

Short communication

Efficacy of cumulative doses of salbutamol administered via Turbuhaler[®] or Diskhaler[®] in patients with reversible airway obstruction

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The study aimed to estimate the relative dose potency of salbutamol inhaled via Turbuhaler[®] and Diskhaler[®]. The 24 adult patients participating had chronic reversible airway obstruction. The study was of a double-blind, double-dummy, crossover, randomized design. Five doses of salbutamol Turbuhaler, 50, 50, 100, 200, and 400 µg, were given on one study day at intervals of 30 min. On another study day, five doses of salbutamol Diskhaler, 200, 200, 400, 800, and 1600 µg, were given with the same interval. The treatment days were separated by a washout period of at least 24 h. The inhalation technique was standardized and supervised. Efficacy variables were recorded before and after each study dose. The primary efficacy variable was forced expiratory volume in 1 s (FEV₁). When parallel and linear cumulative dose-response curves were statistically compared on a logarithmic scale, the dose potency of salbutamol Turbuhaler vs salbutamol Diskhaler was 1.99 (95% confidence interval 1.52–2.54). This study indicates that only half the dose of salbutamol is required via Turbuhaler as via Diskhaler for the same bronchodilating effect.

At present, most patients requiring inhaled salbutamol therapy administer the drug from a pressurized metered-dose inhaler (pMDI). The chlorofluorocarbons (CFCs) used as propellants and lubricants are harmful to the environment and are suspected of causing bronchoconstriction in some asthmatic individuals (1, 2).

Turbuhaler[®] is an inspiratory-flow-driven, multi-dose, dry-powder inhaler (DPI) (3). A single-dose study and a cumulative dose-response study have shown that half the dose of salbutamol given via Turbuhaler as via a pMDI has the same bronchodilating effect (4, 5). Earlier studies comparing Rotahaler[®], Diskhaler[®], and a pMDI have shown that the same dose or twice the salbutamol dose has to be administered from the Rotahaler and Diskhaler for the same bronchodilating effect as with the pMDI (6–9).

The primary objective of this study was to estimate the relative dose potency of salbutamol inhaled via Turbuhaler compared with Diskhaler when cumulative doses are given in patients with chronic reversible airway obstruction. The primary efficacy variable was the bronchodilating effect measured by FEV₁. A secondary objective was to evaluate systemic effects.

Material and methods

A total of 24 patients (16 men and eight women) with a mean age of 49 years (range 24–69) and a mean height of 176 cm (range 162–190) took part in the study. Two enrolled patients were excluded before randomization, one due to failure to fulfil the inclusion criteria and the other due to deterioration of asthma before treatment started.

The patients had reversible obstructive airway diseases characterized by a mean forced expiratory volume in 1 s (FEV₁) of 2.6 l (range 1.4–4.9), i.e., 75% of predicted normal value (range 45–103), and a mean reversibility of FEV₁ of 24% (range 16–42) 15 min after inhalation of from two to five doses of salbutamol (Ventoline® Diskhaler), 200 µg/dose. One patient inhaled five doses of salbutamol to reach above the 15% reversibility required for inclusion in the study. Another general inclusion criterion was that the reversible airway disease was to be of at least 6 months' duration, in a stable phase, and of a perennial character.

Two patients were current smokers, 14 were ex-smokers, and eight had never smoked. All patients were on treatment with inhaled short-acting β_2 -agonists, and 21 were being treated with inhaled glucocorticosteroids. All patients gave their signed, informed consent. The study was approved by the ethics committee of the University of Gothenburg and was carried out according to the principles of good clinical practice adopted by the European Community. The study was performed in accordance with the principles stated in the Declaration of Helsinki.

The study was of a two-way, double-blind, double-dummy, crossover, and randomized design, conducted at three centers in Sweden. The patients were randomized to receive cumulative inhaled doses of salbutamol given either via Turbuhaler or via Diskhaler on two separate study days. The starting time of the treatment was to be the same (± 30 min) for each patient on both study days.

