

Comparison of the relative airways and systemic potencies of inhaled fenoterol and salbutamol in asthmatic patients

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Abstract

Background – There is controversy as to the relative safety of fenoterol and salbutamol. No differences have been found in the relative cardiac β_1/β_2 receptor activity of inhaled fenoterol and salbutamol in normal subjects. These initial findings have been extended by comparing the respective potencies of equivalent doses by weight of fenoterol and salbutamol in asthmatic subjects, in terms of airways and systemic responses.

Methods – Eighteen asthmatic patients of mean (SD) age 40 (14) years and a forced expiratory volume in one second (FEV₁)% predicted of 56 (14)% (1.97 (0.66) l) were randomised to inhale fenoterol (100 µg/puff or 200 µg/puff), salbutamol, or placebo (100 µg/puff or 200 µg/puff) on three separate days. Dose-response curves were constructed using cumulative doses of 100 µg, 200 µg, 400 µg, 1000 µg, 2000 µg, and 4000 µg, and airways and systemic responses were measured 20 minutes after each dose with 40 minute increments. Dose ratios for the relative potency of fenoterol *versus* salbutamol were calculated from the dose-response curves using regression analysis of parallel slopes.

Results – There was no difference in bronchodilator potency between fenoterol and salbutamol (as median dose ratio): FEV₁ 1.1 (95% CI 0.4 to 4.6). In contrast, dose ratios for systemic responses showed that fenoterol was more potent than salbutamol: serum potassium 3.7 (95% CI 2.0 to 6.0), tremor 5.7 (95% CI 1.4 to 10.2), heart rate 1.6 (95% CI 1.0 to 2.3). At a conventional dose of 200 µg the only difference in response between the two drugs was observed for tremor (as mean difference): 0.23 log units (95% CI 0.06 to 0.41 log units).

Conclusions – There was no difference in the bronchodilator potency between fenoterol and salbutamol on a microgram equivalent basis. In contrast, systemic potency was greater with fenoterol, although this difference was not clinically relevant at conventional dosages up to 200 µg.

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Keywords: potency, fenoterol, salbutamol, asthma, β_2 adrenoceptor.

We have previously compared the relative cardiac β_1 and β_2 receptor activity of inhaled fen-

oterol and salbutamol in normal subjects and demonstrated no significant differences in the respective β_1/β_2 receptor selectivity between the two drugs.¹ However, previous studies in asthmatic and normal subjects comparing equivalent doses (by weight) of inhaled fenoterol and salbutamol have shown fenoterol to produce a greater hypokalaemic response²⁻⁴ as well as greater chronotropic and electrocardiographic effects.^{3,4} The explanation for these differences is unclear, although it has been postulated that the greater lipophilicity of fenoterol might result in enhanced absorption across the lung vascular bed.⁵ An alternative explanation might be that fenoterol is a more potent stimulant of β_2 adrenoceptors and will hence produce greater β_2 mediated responses.⁶ However, previous studies in asthmatic patients have not addressed whether fenoterol and salbutamol produce different systemic effects when doses which produce equivalent bronchodilator responses are compared.^{2,7}

The aim of the present study was to evaluate the relative airways and systemic potencies of inhaled fenoterol and salbutamol at microgram equivalent doses in patients with stable asthma.

Methods

PATIENTS

Eighteen asthmatic patients gave written informed consent and were randomised, using a latin square design, into the double blind, placebo controlled crossover study which was approved by Tayside ethics committee. They were required to have a normal physical examination, electrocardiogram, biochemical, and haematological parameters prior to inclusion. All patients were required to have stable asthma with at least 15% reversibility in FEV₁ response to inhaled salbutamol 200 µg given by metered dose inhaler. The demographic characteristics of all 18 patients are given in table 1.

Fifteen patients were taking inhaled corticosteroids and all were taking inhaled β_2 agonists. Three were taking regular inhaled β_2 agonists, with the remainder using on demand β_2 agonists with a total daily dose of less than 400 µg salbutamol or 1000 µg terbutaline. None had received oral prednisolone for at least three months and none had had a recent exacerbation of their asthma. Patients were all current non-smokers and were shown how to use a Vitalograph inhalation aid and monitor (Vitalograph Ltd, Buckingham, UK) to ensure that they had

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Table 1 Demographic data

Patient no.	Sex	Age (years)	FEV ₁ (l)	FEV ₁ (% pred)	Reversibility (%)	Medication
1	M	39	1.49	39	41	Spm
2	F	30	2.01	65	19	Spm, B(800), TH(300)
3	M	57	1.39	48	17	Spm, B(800)
4	M	53	2.43	70	15	Tprn, B(600), TH(800)
5	M	23	2.16	50	30	Dprn, B(1200), TH(225)
6	F	56	1.43	66	14	Spm, B(1500)
7	F	53	1.44	59	28	Spm, B(400)
8	F	39	2.13	69	15	Spm, B(400)
9	M	26	2.82	61	56	Spm
10	M	36	2.16	51	18	S(800), B(1000), TH(500)
11	F	51	1.37	63	26	S(600), B(1000)
12	F	21	2.12	61	19	S(800), B(1000), N(8), TH(900)
13	M	52	1.15	31	63	Spm, B(1000), OX(600)
14	M	40	2.65	68	32	Spm, B(200)
15	M	37	1.36	31	61	Spm, B(1000)
16	M	22	3.13	70	16	Spm, B(2000)
17	M	21	3.14	70	27	Spm
18	M	60	1.15	33	37	Spm, B(800), OX(600)
Mean (SD)		40 (14)	1.97 (0.66)	56 (14)	30 (16)	

