Relative therapeutic index between inhaled formoterol and salbutamol in asthma patients

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Abstract A double-blind, randomized crossover study in 28 asthmatic patients assessed the relative therapeutic index for inhaled formoterol and salbutamol. Pre-drug administration FEV₁ (mean 2.08 l) was 49–93% of predicted and reversibility 16–82% after inhalation of salbutamol. Patients inhaled single doses of formoterol (Oxis®) (4.5, 18 and 54 μg, delivered doses) via Turbuhaler, salbutamol (Ventolin®) (200 and 1800 μg) via pressurized metered dose inhaler (pMDI) and placebo at intervals of 48 h or more. Individual maximum FEV₁ and minimum S-K⁺ were calculated. Relative local (maximum FEV₁) and systemic (minimum S-K⁺) dose potencies, and their ratio, the relative therapeutic index, were estimated using a non-linear mixed effect model. The drug effects were well tolerated and dose dependent. A log-linear approximation was used to describe the bronchodilatory effect, whereas a sigmoid approximation was more apt to describe the decrease in serum potassium concentration. A bivariate dose–response model based on these principles was fitted simultaneously to all data. The mean relative therapeutic index between formoterol 4.5–54 μg given via Turbuhaler and salbutamol 200–1800 μg given via pMDI was estimated to be 2.5 in favour of formoterol; this trend was not statistically significant.


Keywords formoterol, salbutamol, relative therapeutic index.

INTRODUCTION

β₂-receptor agonists, such as salbutamol and formoterol, are widely used for bronchodilation in the treatment of asthmatic patients. Inhaled, they are effective bronchodilators with fast onset of action and a minimum of systemic adverse reactions (1). Formoterol fumarate dihydrate (hereafter “formoterol”) is a fast- and long-acting β₂-agonist when delivered by the pulmonary route (2,3). Two strengths of formoterol (Oxis®) are available for administration via the dry powder inhaler Turbuhaler, 4.5 and 9 μg per inhalation (on some markets denoted as metered doses of 6 and 12 μg per inhalation), and two strengths of salbutamol, 100 and 200 μg per inhalation are normally available for administration via the pressurized metered dose inhaler (pMDI).

β₂-agonists mediate uptake of potassium into skeletal muscle leading to the concentration of serum potassium being suppressed (4). The effect on serum potassium declines during repeated administration of β₂-agonists (5,6). A higher dose of β₂-agonist is required to detect serum potassium suppression than to detect bronchodilation. Thus, the serum concentration of potassium is negligibly affected after inhalation of salbutamol at doses below 500 μg (7). The single-dose effect of inhaled formoterol on serum potassium is negligible after 4.5 μg administered via Turbuhaler (data on file, Astra-Zeneca).

The therapeutic index of a drug, defined as the ratio between potencies of desired and undesired effects, can serve as an indication of the therapeutic window or as a measure of the overall usefulness. Judged from serum potassium suppression, a marker for undesired systemic effects of β₂-agonists, formoterol is about 60 times as potent as salbutamol (8). Simultaneous re-estimations of this measure of relative systemic dose potency and relative dose potency for the desired bronchodilating effect for inhaled formoterol and salbutamol, respectively, were made. The objective was to assess a relative therapeutic index, defined as the ratio between relative bronchodilating potency and relative serum potassium suppressing potency of these drugs.

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MATERIALS, METHODS AND PATIENTS STUDIED

The study was performed in accordance with the Declaration of Helsinki and approved by the local Ethics Committees in Eger, Budapest, Nogradgardeny, Pécs, and Györ, Hungary. Before enrolment, asthmatic patients gave their informed consent after receiving oral and written information.