At intervals of 30 min, five doses of salbutamol Turbuhaler, 50, 50, 100, 200, and 400 µg, or salbutamol Diskhaler, 200, 200, 400, 800, and 1600 µg, were given.

The total dose of salbutamol sulfate via Turbuhaler was 800 µg. The total dose of salbutamol sulfate via Diskhaler was 3200 µg, which is the recommended maximum dose for Ventoline (salbutamol) Diskhaler (10). The two treatment days were separated by a washout period of at least 24 h after the last intake of the study drug.

Intake of inhaled or nasal glucocorticosteroids, sodium cromoglycate, and antihistamines had to be kept constant for 30 days before enrolment and during the study. Maintenance immunotherapy had to be at a constant regimen. Nebulized or parenteral β_2 -agonists were withdrawn 12 h, and long-acting inhaled β_2 -agonists 5 days before each study day. Anticholinergics were withdrawn 48 h before, xanthines 24 h, oral β_2 -agonists 12 h, and slow-release and oral long-acting β_2 -agonists 36 h before each visit day. Oral or parenteral glucocorticosteroids and β -blockers were not allowed during the study.

The patients were instructed not to inhale short-acting β_2 -agonists, ingest caffeine, or perform any strenuous activity during the 8 h before each visit.

The inhalation technique of the study drug inhalers was performed in accordance with the manufacturers' recommendations (i.e., Turbuhaler: deeply and forcefully; Diskhaler: quickly and forcefully). The patients held their breath for 5–10 s after each inhalation. At each visit, the patients practiced inhalation techniques with placebo drug in both study inhalers under the supervision of a study nurse.

Two dose strengths of salbutamol Turbuhaler were used: salbutamol 50 and 100 µg, lactose q.s. The placebo Turbuhaler inhaler contained lactose and was identical in appearance to the active salbutamol Turbuhaler inhaler. Two dose strengths of salbutamol Diskhaler were used: salbutamol 200 and 400 µg, lactose q.s. The Diskhaler inhaler contained a disk of either salbutamol or placebo (containing lactose) identical in appearance.

On each study day, the patients inhaled from four inhalers, two Turbuhaler inhalers and two Diskhaler inhalers. The four inhalers were labeled with an inhalation order number. The inhalation doses were given according to the treatment plan at 30-min intervals. The patients were randomized to start to inhale via either Turbuhaler or Diskhaler.

Clinical and laboratory assessments were performed before and for 3 h after study drug administration. Baseline assessments on each study day were performed after a rest of at least 30 min. Blood pressure, electrocardiogram (ECG), and tremor were recorded, and blood sampling for determination of serum potassium and spirometry was performed before the first dose and 15–25 min after each dose, always in the same order as mentioned. Spirometry was conducted with a Vitalograph Alpha (Vitalograph Ltd, UK). FEV₁ and forced vital capacity (FVC) were recorded according to the recommendations by the American Thoracic Society (11). Baseline FEV₁ was not allowed to vary more than $\pm 15\%$ from FEV₁ recorded at the enrolment visit. If the variation was of $>15\%$, the patient was rescheduled for a new study day within 7 d. Patients were excluded if they did not fulfil the variation criteria at the second attempt.

A 12-lead automated resting ECG was taken at the first visit, and a bipolar, I, II, and III limb ECG was obtained during the study days. Tremor was recorded subjectively by the patients on a visual analog scale.

Objective tremor was recorded at two centers by a computerized one-plane accelerometer (12). Patients were asked about adverse events before inhalation of the first dose, 1 h after the last dose, and 24 h after inhalation of the first study dose on each study day.

Table 1. FEV₁ (l) measured 10 min before first administration of salbutamol Turbuhaler and 25 min after each dose (n=24)

	Cumulative dose administered (µg)					
	Before	Turbuhaler				
	0	50	100	200	400	800
Mean	2.60	3.00	3.09	3.14	3.22	3.30
% Increase*		15.4	18.8	20.8	23.9	26.9
SD	0.91	0.97	1.03	1.05	1.05	1.07

	Cumulative dose administered (µg)					
	Before	Diskhaler				
	0	200	400	800	1600	3200
Mean	2.60	3.04	3.16	3.26	3.31	3.39
% Increase*		16.9	21.5	25.4	27.3	30.4
SD	0.88	1.01	1.04	1.07	1.07	1.05

*From baseline.

