Safety and efficacy of a high cumulative dose of salbutamol inhaled via Turbuhaler® or via a pressurized metered-dose inhaler in patients with asthma

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An open, crossover and randomized study was carried out to compare the safety and efficacy of salbutamol inhaled using the dry-powder inhaler Turbuhaler®, and using a pressurized metered-dose inhaler (pMDI). Twelve patients with moderate to severe asthma, aged 47-68 years, were included in the study. On two separate days, patients received a total dose of 1600 µg of salbutamol administered in a cumulative dose fashion: 100, 100, 200, 400 and 800 µg at 3-min intervals.

Salbutamol inhaled via Turbuhaler caused a larger decrease in serum potassium concentration than did salbutamol inhaled via pMDI. The estimated relative dose potency of the hypokalaemic effect of salbutamol Turbuhaler vs salbutamol pMDI was 2.0 with a 95% confidence interval of 1.3-3.6. Turbuhaler caused a small (but statistically significantly greater than with pMDI) increase in heart rate, QTc interval and tremor. Blood pressure was unaffected by the treatments. No adverse events of clinical relevance were reported. The estimated relative dose potency of the bronchodilating effect (FEV1) of salbutamol Turbuhaler vs salbutamol pMDI was 3.0 with a 95% confidence interval of 1.8-5.8.

In conclusion, salbutamol inhaled via Turbuhaler was more potent and seemed to have a better therapeutic ratio than salbutamol inhaled via pMDI. Both treatments were equally well tolerated.

Introduction

Inhaled short-acting β2-agonists have played an important role in the management of asthma for more than two decades. Their immediate bronchodilating effect makes them the medication of choice for treatment of acute asthma attacks and for pre-treatment of exercise- and allergen-induced bronchoconstriction (1). Salbutamol, a relatively selective β2-agonist (2), is well established in the treatment of reversible obstructive airway diseases. The predominantly used formulation of inhaled salbutamol has been the chlorofluorocarbon (CFC)-propelled pressurized metered-dose inhaler (pMDI). Turbuhaler® (Astra Draco), an inspiratory-flow-driven, multidose, dry-powder inhaler delivers micronized drug without the need of propellants (3). When using Turbuhaler, patients do not need to co-ordinate dose actuation with inhalation of the drug; a problem which is commonly associated with the use of pMDIs and which may influence patient compliance and drug efficacy (4,5). A previous study showed that Turbuhaler delivers about twice the amount of terbutaline, another short-acting β2-agonist, to the lungs as the corresponding pMDI, and that the observed difference in deposition is reflected in the bronchodilating effect of terbutaline (6).

In general, β2-agonists are well tolerated and have sufficient safety margins even at high doses. However, at doses higher than 500 µg, inhaled salbutamol has been shown to cause extrapulmonary effects, such as changes in blood pressure, increased heart rate, tremor and hypokalaemia (7).

The aim of this study was to determine the relative dose potency, with regard to safety and efficacy, of the new drug formulation, salbutamol Turbuhaler, vs salbutamol pMDI in patients with asthma.

Patients and Methods

PATIENTS

Twelve outpatients (three women) with reversible airways obstruction were included in the study (Table 1). They had
a mean age of 59 years (range: 47-68), a mean baseline forced expiratory volume in 1 s (FEV₁) of 50% (range: 36-79) of predicted normal value, and a mean reversibility of FEV₁ of 20% (range: 15-26) measured 15 min after inhalation of 200 µg of salbutamol. Seven patients were former smokers, four were current smokers and one had never smoked.

Patients were not included if they had a theophylline serum level >28 µmol l⁻¹. Hospitalization for treatment of airway disease within 1 month or significant disorders other than airway disease also disqualified patients from inclusion in the study, as did pregnancy, breast-feeding or active planning of pregnancy. Concomitant β₂-agonist medication was withheld as follows: inhaled short-acting, 8 h; inhaled long-acting, 24 h; and oral, nebulized or parenteral, 36 h prior to and throughout the study. Oral steroids were not to be used within 30 days prior to enrolment, and patients using orally or nasally inhaled steroids were to keep the dose constant 30 days prior to and throughout the study. The patients were allowed to use salbutamol pMDI as rescue medication at any time during the study, except within 8 h prior to the baseline spirometry at the enrolment visit and on the two study days.

The study was performed in accordance with the principles stated in the Declaration of Helsinki and the principles of Good Clinical Practice adopted by the European Community. It was approved by the Swedish Medical Products Agency and the Ethics Committee at the University of Gothenburg. The patients gave their signed informed consent before they were enrolled in the study.