S=inhaled salbutamol ($\mu\text{g/day}$ or prn), T=inhaled terbutaline (prn), OX=inhaled oxitropium bromide ($\mu\text{g/day}$), D=inhaled Duovent (ipratropium bromide plus fenoterol) (prn), B=inhaled beclomethasone dipropionate or budesonide ($\mu\text{g/day}$), N=inhaled nedocromil sodium (mg/day), TH=oral theophylline (mg/day).

a satisfactory inhaler technique using a metered dose device (MDI) before entry into the study.

PROTOCOL

Patients attended the laboratory at 08.00 hours on three separate days, at least 72 hours apart, having withheld bronchodilator therapy for at least eight hours and theophylline for 48 hours. A cannula was inserted into an antecubital vein and kept patent with bolus injections of heparinised saline. Cannula dead space of 2 ml was withdrawn before blood samples were collected. After a 30 minute supine rest period a dose-response curve was constructed with inhaled fenoterol (100 $\mu\text{g/puff}$ or 200 $\mu\text{g/puff}$), salbutamol (100 $\mu\text{g/puff}$ or 200 $\mu\text{g/puff}$), or placebo by MDI using cumulative doses of 100 μg , 200 μg (100 μg + 100 μg), 400 μg (200 μg + 200 μg), 1000 μg (400 μg + 600 μg), 2000 μg (1000 μg + 1000 μg), and 4000 μg (2000 μg + 2000 μg), with doses separated by 40 minutes. Measurements of FEV₁, forced vital capacity (FVC), peak expiratory flow rate (PEFR), serum potassium, heart rate (HR), systolic and diastolic blood pressure (SBP, DBP), stroke distance (SD, a measure of inotropy), finger tremor (Tr) and ECG parameters (T wave, Q-Tc) were undertaken over a 20 minute period at baseline (after the rest period), 20 minutes after each dose, and one and two hours after the final dose. In addition, blood samples were taken at baseline, at 5, 15, and 30 minutes after the 1000 μg dose, and at 5, 15, 30, 60, and 120 minutes after the 4000 μg dose for measurement of plasma fenoterol and salbutamol concentrations. All blood samples were immediately centrifuged, separated, and stored at -25°C . All subjects received 36 mmol effervescent potassium (Sando K, Sandoz Pharmaceuticals, Camberley, UK) at the end of each study day in order to obviate any possible hypokalaemia, since all study medications were blinded.

MEASUREMENTS

Airway responses

Measurements of FEV₁, FVC, and PEFR were performed according to American Thoracic

Society criteria,⁸ using a compact spirometer (Vitalograph Ltd, Buckingham, UK) with a pneumotachograph head and pressure transducer, and on-line computer assisted determination of FEV₁, FVC, and PEFR. Forced expiratory manoeuvres were performed from total lung capacity to residual volume. The best FEV₁ and FVC values were taken from the highest values of three consistent forced expiratory curves.⁸ A coefficient of variation of less than 3% for three reproducible measurements of FEV₁ and 5% for FVC was considered as being acceptable.

Systemic responses

All biochemical analyses were performed in batches at the end of the study and were assayed in duplicate. Serum levels of potassium were measured by flame photometry (IL943 analyser, Instrumentation Laboratory Ltd, Warrington, UK). The coefficients of variability for analytical imprecision within and between assays were 0.38% and 0.44%, respectively. The normal reference range for our laboratory is 3.5–5.5 mmol/l.

Salbutamol levels were measured by capillary gas chromatography using a 5160 Mega gas chromatograph (Carlo Erba, Milan, Italy) with a coupled mass spectrometer (Finnigan 4021, San Jose, California, USA). The coefficients of variation within and between assays were 5% and 20–30%, respectively. The limit of detection was 25 pg/ml. Fenoterol levels were measured by radioimmunoassay as described by Rominger *et al.*⁹ The coefficient of variation within assays was 7.9% at 50 pg/ml and 5.6% at 500 pg/ml with a variation between assays of 5.5%. The limit of detection was 20 pg/ml.

