Interaction and dose equivalence of salbutamol and salmeterol in patients with asthma

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Abstract

***Objective*—To examine the pharmacological interaction of salmeterol and salbutamol and to derive an estimate of dose equivalence of salmeterol for airway and systemic effects in patients with asthma.**

***Design*—Randomised double blind crossover study.**

***Subjects*—12 patients with mild asthma.**

***Intervention*—Placebo or salmeterol 50, 100, 200 μg given on separate days followed two hours later by inhaled salbutamol in cumulative doses up to 3600 μg.**

***Main outcome measures*—Change in forced expiratory volume in one second (FEV_1), heart rate, plasma potassium concentration, QTc interval, tremor amplitude, and creatine kinase myocardial isoenzyme concentration.**

***Results*—Compared with placebo, the mean (95% confidence interval) changes in FEV_1 and heart rate after salmeterol 200 μg were 0·61 (0·32 to 0·90) l and 7·0 (3·8 to 10·2) beats/min. Adding salbutamol caused a large increase in FEV_1 after placebo (0·69 l) with progressively smaller changes after increasing doses of salmeterol (0·19 l after salmeterol 200 μg). Heart rate and QTc interval increased and plasma potassium concentration decreased roughly in parallel on the four study days with a suggestion of convergence at higher doses of salbutamol. Geometric mean dose equivalences for salmeterol 50 μg and 100 μg compared with salbutamol were 4·9 and 7·8 (mean 6·4) for FEV_1 and ranged from 7·1 (2·9 to 17·0) to 12·6 (4·4 to 36·4) for heart rate, plasma potassium, and tremor (mean 9·5).**

***Conclusions*—The effect of adding salbutamol to salmeterol is largely additive. Weight for weight salmeterol may be up to 10 times more potent than salbutamol. Considering its longer duration of action salmeterol 50 μg twice daily could be equivalent to salbutamol in doses up to 500 μg four to six hourly.**

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Introduction

Salmeterol, a new long acting β_2 agonist, produces bronchodilatation for at least 12 hours in patients with asthma[1-3] and when given in doses of 50 μg twice daily provides more effective control of asthma symptoms than salbutamol 200 μg four times daily.[4,5] Whether this difference represents an important additional effect of salmeterol or is simply due to a higher relative dose is uncertain. The dose equivalence of salmeterol compared with salbutamol determined from single dose studies of acute changes in lung function has ranged from 1 to 16—that is, doses of salmeterol from 12·5 μg to 200 μg have produced similar bronchodilatation as 200 μg salbutamol.[1,6] This shows the insensitivity of single dose comparisons as a method of estimating relative potency. The importance of knowing the dose equivalence of β_2 agonists is highlighted by the recent experience in New Zealand, where the excess mortality associated with fenoterol[7-9] has been attributed to marketing of a metered dose inhaler that contained a two to four times higher relative dose of fenoterol compared with salbutamol.[10]

It is recommended that salmeterol be taken regularly twice daily and that a shorter acting β_2 agonist such as salbutamol be added for additional relief.[11] The effect of combining the two agonists, however, has received little attention. Salmeterol is a partial agonist in vitro compared with salbutamol[12] and could therefore reduce the access and effectiveness of salbutamol by occupying β receptors. We studied the effect of adding increasing doses of salbutamol to salmeterol 50, 100, and 200 μg to examine the drugs' interaction and estimate dose equivalence.

Subjects and methods

We studied 12 subjects (three women) aged 18-54 years with asthma but no other medical problems. All were lifelong non-smokers, had a normal electrocardiogram, a baseline forced expiratory volume in one second (FEV_1) greater than 60% predicted, and at least a 15% rise in FEV_1 after 400 μg inhaled salbutamol. All were taking an inhaled short acting β_2 agonist as required and nine a regular inhaled steroid. Subjects gave informed written consent and the study was approved by the Nottingham City Hospital ethics committee.

FEV_1 was measured by dry bellows spirometer with the subject seated and the better of two successive measurements was recorded. Heart rate, QTc interval, tremor, and plasma potassium were measured as described[10]; plasma creatine kinase concentration by the N-acetyl cysteine activated method; and creatine kinase myocardial isoenzyme by immunochemical separation (Isomune-CK, Roche, Welwyn Garden City, Hertfordshire).

