored at −20° C. Cyclic AMP (cAMP) was measured in 11 patients using a 'CIS' radioimmunoassay kit. Following ethanol extraction, samples were incubated and measured with a gamma counter. All samples were analysed in duplicate. The analytical C. V. value for the assay was 2.9%. Values are given as nmol l^{-1}.

Statistical analysis

The change in each variable from baseline was calculated at each dose increment. Linear regression analysis (using the method of least squares) was used to assess whether there was a linear log dose-response relationship. Analysis of variance (ANOVA) was applied to the regression analysis. A significant ANOVA ($P < 0.05$) shows that there is significant effect between doses of salbutamol. Paired Student's *t*-tests were then used to compare responses between successive doses. A probability value of less than 5% ($P < 0.05$) was taken as being significant for all statistical tests. All statistics were performed on a 'Statgraphics' software programme. Results are shown in the text as mean ± standard error of mean (s.e. mean).

Results

Airways responses

Log-dose response curves (DRC) showed linear responses for all four airways parameters (Figure 1 a–d) up to the 4000 μg dose. Paired *t*-tests between successive doses showed that maximum responses for all four airways parameters occurred at the highest dose of 4000 μg (FEV_1 $P < 0.05$, VC $P < 0.01$, sGaw $P < 0.01$, FEF 50% $P < 0.05$). The plateau in the DRC was not reached within our dose range. Mean values for baseline and maximum changes (from baseline) are as follows, FEV_1 (ml): 2012 ± 281, 1075 ± 189; VC (ml): 3414 ± 340, 1192 ± 233; sGaw (s^{-1} kPa^{-1}): 0.55 ± 0.13, 2.71 ± 0.83; FEF 50% ($l\,s^{-1}$): 1.81 ± 0.36, 1.54 ± 0.28. There was a strong negative correlation ($r = -0.83$, $P < 0.001$) between the maximum percent Δ FEV_1 and baseline percent predicted value of FEV_1 (Figure 2). There was however no correlation between the dose required for maximum Δ FEV_1 and baseline predicted FEV_1 (Figure 3). There was a wide individual dose range for maximum airways response, although most patients required the highest dose in order to achieve maximum bronchodilatation (Figure 4). This was independent of whether FEV_1 or sGaw was used as the parameter of airflow.