The electrocardiogram was recorded on standard lead II using a monitor (Hewlett Packard, Palo Alto, California, USA) and printer with paper speed set at 50 mm/s and 0.5 mV/cm gain. The following parameters were measured from the mean of five consecutive complexes: R-R interval (s), Q-T interval (ms), T wave amplitude (mV), U wave frequency, and ST segment depression (mV). The Q-T interval was measured using the method described by Shamroth¹⁰ to account for the presence of U waves. The formula of Bazett¹¹ was used to

Table 2 Mean (SD) baseline values for airways and systemic responses

	Placebo	Fenoterol	Salbutamol
FEV ₁ (l)	1.87 (0.63)	1.86 (0.63)	1.83 (0.59)
FVC (l)	2.87 (0.88)	2.87 (0.88)	2.84 (0.80)
PEFR (l/min)	315 (108)	315 (119)	306 (95)
Potassium (mmol/l)	4.02 (0.31)	3.96 (0.20)	3.97 (0.19)
HR (beats/min)	71 (10)	69 (8)	68 (9)
Tr (log units)	2.12 (0.42)	2.13 (0.42)	2.15 (0.29)
SBP (mm Hg)	121 (12)	122 (11)	125 (11)
DBP (mm Hg)	68 (9)	69 (8)	69 (8)
SD (cm)	15.6 (4.6)	14.9 (4.8)	14.2 (3.0)
Q-Tc (ms)	390 (25)	380 (21)	380 (21)
T wave (mV)	0.26 (0.10)	0.30 (0.11)	0.30 (0.13)

FEV₁=forced expiratory volume in one second, FVC=forced vital capacity, PEFR=peak expiratory flow rate, HR=heart rate, Tr=finger tremor, SBP/DBP=systolic and diastolic blood pressure, SD=stroke distance; Q-Tc=corrected Q-T interval, T wave=T wave amplitude.

correct the Q-T interval for heart rate (Q-Tc). The heart rate was calculated from the R-R interval.

Systolic and diastolic blood pressures were recorded by a semi-automatic sphygmomanometer (Dinamap vital signs monitor, Critikon, USA). All measurements were taken from the right arm at one minute intervals until readings stabilised. The mean of three consistent readings was used in analysis. Stroke distance was measured non-invasively^{12,13} using a 1.9 MHz continuous wave non-imaging pencil probe (Hewlett Packard System 77020A). Recordings of ascending aortic blood flow were taken from the suprasternal notch and the mean of three consistent measurements of the systolic velocity integral (stroke distance) was used for the purpose of analysis. Stroke distance (cm) is the linear analogue of stroke volume (cm³), as the cross-sectional area of the aortic root is constant.

Finger tremor was recorded by a previously validated method¹⁴ using an accelerometer transducer (Entran Ltd, Ealing, London, UK). Four recordings were taken and results were stored on computer disc for subsequent spectral analysis of tremor power (>2 Hz) by computer-assisted autocovariance. The mean of three consistent readings was recorded and used for analysis.

STATISTICAL ANALYSIS

Power

The primary end points were chosen before the study as potassium and FEV₁. The sample size was chosen to be able to detect a treatment difference (fenoterol *versus* salbutamol) in serum potassium levels of 0.3 mmol/l, with 13 patients giving 80% power. The sample size was increased to 18 to make it possible to use a latin square design, balanced for treatment, period and crossover. More than 19 patients would have been required in order to detect a clinically relevant difference in FEV₁ (0.3 l).

Analysis

The treatment response was analysed as change from baseline, with tremor data being log transformed. Dose ratios were calculated from the dose-response curves using Theil's non-parametric regression,¹⁵ assuming that the slopes for fenoterol and salbutamol were the same within a given patient (parallel line assay). For

each patient the difference between the intercepts for fenoterol and salbutamol was divided by the slope. The results were summarised by taking the median difference and the 95% confidence intervals for the median were estimated based on the sign test.¹⁶ Those intervals which exclude unity suggest a difference in potency between the two drugs, indicating a shift in the dose-response curve. The dose ratios may be interpreted as the amount in weight by which one would have to multiply the dose of salbutamol in order to obtain the same response as with fenoterol.

In addition, 95% confidence intervals and p values for the treatment difference were obtained using a separate ANOVA at the 200 µg and 4000 µg doses. The rationale for choosing these doses was to compare the two drugs at a conventional dose as well as at the highest dose used in the study. No adjustment was made for multiple tests because of the correlation between time points and end points.