STUDY DESIGN

The study was of an open, crossover and randomized design. Patients received cumulative doses of salbutamol: 100, 100, 200, 400 and 800 µg at 30-min intervals, using Turbuhaler (Astra Draco) or pMDI (Glaxo), on two study days separated by at least 24 h. Inspiratory flow through Turbuhaler and pMDI was measured by connecting the inhalers one at a time in a serial mode to a Vitalograph MD1 modified Compact spirometer (Vitalograph Ltd, U.K.). Patients inhaled salbutamol while in a sitting, upright position. When using Turbuhaler, they were instructed to inhale deeply and forcefully. When using pMDI, they were instructed to inhale as slowly as possible and to actuate the dose at the beginning of the full inhalation. After completed drug inhalation, the patients were asked to hold their breath for 10 s. Patients practised the inhalation manoeuvres at the enrolment visit using empty Turbuhaler inhalers and placebo pMDIs.

Baseline measurements were made within 30 min before the first study drug administration on each study day. Blood pressure was then measured at 15 min after each dose using a standard sphygmomanometer. Readings were taken with the patient in the sitting position after a 5-min rest. Heart rate was measured over consecutive 5-min intervals between 10 and 30 min after each dose in a continuous three-lead electrocardiogram (Marquette Series 8500 Holter recording). The QT interval was measured at 15 and 25 min after each dose in five consecutive QRS complexes using a Siemens Elema Mingograf. The QT interval was corrected for heart rate (QTc) according to Bazett (8). Subjective tremor was estimated on a four-point scale (0=no tremor; 1=just perceivable; 2=perceivable; 3=troublesome;) at 20 min after each dose, followed by an objective tremor measurement using a one-plane accelerometer applied to the patient's right-hand middle finger (9). During the measurement, the patient's wrist rested on the table and the finger was held moderately stretched. Acceleration in the up-down direction was measured during 5 x 10 s using an accelerometer connected to an analogue pre-amplifier (Anglo Devices), a Macintosh II computer with an
Table 2. Mean baseline values (range) of extrapulmonary variables

<table>
<thead>
<tr>
<th></th>
<th>Turbuhaler</th>
<th>pMDI</th>
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<tbody>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mmHg)</td>
<td>112 (90-150)</td>
<td>111 (85-155)</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>72 (60-80)</td>
<td>71 (60-85)</td>
</tr>
<tr>
<td>Maximum heart rate (bpm)</td>
<td>87 (75-101)</td>
<td>87 (67-108)</td>
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<tr>
<td>QTc interval (ms)</td>
<td>400 (380-420)</td>
<td>390 (360-410)</td>
</tr>
<tr>
<td>Tremor (units)</td>
<td>4.3 (3.8-5.4)</td>
<td>4.3 (3.9-4.9)</td>
</tr>
<tr>
<td>Serum potassium (mmol·L⁻¹)</td>
<td>4.3 (3.8-7.6)</td>
<td>4.2 (3.2-7.1)</td>
</tr>
</tbody>
</table>

CARDIOVASCULAR EFFECTS

Systolic and diastolic blood pressures remained unchanged after inhalation of salbutamol via Turbuhaler or pMDI, even at the highest dose level. Salbutamol inhaled via Turbuhaler caused a larger increase in heart rate than did salbutamol inhaled via pMDI (P<0.001). Maximum heart rate was reached between 25 and 30 min after the last dose on each study day. Mean of the maximum values recorded within this interval was 95 beats min⁻¹ (range: 78-109) for Turbuhaler and 89 beats min⁻¹ (range: 76-106) for pMDI. Salbutamol slightly lengthened the QTc interval. Although small, the effect was more pronounced with Turbuhaler, than with pMDI (P<0.001). Assuming parallel profiles, the difference between the inhalers was estimated to 11 ms with a 95% confidence interval of 5-16 ms. Individual QTc intervals were considered normal, i.e. less than 430 ms for men and less than 450 ms for women (14), at all dose levels except in one case (a prolonged QTc interval of 460 ms, followed by a normal QTc interval of 420 ms, was observed for one male patient after cumulative doses of 800 and 1600 µg, respectively, inhaled via Turbuhaler).

TREMOR

Tremor was experienced by four patients, one of whom reported tremor after each Turbuhaler dose, as well as after the highest cumulative dose (1600 µg) inhaled via pMDI.
Cumulative doses of 800 and 1600 µg inhaled via Turbuhaler caused tremor in the other three patients, two of whom reported tremor also after 1600 µg inhaled via pMDI. Tremor was scored 1 (just perceivable) in all cases. The increase in objectively measured tremor was larger with Turbuhaler than with pMDI (P<0.0001) (Fig. 1). Based on the three highest doses, the relative dose potency of Turbuhaler vs pMDI was estimated to 2.3 with a 95% confidence interval of 1.5-4.4.

SERUM POTASSIUM

Serum potassium concentration increased after the first one to two doses of salbutamol and then declined by additional doses inhaled via Turbuhaler or pMDI (Fig. 2). Based on the three highest doses, the relative dose potency of Turbuhaler vs pMDI was estimated to 2.3 with a 95% confidence interval of 1.5-4.4. The lowest serum potassium concentration value for an individual patient was 3.7 mmol L⁻¹ recorded after the highest cumulative dose (1600 µg) inhaled via Turbuhaler.