Study patients

Asthmatic patients were recruited provided they had a normal serum potassium concentration and no history of clinically relevant heart disease, ECG abnormality or hypertension. Eligibility was based on a physical examination, vital signs and standard clinical laboratory tests. Asthma was diagnosed according to the American Thoracic Society guidelines (9). Patients were included only if they could show a stepwise dose-response to salbutamol inhaled via pMDI in the range 100–200 or 100–400 μg, overall by at least 15%. Baseline FEV₁ was not to vary by more than ±12% between the enrolment visit and study days. Furthermore, baseline FEV₁ was not to increase by more than 15% from one study day to the next.

Twenty-nine patients were randomized to six treatment periods. One patient, who discontinued the study after one treatment because baseline criteria for FEV₁ were not fulfilled, was excluded from the statistical analysis.

The 28 asthmatic patients who completed the study were all Caucasian non-smokers (three ex-smokers). Their mean age was 43 (range 20–64) years and mean weight 72 (range 49–91) kg. Mean baseline FEV₁ was 2.08 (range 1.46–2.90) l or 69 (range 49–93)% of predicted normal value. The reversibility after inhalation of salbutamol was 16–82%. All patients showed at least 50% additional reversibility after a cumulative dose of 200 or 400 μg salbutamol compared with a single dose of 100 μg. Two asthmatic patients completed the study and were included in the evaluation although they were not fully eligible—one had angina pectoris and one had unspecific hypertension. Twenty-four of the 28 patients were on asthma medication: 18 on bronchodilators, and 18 on corticosteroids (not necessarily the same patients).

All active treatments were expected to have a bronchodilating effect, and at least 18 and 54 μg of formoterol and 1800 μg of salbutamol were expected to be serum potassium suppressive. Inspiratory flow via Turbuhaler and pMDI was monitored by use of a modified Vitalograph® MDI-Compact spirometer (10). Strenuous activity and intake of beverages containing caffeine or alcohol were not allowed before and during study days. A light breakfast was served before and a light lunch at 4 h after drug administration on study days. Water was allowed ad libitum.

Salbutamol 100 μg was to be inhaled regularly at least twice daily via pMDI for 10 days before the first treatment. Thereby, a clinically relevant degree of tolerance to the tested drugs was to be ensured. Other regular treatments were kept constant during the study.

FEV₁ and serum potassium were assessed before (−15 min) and at 0.5, 1, 1.5, 2, 3 and 4 h after drug administration. FEV₁ was measured, with the patient sitting in an upright position, using a Vitalograph Alpha spirometer (Vitalograph Ltd., U.K.) according to standards defined by the American Thoracic Society (11). Venous blood was drawn via an indwelling catheter into tubes without anticoagulant, with the patient supine or sitting reclined. After blood coagulation, serum was prepared by centrifugation at 1400 g and then stored at −20 °C. An ion-selective electrode was used to measure the serum concentration of potassium.

Pulse and blood pressures were checked at −15 min, and 0.5, 1, 1.5, 2, 3, 4 and 8 h using standard methods. Q–Tc (heart rate corrected Q–T interval), obtained from I2-lead electrocardiograms, was recorded at −15 min and 8 h. Information regarding adverse events was collected by means of a standard question: “Have you had any health problems since your last visit or since you were last asked?”.

Definitions, symbols, and calculations of individual parameters

| Baseline | Measurement made in the morning before administration of randomized study treatment. |
| F4.5, F18, F54 | Formoterol 4.5, 18, and 54 μg inhaled via Turbuhaler. |
| FEV₁ | Forced expiratory volume in 1 s (l) |
| Placebo | Randomized and double-blind control treatment. |
| Pulse | Measurement via radial artery (bpm, beats/min). |
| Q–Tc | Heart rate corrected Q–T interval, \( Q - T \times \sqrt{\frac{\text{heart rate}}{60}} \) (ms) |
| S200, S1800 | Salbutamol 200 and 1800 μg inhaled via pMDI. |
| S–K⁺ | Serum concentration of the potassium ion (mmol/l). |
**Data analysis**

*Analysis of maximum or minimum values*

Analysis of variance models with patient, period, and treatment as factors and baseline as covariate were used for the maxima of FEV₁, pulse and systolic blood pressure, and for the minima of serum potassium concentration and diastolic blood pressure. Missing individual baseline values for serum potassium concentrations were replaced by the within-patient mean baseline for the other treatments. A multiplicative model was used for FEV₁. Treatment means were compared pairwise.