Derived pharmacokinetic parameters for the maximal concentration reached (C_{max}) after the 1 µg and 4 µg doses, and the area under the curve for 0–120 minutes (AUC 0–120)

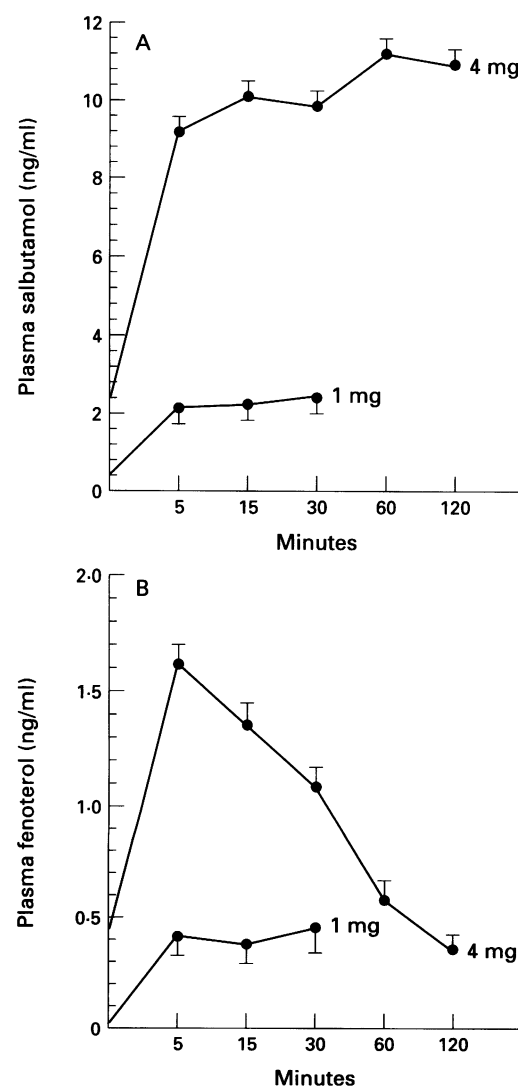


Figure 1 Mean plasma levels (ng/ml) of (A) salbutamol and (B) fenoterol at 5, 15, and 30 minutes after inhalation of 1000 µg and 5, 15, 30, 60, and 120 minutes after inhalation of 4000 µg.

after the 4 mg dose were calculated for both drugs.

All data analysis was performed using the Statistical Software package SAS (SAS Institute Inc, Cary, North Carolina, USA).

Results

There were no significant differences in baseline values between treatments for any of the parameters measured (table 2).

PHARMACOKINETICS (fig 1)

Plasma fenoterol concentrations were lower than those of salbutamol but an approximately fourfold, dose-related increase occurred for both drugs. At the 1 mg dose the C_{max} (ng/ml) was 0.54 (95% CI 0.35 to 0.73) for fenoterol, and 2.54 (95% CI 1.33 to 3.74) for salbutamol. At the 4 mg dose values were 1.59 (95% CI 1.40 to 1.78) and 12.3 (95% CI 11.2 to 13.4) respectively. The AUC 0–120 (ng/

min/ml) at the 4 mg dose for fenoterol was 110.1 (95% CI 92.9 to 127.3) and for salbutamol was 1075.8 (95% CI 988.6 to 1163.1).

BRONCHODILATOR RESPONSES (fig 2)

Dose-related increases occurred in delta FEV_1 , FVC, and PEFr, and a plateau was not observed in the mean response within the evaluated dose range up to 4000 µg. Dose ratios for FEV_1 and FVC did not reveal any significant difference in bronchodilator potency between fenoterol and salbutamol (table 3). Likewise, comparison of the bronchodilator response at 200 µg and 4000 µg did not reveal any significant differences between the two drugs (table 4). In terms of duration of response, a maximal or near maximal FEV_1 response was seen for both drugs at 20 minutes after the last dose (table 5).

SYSTEMIC RESPONSES (figs 2 and 3)

There was a leftward shift in the dose-response curve for fenoterol compared with salbutamol in terms of mean responses. In general, dose ratios for systemic responses showed that fenoterol was more potent than salbutamol (table 3). However, differences in potency were significant only for potassium, tremor, and diastolic blood pressure responses in terms of confidence intervals excluding unity. Comparison of systemic responses to 200 µg showed a significant difference for tremor alone ($p < 0.05$). At the 4000 µg dose (table 4) there were significantly greater effects with fenoterol for potassium ($p < 0.001$), tremor ($p < 0.005$), heart rate ($p < 0.05$), and Q–Tc ($p < 0.05$). Maximal or near maximal systemic responses occurred at 20 minutes after the last dose for both drugs (table 5). The lowest individual potassium levels after the last dose were 2.42 mmol/l with fenoterol and 2.68 mmol/l with salbutamol, and for heart rate the respective values were 130 beats/min and 115 beats/min (table 5).

Discussion

The results of this study show that the bronchodilator potency of fenoterol is equivalent to that of salbutamol on a microgram for microgram basis. In contrast, fenoterol had greater systemic activity than salbutamol, being 3.7 times more potent for hypokalaemic effects. Although the dose-response curve for systemic effects was shifted leftward with fenoterol, it was evident that differences between the two drugs were not clinically relevant at a conventional dose of 200 µg – that is, two puffs of fenoterol 100 µg/puff or salbutamol 100 µg/puff.