ADVERSE EVENTS

There were no reports of adverse events. There were no findings of clinical relevance on physical examination or in the clinical chemistry and haematology tests performed during or after the completion of the study.

SPIROMETRY

Baseline FEV₁ (mean ± sd) was similar on the two study days (1.43 ± 0.45 L and 1.43 ± 0.48 L). Individual changes from the first to the second study day varied from a reduction of 10.5% to an increase of 7.3%, indicating that the patients' asthma was fairly stable throughout the study. After inhalation of salbutamol, FEV₁ increased successively up to 2.04 L (Turbuhaler) and 1.92 L (pMDI) after inhalation of a cumulative dose of 1600 µg (Fig. 3). Based on the horizontal distance between the parallel lines in Fig. 4, the relative dose potency of Turbuhaler vs pMDI with regard to FEV₁ was estimated to 3.0 with a 95% confidence interval of 1.8-5.8. When based on FVC, the relative dose potency was estimated to 4.1 with a 95% confidence interval of 2.2-10.0.

Discussion

This investigation was performed to compare the safety and efficacy of a new formulation, salbutamol Turbuhaler, with that of a conventional pMDI formulation containing the same active drug substance. When comparing different inhalers, it is preferable to use a double-blind and double-dummy technique. However, considering the number of inhalations taken at each dosing, especially at the higher dose levels, this was not feasible in the present study. Not only would it have increased the effort required by the...
patients, but it would also have considerably prolonged the time between inhalations and assessments.

The results of this study showed changes in extrapulmonary and bronchodilating responses to salbutamol inhaled Turbuhaler or pMDI. Serum potassium concentration was chosen as the primary safety variable because of its sensitivity and reproducibility (6). The hypokalaemic effect of salbutamol inhaled via Turbuhaler was found to correspond to that produced by twice the dose inhaled via pMDI. It was noticed, however, that the serum potassium concentration remained above the lower limit of the reference range (3.5-5.0 mmol l⁻¹) even after a cumulative dose of 1600 µg using either inhaler, and that it was not associated with any symptoms of clinical relevance. Salbutamol inhaled via Turbuhaler caused a larger increase in heart rate, QTc interval and tremor than did equal doses of salbutamol inhaled via pMDI. The magnitude by which these variables were affected was small and considered to have no implications for normal, clinical use of salbutamol.

Salbutamol inhaled via Turbuhaler produced a significantly greater bronchodilation than did equal doses of salbutamol inhaled via pMDI. The relative dose potency of salbutamol Turbuhaler vs salbutamol pMDI was 3.0. This means that a Turbuhaler inhaler, on average, should contain about one-third of the nominal dose of pMDI for the same bronchodilating effect to be achieved. This is in line with a recent single-dose study showing that the same bronchodilating effect produced by salbutamol inhaled via pMDI can be obtained by half the dose inhaled via Turbuhaler (15). Despite the high cumulative dose of 1600 µg of salbutamol in the present study, a maximum bronchodilating effect was not reached with either of the two inhalers. This absence of a dose-response plateau is consistent with results of several other β₂-agonists studies using cumulative dosing regimens (16,17). The mechanism behind the finding is assumed to be bronchodilation of airways after the initial doses with a cumulative technique allowing increased penetration of succeeding doses. Since the first dose was inhaled at 8:30 a.m. and the last FEV₁ was measured at 11 a.m., it cannot be precluded that natural elevation of FEV₁ due to the circadian rhythm (18) may also have contributed to the increased bronchodilation with sequential doses.

The higher potency of salbutamol Turbuhaler in producing extrapulmonary and bronchodilating effects was probably a result of a higher lung deposition, as the latter causes an increased concentration of active drug not only in the airways, but also in the systemic circulation (6). The beneficial effect of inhaled salbutamol seemed to outweigh the adverse effects when Turbuhaler was used instead of pMDI, as indicated by the relative dose potencies for salbutamol Turbuhaler vs salbutamol pMDI of 3:0 and 4:1 for FEV₁ and FVC, respectively, and 2:3 and 2:0 for tremor and serum potassium, respectively. From this, it follows that, within the dose range studied, salbutamol inhaled via Turbuhaler had an equal or better therapeutic ratio than salbutamol inhaled via pMDI.

In conclusion, salbutamol Turbuhaler was found to be more potent than salbutamol pMDI with regard to extrapulmonary effects in patients with moderate to severe asthma. The potency difference was numerically even more pronounced when considering the bronchodilating effect, suggesting that salbutamol Turbuhaler had a better therapeutic ratio than salbutamol pMDI. Neither inhaler caused any clinically significant adverse effects at cumulative doses of salbutamol up to 1600 µg.

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References

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