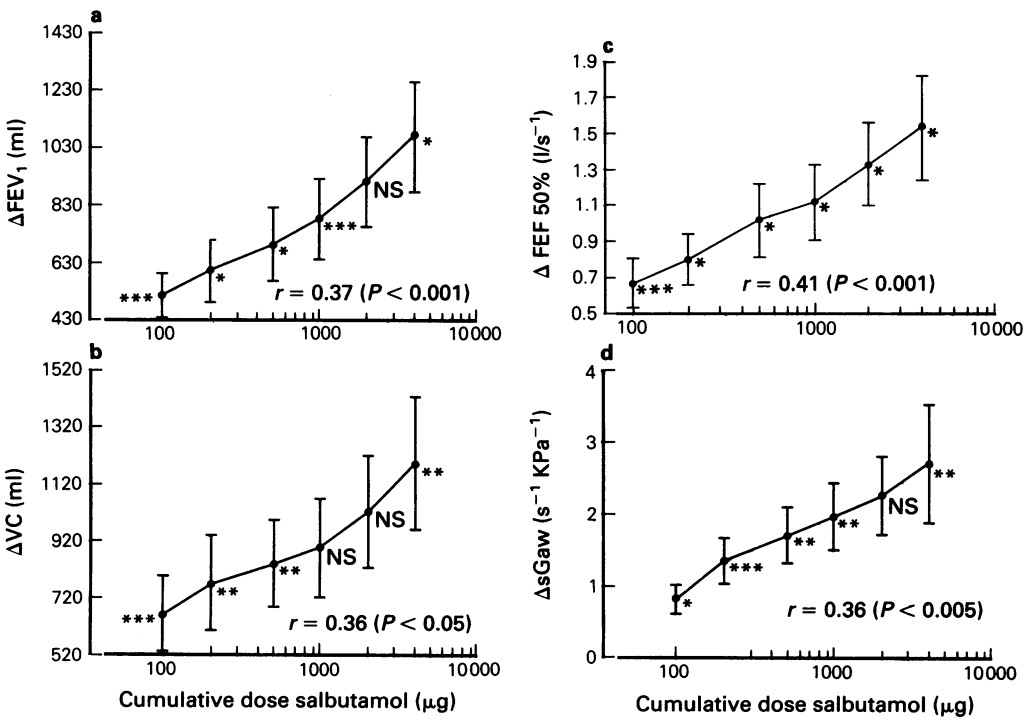

Figure 1 Cumulative log dose-response curves for a) FEV_1, b) VC, c) FEF 50% and d) sGaw in 14 asthmatic patients given 100–4000 μg of inhaled salbutamol. Values are shown as mean ± s.e. mean. Asterisks denote the significance level for comparison between successive doses by paired *t*-tests (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$). Correlation coefficient (r) and P value (by ANOVA) for regression analysis are also shown.

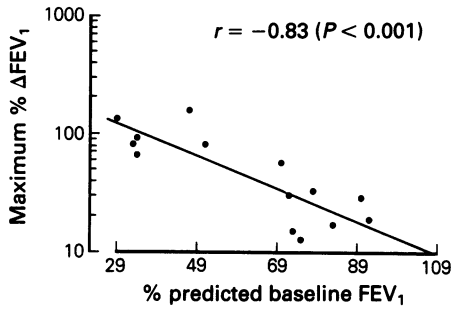

Figure 2 Regression line between maximum percent change in FEV_1 and percent predicted baseline FEV_1. Each point represents an individual patient. Correlation coefficient (r) and P value (by ANOVA) for the regression line are also shown.

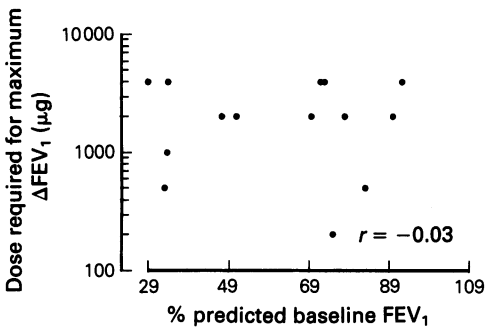

Figure 3 Dose of salbutamol required for maximum Δ FEV_1 plotted against % predicted baseline FEV_1 for each patient.

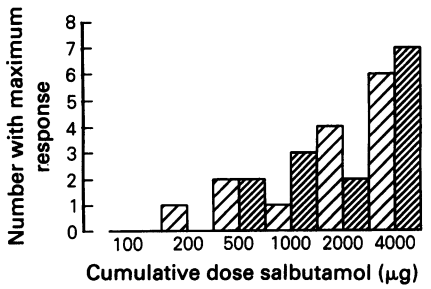

Figure 4 Number of patients who achieved maximum airway response at each dose of salbutamol. ▨ FEV_1, ▨ sGaw.

Haemodynamic responses

Mean baseline HR was 62 ± 3 beats min^{-1}, SBP 126 ± 6 mm Hg and DBP 69 ± 3 mm Hg. There was no effect on HR until the 500 μg dose (Figure 5a), thereafter there was a linear response with an increase of 14 ± 5 beats min^{-1} at 4000 μg

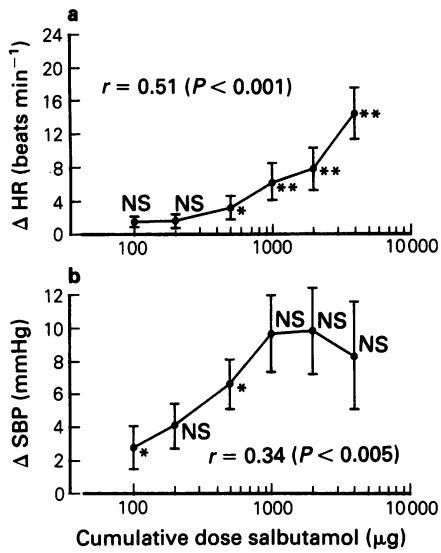

Figure 5 Cumulative log dose-response curves (mean ± s.e. mean) for a) heart rate and b) systolic blood pressure. Asterisks denote the significance level for comparison between successive doses by paired t-tests (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$). Correlation coefficient (r) and P value (by ANOVA) for regression analysis are also shown.