Subjects were studied at the same time of day on four occasions at least seven days apart. Inhaled β_2 agonists and drinks containing caffeine were withheld for 12 hours before each study. After 20 minutes' rest baseline heart rate, QT interval, tremor amplitude, FEV_1, and plasma potassium and creatine kinase myocardial isoenzyme concentrations were measured. Subjects then received placebo or salmeterol 50, 100, or 200 μg by metered dose inhaler according to a randomised, crossover, double blind design (by Latin square randomisation). Two hours later inhaled salbutamol was given in doses of 100, 500, 1000, and 2000 μg at 20 minute intervals, to give a cumulative dose of 3600 μg. Doses of salbutamol other than the 100 μg dose were administered by putting multiples of 500 μg into a spacing device (Volumatic, Allen and Hanburys, Uxbridge, Middlesex) and asking the

subject to inhale deeply three times. Measurements were taken in the same order at baseline, two hours after placebo or salmeterol, and 15 minutes after each dose of salbutamol. Symptoms were documented before each dose of drug. The study was stopped if symptoms became severe or if heart rate rose above 140 beats per minute. Patients stayed in the department until symptoms settled and heart rate had fallen below 110 beats per minute.

ANALYSIS

The study had 90% power to detect a difference in heart rate of 6·5 beats/min according to our previous study.[10] Baseline, maximum changes, and final measurements on the four study days were compared by analysis of variance with the generalised linear interactive modelling (GLIM) statistical package and expressed as means with 95% confidence intervals. Symptoms were compared by the χ^2 test. Dose equivalence was estimated from the salbutamol dose which caused the same effect as that seen with each dose of salmeterol. This was done by plotting each person's response to each dose of salmeterol on the log dose response curve after placebo and salbutamol for each index. Raw data were used and geometric means and 95% confidence intervals were calculated with the confidence interval analysis (CIA) statistical package. When the change with salmeterol was above the highest or below the lowest change seen with salbutamol the highest or lowest salbutamol dose was used in the analysis as a censored value.

Results

Baseline, FEV_1, heart rate, plasma potassium concentration, QTc interval, tremor amplitude, and creatine kinase concentration (including myocardial isoenzyme) did not differ significantly at the four visits (table I). All patients completed the full study on all four occasions.

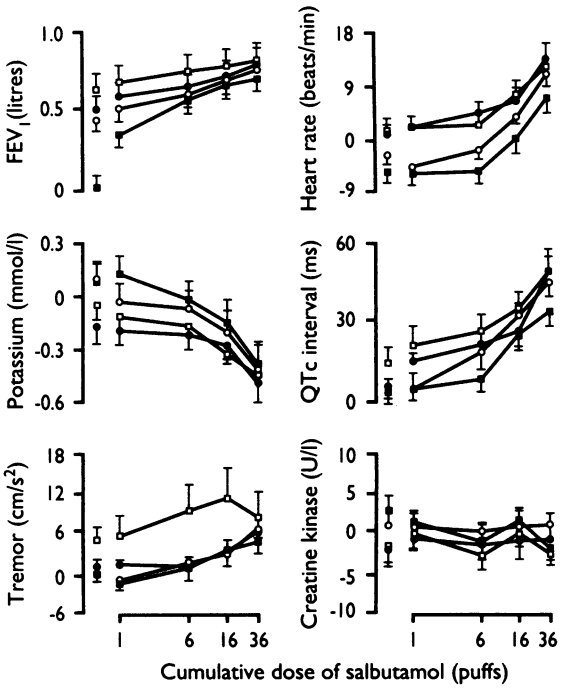
Salmeterol caused a largely dose dependent increase in FEV_1, heart rate, QTc interval, and tremor amplitude and a fall in plasma potassium concentration (table I, figure). Salbutamol caused a large increase in FEV_1 after placebo and progressively smaller increases after salmeterol 50, 100, and 200 μg (table I, figure). Heart rate and tremor amplitude increased and plasma potassium concentration decreased roughly in parallel on the four study days (figure). No significant difference was found in the maximum change seen for any of the measures on the four study days (table I). Creatine kinase concentration (including the myocardial isoenzyme) did not increase significantly after salmeterol or salbutamol.