The finding of bronchodilator equivalence between fenoterol and salbutamol on a microgram for microgram basis has been reported in previous studies using either single or cumulative dosing protocols.^{2,17,18} In the study by Windom *et al*² in mild asthmatics a plateau in FEV_1 response occurred, not surprisingly, after only two doses had been given (800 µg fenoterol

Table 3 Dose ratios for fenoterol versus salbutamol

	Dose range (mg)	Median dose ratio	95% CI
FEV_1	0.1–4	× 1.1	0.4 to 4.6
FVC	0.1–4	× 1.6	0.3 to 7.6
Potassium	0.4–4	× 3.7	2.0 to 6.0
Tremor	0.2–4	× 5.7	1.4 to 10.2
Heart rate	0.4–4	× 1.6	1.0 to 2.3
Systolic BP	0.4–4	× 5.5	0.1 to 31.8
Diastolic BP	0.2–4	× 4.6	1.3 to 20.5
Stroke distance	0.1–4	× 2.5	0.0 to 158.3
Q–Tc interval	0.4–4	× 1.7	1.0 to 2.8
T wave	0.2–4	× 1.6	1.0 to 3.3

Values shown are medians and 95% CI for differences between fenoterol and salbutamol calculated from regression analysis of parallel slopes. The dose range for regression is also shown for each parameter. The dose ratios represent the amount of salbutamol required to produce the same effect as fenoterol (weight for weight). Those confidence intervals excluding unity suggest a difference in potency between the two drugs.

Table 4 Responses for fenoterol versus salbutamol

	200 µg	4000 µg
FEV_1 (l)	0.67 (0.09) v 0.61 (0.09) (95% CI –0.03 to 0.16)	1.07 (0.11) v 0.97 (0.11) (95% CI –0.01 to 0.21)
FVC (l)	0.82 (0.12) v 0.75 (0.11) (95% CI –0.11 to 0.25)	1.17 (0.15) v 1.16 (0.12) (95% CI –0.18 to 0.22)
PEFR (l/min)	114 (18) v 92 (16) (95% CI –2 to 45)	148 (19) v 156 (14) (95% CI –41 to 25)
Potassium (mmol/l)	0.08 (0.04) v 0.16 (0.04) (95% CI –0.16 to 0)	–1.02 (0.09) v 0.59 (0.10) (95% CI –0.59 to –0.25)
Tr (log units)	0.22 (0.06) v –0.01 (0.05) (95% CI 0.06 to 0.41)	1.02 (0.09) v 0.65 (0.08) (95% CI 0.15 to 0.60)
HR (beats/min)	–2 (1) v 0 (1) (95% CI –6 to 3)	29 (3) v 19 (3) (95% CI 2 to 18)
SBP (mm Hg)	1 (1) v –3 (2) (95% CI –1 to 10)	7 (2) v 5 (2) (95% CI –4 to 8)
DBP (mm Hg)	–1 (1) v 0 (1) (95% CI –3 to 2)	–7 (1) v –5 (1) (95% CI –6 to 1)
SD (cm)	3.0 (0.50) v 2.8 (0.72) (95% CI –1.7 to 2.0)	6.2 (0.80) v 4.9 (0.71) (95% CI –1.2 to 3.8)
Q–Tc (ms)	0 (5) v 0 (5) (95% CI –20 to 10)	60 (6) v 40 (6) (95% CI 0 to 30)
T wave (mV)	–0.03 (0.01) v –0.01 (0.01) (95% CI –0.04 to 0)	–0.14 (0.02) v –0.15 (0.02) (95% CI –0.02 to 0.05)

Responses are shown as change from baseline at 200 µg and 4000 µg doses as means (SE) and 95% CI for difference.

Table 5 Mean (range) duration of response to fenoterol (F) and salbutamol (S) at 20, 60, and 120 minutes after the final dose

		20	60	120
FEV_1 (l)	F	2.93 (1.76 to 5.05)	2.90 (1.63 to 5.15)	2.86 (1.66 to 5.05)
	S	2.80 (1.66 to 4.76)	2.83 (1.74 to 4.73)	2.72 (1.55 to 4.45)
Potassium (mmol/l)	F	2.94 (2.42 to 3.60)	3.09 (2.53 to 3.81)	3.20 (2.64 to 3.91)
	S	3.38 (2.76 to 4.24)	3.37 (2.77 to 4.20)	3.31 (2.68 to 3.89)
Heart rate (beats/min)	F	98 (67 to 130)	94 (72 to 115)	90 (70 to 107)
	S	87 (65 to 115)	92 (69 to 106)	87 (68 to 107)
Tr (log units)	F	3.15 (2.38 to 3.87)	2.97 (2.30 to 3.51)	2.96 (2.16 to 4.15)
	S	2.79 (2.09 to 3.62)	2.79 (2.18 to 3.37)	2.81 (2.14 to 3.33)