($P < 0.01$). The plateau in the DRC was not reached within our dose range. Despite dose-related increases in HR, no patients complained of subjective palpitations at higher doses and no extrasystoles were observed on the electrocardiograph. There was a linear response in SBP up to the 1000 μg dose (Figure 5b). However there was no significant increase over and above the 500 μg response which was 7 ± 2 mm Hg over baseline ($P < 0.05$). There were no significant changes in diastolic blood pressure.

Tremor response

There was no significant effect on tremor power until the 1000 μg dose (Figure 6). Thereafter there was a linear response, although there was no significant increase over and above the 2000 μg response, which was 115 ± 44% over baseline ($P < 0.05$). Despite objective increases in tremor, only one patient complained of mild subjective tremor at the highest dose. There were no significant changes in tremor frequency with salbutamol.

Cyclic AMP

Mean baseline cAMP was 16.3 ± 3.12 nmol l^{-1}, with a maximum change of 16.60 ± 2.54 nmol l^{-1}

at 4000 μg ($P < 0.01$). There was a significant increase in cAMP after the first dose (Figure 7) with a linear response up to the highest dose. The plateau in the DRC was not attained.

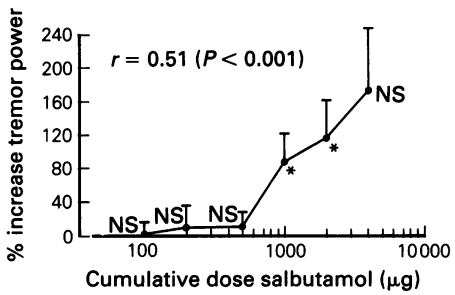

Figure 6 Cumulative log dose-response curve (mean ± s.e. mean) for % increase in tremor power. Asterisks denote the significance level for comparison between successive doses by paired *t*-tests (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$). Correlation coefficient (r) and P value (by ANOVA) for regression analysis are also shown.

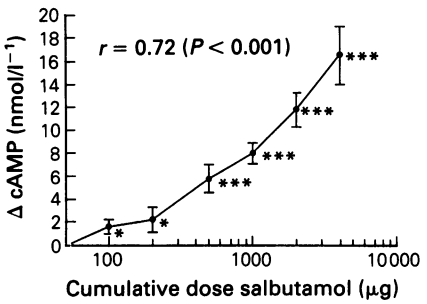

Figure 7 Cumulative log dose-response curve for cAMP in 11 patients. Asterisks denote the significance level for comparison with baseline by paired *t*-tests (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$).

Correlations

Table 1 summarises correlations between variables which were significant. There was in general poor correlation between airways and other responses mediated through β-adrenoceptors.

Table 1 Correlations between airways, tremor and haemodynamic β-adrenoceptor responses. Numbers denote the correlation coefficient (r), asterisks denote the P value for analysis of variance of the regression line (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$). Only significant correlations are shown

	sGaw	*FEF50%*	*VC*	*HR*	*Tr*	*SBP*
sGaw		0.72 ***		0.33 **	0.40 ***	0.28 *
FEV_1	0.33 **	0.66 ***	0.70 ***			
HR					0.59 ***	0.38 ***

Discussion

The results of the present study show that higher than conventional doses of salbutamol given by metered-dose inhaler may produce a marked improvement in asthmatic airways response. In our patients, mean maximum bronchodilatation was achieved with the highest dose of salbutamol (4000 μg), irrespective of the parameter of airflow. We did not attain the plateau in the dose-response curve within our dose range. There was a strong negative correlation ($r = -0.83$, $P < 0.001$) between percent change in FEV_1 and percent predicted baseline for each patient (Figure 2). This would seem to suggest that the patients with more severe asthma had a greater airways response to inhaled salbutamol. However, there was a wide range in maximum airways response when expressed in absolute terms. Furthermore individual patients showed considerable variation in the dose required for maximum bronchodilatation, although most patients needed the highest dose (Figure 4). The severity of asthma did not predict the dose required for maximum airways response (Figure 3). Our results are in agreement with previous dose-response studies which have shown a wide dose-range for maximum bronchodilatation (Larsson & Svedmyr, 1977; Prior *et al.*, 1982). However our results differ in that we did not achieve the plateau in the dose-response curve. Although we did not perform a placebo day, we felt that careful measurement of baseline airway parameters was sufficient for comparison with subsequent responses. Previous time course studies with placebo have found no significant increase in airway parameters with repeated measurements over a 6-hour period from early morning (Tomashefski, 1981; Walters *et al.*, 1981). Furthermore, diurnal variability over the study period (3 h) is unlikely to account for the magnitude of the airways response in our patients.