*Estimation of the relative therapeutic index for formoterol and salbutamol*

A bivariate non-linear mixed-effect model was used to estimate the relative dose potencies and the relative therapeutic index based on minimum serum potassium and maximum FEV₁ (Appendix A).

The fitted model is presented graphically superimposed on the adjusted mean maximum increase in FEV₁ and minimum serum potassium concentration values obtained from the analyses of variance (cf. above).

**RESULTS**

All treatments were well tolerated. No specific adverse event pattern was discernible. ECGs were normal; sinus rhythm was always seen. Two patients had extrasystoles at the check 8 h after dosing that were not present before dosing (in one patient after F4.5 and S200, and in the other after S1800). Normal ECGs were recorded from these patients at subsequent visits. Some patients did not inhale salbutamol regularly as prescribed by the protocol.

*Description of data and analysis of maximum effects*

Mean baseline FEV₁ and S–K⁺ on study days was 2.09–2.14 l and 4.27–4.34 mmol/l, respectively.

Bronchodilation was seen after inhalation of formoterol and salbutamol (mean FEV₁ at scheduled assessment times are shown in Fig. 1). The maximum FEV₁, seemingly reached within 4 h after dosing, was statistically significantly greater after the active treatments compared with placebo: 13, 17, and 20% after F4.5, F18 and F54, respectively, and 7 and 15% after S200 and S1800, respectively. Statistically significantly greater maxima were seen after F54 compared with F18 (6.5%) and after S1800 compared with S200 (7.5%), showing that bronchodilation was dose dependent within the studied range for both drugs. The maxima after all doses of formoterol were statistically significantly greater than S200 and so was the maximum after F54 compared with S1800.

The serum potassium concentration was suppressed by both formoterol and salbutamol (mean concentrations at scheduled assessment times are given in Fig. 2). The minimum concentration, seemingly reached within 4 h, was statistically significantly lower than placebo after formoterol 18 μg (–0.29 mmol/l) and 54 μg (–0.61 mmol/l), and salbutamol 1800 μg (–0.30 mmol/l), but not after formoterol 4.5 μg (–0.04 mmol/l) or salbutamol 200 μg (–0.07 mmol/l). More individual values below the reference range of serum potassium (3.5–5.0 mmol/l) and statistically significantly lower minima were seen after F54 compared with F18.
(-0.32 mmol/l) and after S1800 compared with S200 (-0.23 mmol/l), showing that serum potassium suppression was dose dependent within the studied range.

The mean baseline values for cardiovascular variables were 71–75 bpm (pulse), 126–132 mm Hg (systolic blood pressure), 79–82 mm Hg (diastolic blood pressure), and 384–394 ms (QTc). Maximum effects seemed to be reached within 4 h after dosing (not shown). The maximum pulse was statistically significantly greater than placebo after F54 (+10 bpm) and S1800 (+8 bpm) but not after the other treatments. The systolic blood pressure did not increase, but rather unexpectedly seemed to decrease during the first 4 h after dosing (not shown). The minimum diastolic blood pressure was statistically significantly lower than placebo after salbutamol 1800 µg (-4.9 mm Hg) but not after the other treatments. The mean QTc at 8 h was statistically significantly longer than placebo after F54 (+17.5 ms) but not after the other treatments.