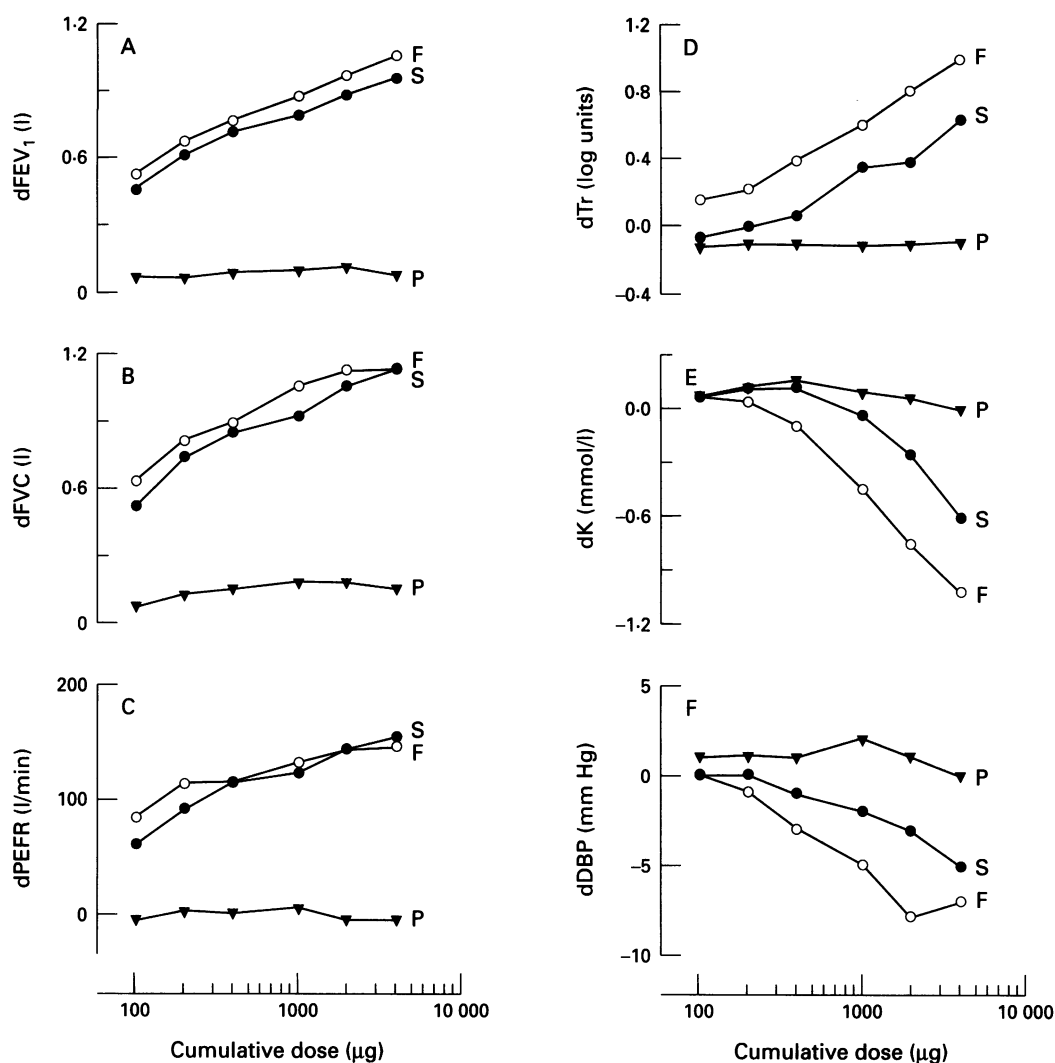


Figure 2 Cumulative log dose-response curves showing mean responses as change from baseline ($\Delta = d$) for (A) forced expiratory volume in one second (FEV_1), (B) forced vital capacity (FVC), (C) peak expiratory flow rate (PEFR), (D) finger tremor (Tr), (E) serum potassium (K), and (F) diastolic blood pressure (DBP). Responses are shown after inhalation of fenoterol (F) or salbutamol (S) in doses of 100 μ g, 200 μ g (100+100), 400 μ g (200+200), 1000 μ g (400+600), 2000 μ g (1000+1000), and 4000 μ g (2000+2000), and after placebo (P).

and salbutamol). In another study in mild asthmatic patients equivalent bronchodilator responses were also demonstrated with a ceiling being almost reached after two puffs using fenoterol 200 μ g/puff and salbutamol 100 μ g/puff.⁷ Although the initial 100 μ g dose in our study produced a significant bronchodilator response, the dose-response curve continued in linear fashion and a plateau in mean response had not been reached even at the highest dose of 4000 μ g. We were therefore able to compare doses of fenoterol and salbutamol on the linear part of the dose-response curve for both airways and systemic effects by calculating dose ratios. Furthermore, in terms of duration of response it was evident that airways and systemic effects were maximal or near maximal at 20 minutes after the last dose for both drugs.