There is some evidence to suggest that the substantial improvement in airways response seen in our study may not be maintained following a period of chronic dosing with β-adrenoceptor agonists. Three studies have demonstrated small degrees of bronchodilator tolerance within 1–2

weeks of therapy with oral β_2 selective agonists (Nelson *et al.* 1977; Jenne *et al.* 1977; Plummer, 1978). However, although Harvey & Tattersfield (1982) showed subsensitivity in airways response after chronic dosing with inhaled salbutamol in normal subjects, this was not seen in asthmatics. Other studies have also failed to show tolerance to bronchial β-adrenoceptor responses during long term treatment (Larsson *et al.*, 1977; Repsher *et al.*, 1981; Tomashefski, 1981).

Our patients also showed dose-related objective increases in heart rate and tremor, although only one patient experienced symptoms of mild tremor and none had palpitations. We have previously shown in normal subjects given an identical dose protocol that there are no changes in heart rate, blood pressure or tremor responses with placebo (Lipworth *et al.*, 1988). Tremor is mediated by skeletal muscle β_2-adrenoceptors and may be objectively measured with an accelerometer transducer (Marsden *et al.*, 1967; Thiringer & Svedmyr, 1975; Arnold & McDevitt, 1983b). The heart rate response to salbutamol results from reflex tachycardia following β_2-adrenoceptor induced peripheral vasodilation and possibly also a direct β_2-adrenoceptor chronotropic effect (Arnold & McDevitt, 1983a; Arnold & McDevitt, 1986). The blunted subjective response seen in our patients could have resulted from β-adrenoceptor tolerance from long term therapy with β_2-adrenoceptor agonists (Trautlein *et al.*, 1976; Larsson *et al.*, 1977; Bengtsson *et al.*, 1982). Similar changes also occur in leukocyte β-adrenoceptors and cAMP responses (Conolly & Greenacre, 1976; Morris *et al.*, 1978).

In the present study no effect on heart rate or tremor was seen until 500 μg and 1000 μg of salbutamol respectively. The time-lag between the early onset (within 15 min) of bronchodilatation and the delayed tremor and heart rate responses may reflect systemic absorption of the drug. Over 80% of an inhaled dose from a metered-dose inhaler may be deposited in the oropharnyx and subsequently swallowed (Davies, 1975; Newman *et al.*, 1981). Kung and coworkers (1987) however, showed that mouthwashing has no effect on the metabolic response to inhaled salbutamol although only 24% of the total dose was recovered in the wash. Pharmacokinetic studies with metered-dose inhalers show that peak plasma levels occur within 1 and 3 h following administration of terbutaline and salbutamol respectively (Walker *et al.*, 1972; Nilson *et al.*, 1976). The plasma cAMP responses in our study (Figure 7) showed a significant increase after the first dose of salbutamol (100 μg). This mirrored the early onset of airways response and suggests activation of adenyl cyclase following rapid absorption from bronchial or pulmonary vascular beds. The poor correlation between airways and other responses could be explained by the wide variation in β-adrenoceptor responsiveness and inhaled pharmacokinetics between individuals. It may also reflect the time-lag between the rapid onset of airways response and delayed systemic absorption of salbutamol.

In conclusion our data suggests that higher than conventional doses of salbutamol given by metered-dose inhaler may produce substantial improvements in asthmatic airways response. Dose related increases in objective tremor and heart rate responses were not dose limiting as subjective symptoms were infrequent. There was a wide individual variation in airways responsiveness, although most patients required higher doses for maximum bronchodilatation. The severity of asthma did not however predict the dose required to achieve maximum airways response.

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