**Estimation of the relative therapeutic index for formoterol and salbutamol**

A log-linear approximation was used to describe the bronchodilatory effect, whereas a sigmoid approximation was more apt to describe the decrease in serum potassium concentration. The fitted model superimposed on mean maximum FEV1 values and minimum serum potassium concentrations obtained from the analyses of variance are shown in Fig. 3. The model provided good approximations of the means and could therefore be used to estimate relative dose potencies and the relative therapeutic index. The estimated relative dose potencies are indicated in the model as the dose of salbutamol inhaled via pMDI corresponding to formoterol 9 µg inhaled via Turbuhaler. Formoterol was estimated to be 88 times as potent as salbutamol with regard to suppression of serum potassium and 215 times as potent regarding increase in FEV1. The relative therapeutic index was therefore estimated to be 2.5 (95% confidence interval: 0.9–6.5) in favour of formoterol. The confidence limits for the relative therapeutic index included 1, so the difference between the two drugs was not statistically significant.

**DISCUSSION**

A relative therapeutic index between formoterol inhaled via Turbuhaler and salbutamol inhaled via pMDI was defined and estimated, to the best of our knowledge, for the first time in asthmatic patients. The estimate, based on the simultaneous assessments of ratios between relative bronchodilating and serum potassium suppressing potencies between the two drugs, favoured formoterol.

**Dose potency**

Studies addressing the dose potency of β2-agonists often fail to show dose bronchodilating response because inadequate dose spans render detection of treatment differences difficult. In the present study, however, clear
The mean maximum \( \text{FEV}_1 \) after delivered doses of formoterol 4.5 and 18 \( \mu \text{g} \) (equivalent to metered doses of 6 and 24 \( \mu \text{g} \) via Turbuhaler) were 113 and 117% of placebo, respectively, which corroborated previous results (3). Maximum bronchodilation of salbutamol was moderate compared with placebo, but the net increase from baseline, about 0.51 (7%) after 200 \( \mu \text{g} \) and 0.71 (15%) after 1800 \( \mu \text{g} \), was similar to that seen previously after such doses of salbutamol inhaled cumulatively via pMDI (12,13). Unexpectedly, there was a potential for bronchodilating improvement for doses of formoterol up to 54 \( \mu \text{g} \) and salbutamol up to 1800 \( \mu \text{g} \).

In vitro estimates suggest that the bronchodilating potency of formoterol may be 100–200 times greater than that of salbutamol on a molar basis (14,15), i.e. about 60–120 times greater on a weight basis. The relative local potency in this study with respect to bronchodilation was on average 215 on a \( \mu \text{g} \) for \( \mu \text{g} \) basis in favour of formoterol, giving fair clinical support for the in vitro data. The lower relative serum potassium suppressing potency essentially confirmed previous in vivo estimates in healthy subjects and asthmatics (8). Recently, caution was called for because inhaled formoterol and salmeterol may have narrow therapeutic windows (16). However, this study indicated that inhaled formoterol may be a therapeutic improvement, at least, compared with a reliable short-acting \( \beta_2 \)-adrenoceptor agonist analogue.

The bronchodilating effect of salbutamol could have been blunted by additives in the pMDIs (17). However, even if this were the case in the present study, it would not have confounded the estimate of relative bronchodilating potency between formoterol Turbuhaler and salbutamol pMDI, since patients inhaled via pMDI (salbutamol or placebo) on all study days in order to maintain the double-blind nature of the study. Patients should have inhaled salbutamol regularly during a 10-day run-in, but that was not always the case. Therefore, the degree of tolerance to \( \beta_2 \)-agonists might have varied between patients. However, the relative systemic potency between formoterol and salbutamol seems to be unaffected by the degree of tolerance induced by regular treatment with a \( \beta_2 \)-agonist (8) and there is no reason to believe that relative local bronchodilating potency would be affected differently. Therefore, the deviations from the prescribed run-in should not have influenced the estimate of the relative therapeutic index.

Relative therapeutic index

This study indicated that the serum potassium suppression caused by inhaled formoterol is less pronounced than the suppression caused by an equieffective bronchodilating dose of inhaled salbutamol. Formoterol and salbutamol are both \( \beta_2 \)-selective agonists and there is no obvious reason why they should behave differently at the receptor level in different organs.