When salmeterol was compared with salbutamol the geometric mean dose equivalence for FEV_1, heart rate, plasma potassium concentration, QTc interval, and tremor amplitude ranged from 3·1 to 12·6 (table II). The dose equivalence tended to fall with increasing doses of salmeterol indicating that the responses were tending to plateau with the 200 μg dose. The geometric mean dose equivalences for the 50 and 100 μg doses were 4·9 and 7·8 (mean 6·4) for FEV_1 and ranged from 7·1 to 12·6 (mean 9·5) for heart rate, tremor, and plasma potassium. The dose equivalence for QTc interval was consistently lower than that for other measures ranging from 3·1 to 5·8 (table II).

One patient developed lower right chest pain and nausea 48 hours after receiving salmeterol 200 μg, which was attributed to biliary colic. Other symptoms (tremor, headache, and "others") occurred more often with salmeterol 200 μg (five, four, and 16 subjects respectively) than with salmeterol 100 μg (one, two, 10), salmeterol 50 μg (one, two, six), and placebo (one, two, eight), though the differences were not significant.

TABLE I—*Baseline values of and changes in FEV_1, heart rate, plasma potassium concentration, QTc interval, and tremor amplitude two hours after placebo or salmeterol and maximum change after cumulative doses of salbutamol. Values are mean (SE) unless stated otherwise*

	Placebo	Salmeterol 50 μg	Salmeterol 100 μg	Salmeterol 200 μg
FEV_1 (l):				
Mean (SD) baseline	2·72 (0·77)	2·56 (0·76)	2·64 (0·76)	2·62 (0·67)
Change from baseline after salmeterol/placebo	0·03 (0·07)	0·45 (0·08)	0·52 (0·08)	0·64 (0·1)
Change from baseline after salbutamol	0·74 (0·09)	0·78 (0·09)	0·82 (0·11)	0·84 (0·11)
Heart rate (beats/min):				
Mean (SD) baseline	68·1 (9·9)	72·3 (7·9)	65·8 (8·6)	67 (7·3)
Change from baseline after salmeterol	−5·4 (1·8)	−2·7 (1·2)	0·9 (1·7)	1·6 (1·9)
Change from baseline after salbutamol	8·0 (2·5)	11·5 (1·9)	15·1 (3·0)	14·4 (1·7)
Plasma potassium (mmol/l):				
Mean (SD) baseline	4·17 (0·35)	4·18 (0·26)	4·16 (0·23)	4·08 (0·27)
Change from baseline after salmeterol/placebo	0·08 (0·11)	0·1 (0·1)	−0·17 (0·09)	−0·05 (0·08)
Change from baseline after salbutamol	−0·38 (0·14)	−0·42 (0·11)	−0·50 (0·10)	−0·48 (0·05)
QTc interval (ms):				
Mean (SD) baseline	280 (14)	283 (11)	282 (17)	281 (19)
Change from baseline after salmeterol/placebo	4 (3)	6 (4)	6 (3)	15 (4)
Change from baseline after salbutamol	40 (6)	48 (4)	50 (9)	51 (6)
Tremor (cm/s²):				
Mean (SD) baseline	7·8 (5·5)	8·0 (4·8)	8·9 (5·0)	8·1 (3·6)
Change from baseline after salmeterol	0·2 (1·0)	0·2 (0·8)	1·4 (1·0)	5·2 (2·1)
Change from baseline after salbutamol	6·5 (1·8)	7·1 (1·3)	8·2 (1·5)	15·3 (4·7)



Mean change from baseline (with standard error bars) in FEV_1, heart rate, plasma potassium concentration, QTc interval, tremor amplitude, and creatine kinase myocardial isoenzyme concentration two hours after placebo (■) or salmeterol 50 μg (○), 100 μg (●), or 200 μg (□) and after the addition of increasing doses of salbutamol up to cumulative dose of 3600 μg

TABLE II—*Mean (95% confidence interval) dose equivalence values for salmeterol compared with salbutamol*

	Salmeterol 50 μg	Sameterol 100 μg	Salmeterol 200 μg
FEV_1	7·8 (3·4 to 17·8)	4·9 (2·2 to 10·7)	3·1 (1·1 to 8·9)
Heart rate	9·1 (3·2 to 26·4)	10·7 (4·9 to 23·4)	7·9 (3·5 to 17·3)
Plasma potassium	7·1 (2·9 to 17·0)	10·0 (3·5 to 28·2)	3·2 (1·3 to 8·3)
Tremor amplitude	12·6 (4·4 to 36·4)	7·2 (3·0 to 18·2)	5·2 (2·0 to 13·2)
QTc interval	5·8 (2·8 to 12·1)	3·1 (1·3 to 7·2)	3·5 (1·4 to 8·7)

Discussion

The *British National Formulary* recommends that salmeterol is taken twice daily and that a shorter acting β_2 agonist such as salbutamol be added for further relief.[11] Since few studies have examined the efficacy

and safety of combining salmeterol and salbutamol we examined the effects of adding salbutamol to salmeterol on the airway response and potential side effects in patients with mild asthma. Measurements were taken when maximal changes in airway and systemic responses would be expected.[1 13-15] A 200 μg dose of salmeterol was included in addition to the recommended doses of 50 and 100 μg to extend the dose range of salmeterol.