Although we did not detect any significant difference in bronchodilator potency between fenoterol and salbutamol, we concede that this may have been due to type II error as the study power was based on serum potassium levels. Interestingly, *in vitro* data have shown that fenoterol is 2.7 times more potent than salbutamol in guinea pig trachea and four times

more potent in human asthmatic bronchi.^{6,19} This highlights the probable differences between *in vitro* and *in vivo* effects of β_2 agonists on airway β_2 adrenoceptors which may be due to effects of aerosol penetration into narrowed asthmatic airways or impaired receptor accessibility due to mucosal inflammation. Furthermore, our study only addressed effects on resting bronchomotor tone, and hence it is unknown whether fenoterol may have been more potent in terms of antibronchoconstrictor activity.

Our data also suggested a trend towards greater chronotropic and inotropic activity with fenoterol. This is supported by *in vitro* data showing that fenoterol is a full agonist and is more potent on human cardiac β_2 receptors than salbutamol which is a partial agonist.^{20,21} The difference in agonist activity between the two drugs may explain why the slope for stroke distance response was steeper with fenoterol and associated with a higher plateau response. Previous studies have found greater inotropic activity with fenoterol in asthmatic patients, although the indirect method of measuring systolic time intervals (QS_2I) was used as a

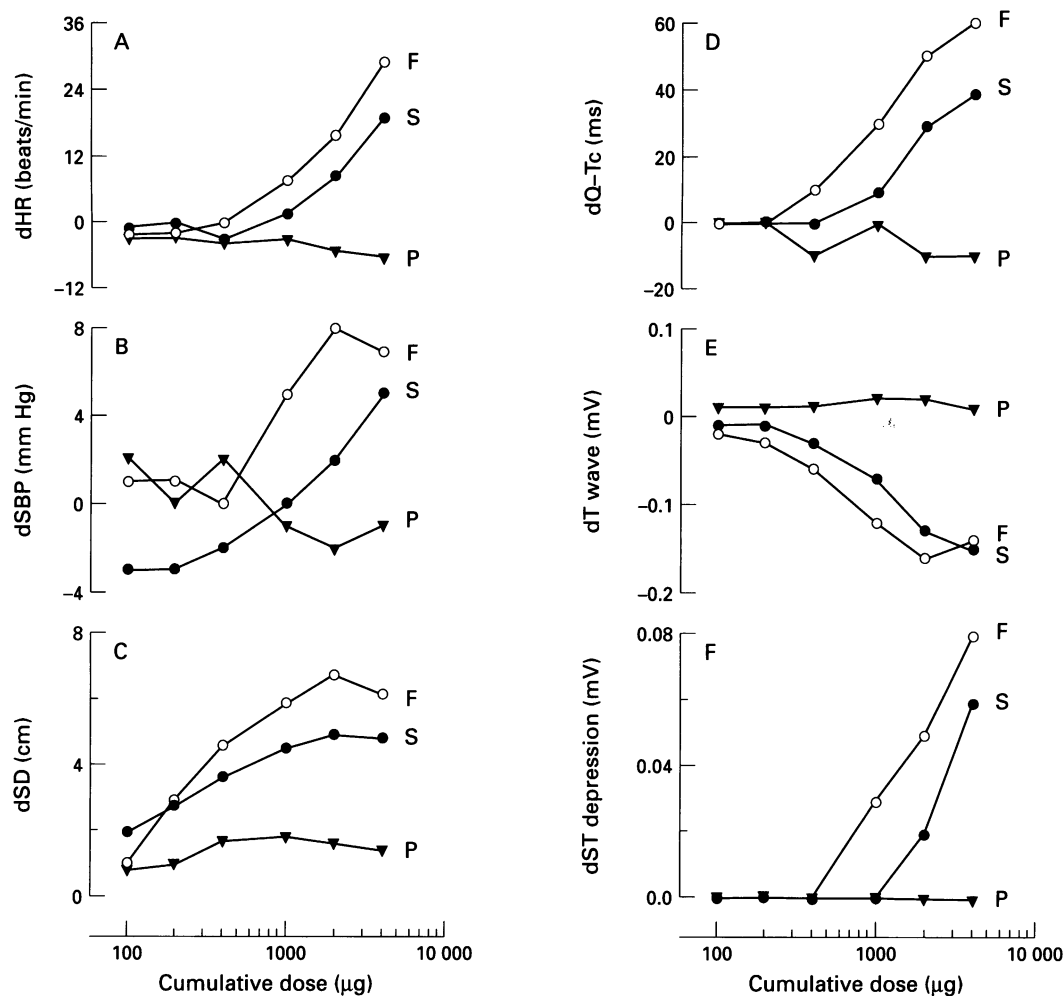


Figure 3 Cumulative log dose-response curves showing mean response for (A) heart rate (HR), (B) systolic blood pressure (SBP), (C) stroke distance (SD), (D) Q-Tc interval, (E) T wave amplitude, and (F) S-T segment depression (as in fig 2).

marker of electromechanical systole.^{23 17} There are conflicting data on chronotropic activity; two similar studies from the same laboratory comparing equal doses by weight up to 1600 µg showed fenoterol to produce greater heart rate responses in normal volunteers but not in asthmatics.²³ In a further evaluation of single 5 mg doses of nebulised fenoterol and salbutamol in asthmatic subjects¹⁷ the mean difference in peak response was approximately 11 beats/min, which is similar to our observations with metered dose aerosol.