Drugs aimed at exerting their effect in the airways are more selective after inhalation than after oral administration. This pharmacodynamic selectivity is further improved if the inhaled drug is somehow retained in the airways (18,19). Distribution into the lipid part of cell membranes is thermodynamically more favourable for a lipophilic \( \beta_2 \)-agonist such as formoterol than for a hydrophilic one such as salbutamol (20). Slow distribution of airway-retained formoterol from the lungs to the systemic circulation helps to maintain a therapeutically relevant concentration of formoterol at the site of action in the lungs, and so prolongs bronchodilation. However, it has been shown that systemic concentration of inhaled formoterol is too low, even after relatively high doses, to prolong the systemic effects to a similar extent as seen with an equieffective dose of salbutamol (8). This study indicated that the two drugs also may differ with respect to the relation between local and system magnitudes of effect. Thus, a more pronounced difference between local and systemic exposure of inhaled formoterol compared with inhaled salbutamol may explain not only the well-known difference in duration of bronchodilation but also why the therapeutic index would be more favourable for formoterol.

CONCLUSION

Formoterol (Oxis) Turbuhaler may have a more favourable ratio between local and systemic potency than salbutamol pMDI. The clinical implication would be that systemically mediated side-effects of inhaled formoterol may be less pronounced than with an equieffective bronchodilating dose of inhaled salbutamol.

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APPENDIX A

A parametric model was fitted to data in order to estimate the relative therapeutic index between formoterol and salbutamol. The dose–response curves for formoterol and salbutamol were assumed to be parallel. Individual minimum S–K+ and — in accordance with the basic
assumption of multiplicity for the relative increase in FEV₁ — I log (Maximum FEV₁) for all doses were analyzed simultaneously as functions of the logarithms of formoterol and salbutamol doses. The parameters of the model (Models I) were assumed to be normally distributed random variables within the group of investigated patients and the within-patient variation was assumed to be independent for S-K⁺ and FEV₁. The model was fitted to data using the Vonesh–Carter method (21). Period effects were adjusted for, using a fixed effect model, and baseline differences were adjusted for using baseline as covariate for the placebo effect.

\[
\text{Minimum S-K}^+ = \begin{cases} 
\alpha_1, & \text{placebo} \\
\alpha_1 \left(1 - \frac{1}{1 + e^{b_1(d_1 - c_1)}}\right), & \text{formoterol} \\
\alpha_1 \left(1 - \frac{1}{1 + e^{b_1(d_2 - c_2)}}\right), & \text{salbutamol}
\end{cases}
\]

\[
\log(\text{Minimum FEV}_1) = \begin{cases} 
\alpha_2 + b_2 \log(\text{Dose}) + c_2, & \text{placebo} \\
\alpha_2 + b_2 \log(\text{Dose}) + d_2, & \text{formoterol} \\
\alpha_2 + b_2 \log(\text{Dose}) + d_2, & \text{salbutamol}
\end{cases}
\]

Model parameters

- \(\alpha_1\): minimum S-K⁺ after placebo
- \(b_1\): Hill factor (curve shape).
- \(c_1\): \(\log(\text{Dose of formoterol causing suppression of minimum S-K}^+ \text{ to 50% of placebo})\)
- \(d_1\): \(\log(\text{Dose of salbutamol causing suppression of minimum S-K}^+ \text{ to 50% of placebo})\)
- \(\alpha_2\): Potency factor for formoterol (horizontal location of the dose–response line)
- \(b_2\): Slope factor
- \(c_2\): Potency factor for salbutamol (horizontal location of the dose–response line)
- \(d_2\): Potency factor for salbutamol (horizontal location of the dose–response line)

The relative dose potency was estimated as \(e^{(c_1-d_1)}\) for S-K⁺ and as \(e^{(d_2-c_2)}\) for FEV₁. The relative therapeutic index was estimated as \(e^{((d_2-c_2)-(c_1-d_1))}\). Confidence intervals for the estimates were calculated using the asymptotic normality of the estimates.