Salmeterol caused a largely dose dependent increase in airway and systemic effects, although only salmeterol 200 μg increased tremor amplitude and QTc interval. The addition of salbutamol caused a roughly parallel fall in plasma potassium concentration and increase in heart rate, tremor amplitude, and QTc interval confirming a largely additive effect; the dose response curves for salbutamol seemed to converge at higher doses.

Although more potent than salbutamol on human airways, salmeterol is a partial agonist achieving about 70% of the maximum effect seen with salbutamol.[12] When a partial and fuller agonist are combined the partial agonist, by occupying receptors, acts as a partial antagonist, thus reducing the effectiveness of the fuller agonist. Salmeterol could therefore reduce the efficacy of salbutamol when the two are given in combination. In vitro, the dose response curve for a fuller agonist in the presence of a partial agonist is shifted to the right with an elevated baseline and a tendency for the curves to converge and cross over with increasing dose.[16] Experiments in vitro permit maximum stimulation of β receptors and relaxation of smooth muscle, which are unlikely to occur in vivo. Although the suggestion of convergence of the dose response curves for salbutamol is in keeping with an interaction between an agonist and a partial agonist, our data suggest that this interaction is unlikely to be large enough to cause a clinically important reduction in beneficial or adverse effects of salbutamol in patients taking salmeterol. Such an interaction, however, remains possible in patients with severe asthma.

DOSE EQUIVALENCES

This is the first study to compare the beneficial and adverse effects of increasing doses of salmeterol and salbutamol. Single dose comparisons of salmeterol 50 μg and salbutamol 200 μg have generally shown similar effects on FEV_1, heart rate, and tremor, leading to the view that 50 μg salmeterol is roughly equivalent to 200 μg salbutamol.[1 4] One study looking at the protection provided by the two drugs against histamine induced bronchoconstriction suggested a more than fourfold difference in potency.[3]

Our study allowed us to estimate dose equivalence from the dose response findings with salbutamol and salmeterol. The response to cumulative doses of salbutamol was compared with that to non-cumulative doses of salmeterol. The estimate of dose equivalence for FEV_1 is probably conservative since the airway response to salbutamol is greater with cumulative doses.[17] The use of a spacing device for the higher salbutamol doses increases the amount delivered to the airways and might also underestimate dose equivalence since airway and systemic effects of β_2 agonists are mainly due to inhaled drug.[15] The dose equivalence for plasma potassium concentration, tremor, and particularly FEV_1 fell with increasing doses of salmeterol as would be expected if the responses were reaching a plateau. The values for the 50 and 100 μg doses of salmeterol (generally between 8 and 10) may therefore be better estimates of dose equivalence. The lower dose equivalence for QTc interval remains unexplained but may reflect compensatory mechanisms or greater β_2 selectivity of salmeterol.

Salmeterol seems to be up to 10 times more potent weight for weight than salbutamol for effects on heart rate, plasma potassium, and tremor. Thus for peak effects salmeterol 50 μg is equivalent to up to 500 μg salbutamol. The dose equivalence over 24 hours is more difficult to estimate but since salmeterol has a longer duration of action salmeterol 50 μg twice daily may be equivalent to salbutamol 500 μg four to six hourly.

Our findings have two important implications. Firstly, studies comparing salmeterol 50 μg twice daily with salbutamol 200 μg four times a day[4 5] are not comparing equi-effective doses and differences between the two drugs may be due to differences in dose rather than differences in drug. Secondly, high doses of β agonist are associated with an increased risk of death[19] and epidemics of death from asthma have been associated with marketing of high doses of β agonists.[7-9 20 21] Whether the relation between high doses of β agonists and mortality is causal remains uncertain but until the question is settled the high dose of salmeterol relative to salbutamol must raise some concerns. Further studies are needed to address the dose equivalence of salmeterol and the optimum dose for long term treatment.

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