The clinical relevance of hypokalaemia is uncertain, although it is possible that factors such as coexisting ischaemic heart disease or hypoxaemia might sensitise the myocardium to a given level of extracellular potassium.^{22 23} It is also known that prolongation of the Q-T interval may predispose to ventricular arrhythmias such as torsades de pointes,²⁴ although β_2 agonist induced tachycardia would tend to protect against its development since rapid cardiac pacing is often used to treat this condition. Indeed, in a recent study comparing high doses (up to 3200 µg) of fenoterol and salbutamol given by spacer in acute severe asthma, no significant arrhythmias were observed with either drug despite significantly greater hypokalaemia and Q-T prolongation with fenoterol.²⁵

There are several factors which may modify

the magnitude of the systemic response to β_2 agonists. It is known that regular exposure to β_2 agonist results in an attenuated response as a result of receptor downregulation.^{26 27} In our study most patients were documented as receiving on-demand β_2 agonists, suggesting that subsensitivity had probably not occurred to any great degree. However, since we did not prospectively control β_2 agonist usage before entry into the study we cannot be absolutely sure of the true amount of drug exposure. In the setting of deteriorating asthma control with increasing β_2 agonist consumption it is probable that systemic β_2 adrenoceptor sensitivity would, if anything, be blunted.

Drug delivery to the lung vascular bed, and hence systemic absorption, will also be reduced by a decrease in airway calibre. The magnitude of systemic β_2 effects would therefore be predicted to become attenuated in patients with more severe airflow obstruction. This hypothesis is supported by comparing peak plasma fenoterol levels at a dose of 4 mg in the present study in asthmatic subjects (1.59 ng/ml) with those in a previous study¹ in normal subjects (3.2 ng/ml). The twofold difference in levels is associated with an approximate 50% reduction in FEV₁ between normal and asthmatic subjects. The inference is that, during an acute attack, the propensity for systemic β_2 effects would tend to be reduced because of severe

peripheral airway narrowing. Concomitant drug treatment may modify the β_2 -mediated systemic response. In particular, corticosteroids are known to upregulate systemic β_2 adrenoceptors which, in turn, results in reversal of tachyphylaxis.²⁸ Potassium depletion by diuretic therapy might also augment the hypokalaemic response induced by β_2 agonists.²⁹

Peak plasma fenoterol concentrations were six times lower than those of salbutamol, and both drugs displayed linearity with about four-fold increases in levels between 1 mg and 4 mg doses. These findings are in agreement with previous pharmacokinetic data in normal subjects.¹ The lower plasma fenoterol levels presumably relate to its greater degree of lipophilicity and hence larger volume of distribution within the extracellular compartment. The more prolonged elimination phase with salbutamol at the 4 mg dose was not observed in our previous study in normal volunteers¹ and may therefore be due to altered clearance in asthmatic lungs, the latter being an important site for systemic absorption.

Despite the difference in dose ratios for systemic potency, it is also relevant to consider the results in terms of absolute responses. For example, at 20 times the conventional dose (4000 μ g) mean nadir levels of potassium were 2.94 mmol/l for fenoterol and 3.31 mmol/l for salbutamol, whilst the lowest values in individual outliers were 2.42 mmol/l with fenoterol and 2.68 mmol/l with salbutamol. Nevertheless, it is somewhat unlikely that patients would inhale 40 cumulative puffs in rapid succession even during an acute asthma attack.

In summary, our findings show that, on a microgram equivalent basis, inhaled fenoterol exhibits greater systemic potency than salbutamol at extrapulmonary β_2 adrenoceptors, whilst having the same bronchodilator potency at airway β_2 adrenoceptors. It is interesting to speculate as to whether the observed differences in systemic β_2 potency with fenoterol may account for the previously described increased asthma mortality from epidemiological case control studies.³⁰⁻³² The main problem with interpreting these studies is in terms of matching cases and controls as well as evaluating confounding effects for asthma severity. One possible explanation for the association with asthma mortality is that, in the past, the greater systemic potency of fenoterol on a microgram equivalent basis might have been compounded by the previous formulation of fenoterol as 200 μ g/puff compared with salbutamol as 100 μ g/puff. This difference has now been addressed by its reformulation to 100 μ g/puff like salbutamol. It is relevant that Spitzer *et al.*³³ reported no difference in asthma mortality between salbutamol and fenoterol when odds ratios were compared on a microgram equivalent basis rather than a canister basis. In terms of adverse effects of high doses of inhaled β_2 agonists, the link between asthma mortality, hypokalaemia, and cardiac arrhythmias remains at present putative. Further controlled studies are required to investigate this issue, particularly with respect to the systemic effects

of β_2 agonists under conditions of increased adrenergic dose and hypoxaemia, as might occur during an acute asthma attack.

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