Twenty-four (24) patients performed both study days and were included in the analysis. The primary efficacy variable was FEV₁. The log-transformed values for FEV₁ were analyzed with an ANOVA model with the factors patient, visit, inhaler, and dose number.

Serum potassium, tremor, blood pressure, and heart rate were analyzed using the same ANOVA model but without log transforming data.

The dose-response curves for salbutamol Turbuhaler and salbutamol Diskhaler were approximated as parallel linear curves on a logarithmic dose scale from which an estimate of the relative dose potency was obtained. Confidence intervals of the log of the dose potency were obtained with Fieller intervals. Sample size determination was based on a study comparing salbutamol Turbuhaler and salbutamol pMDI (5). Differences were considered significant at the $P < 0.05$ level.

Results

FEV₁

The mean baseline value for FEV₁ was 2.60 (±0.91) l before inhalation of salbutamol Turbuhaler and 2.60 (±0.88) l before salbutamol Diskhaler. Baseline FEV₁ values on both study days did not differ by more than ±15% from enrolment, except in one patient who had a difference of 21%. This patient was included in the analysis.

FEV₁ increased by cumulative doses of salbutamol irrespective of inhalation device; thus, a dose-related effect was demonstrated (Table 1). When this dose-effect relation was analyzed statistically, the estimate of the relative dose potency of Turbuhaler compared with Diskhaler was 1.99 with 95% confidence intervals of 1.52 and 2.54 (Fig. 1).

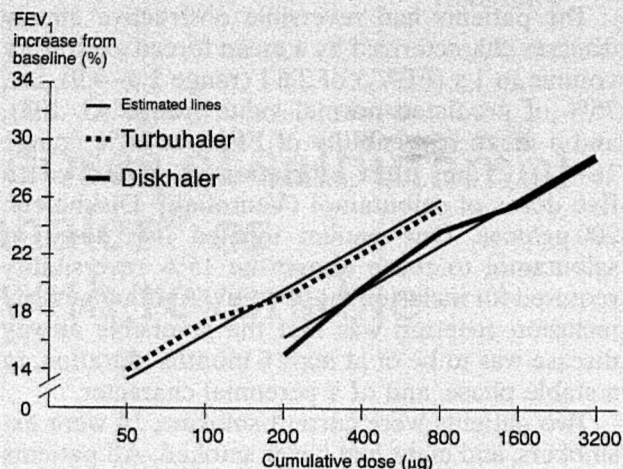
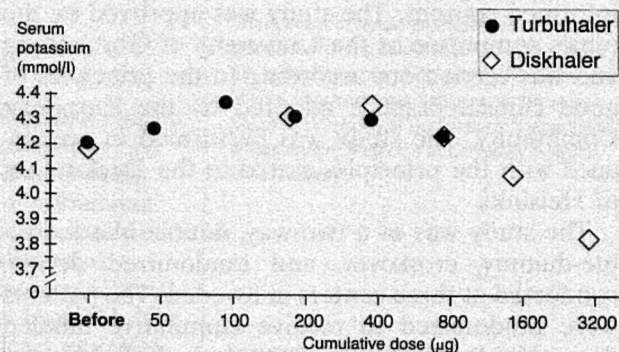
Fig. 1. FEV₁ increase (%) from baseline, 25 min after each dose.

Fig. 2. Serum potassium concentration (mmol/l) sampled before and 21 min after each dose and 1 h after last dose.

Serum potassium

There was a statistically significant ($P < 0.05$) decrease in serum potassium for the two highest doses of salbutamol Diskhaler compared with the two highest doses of salbutamol Turbuhaler (Fig. 2). The mean values of the two highest doses, 1600 and 3200 µg, of salbutamol Diskhaler were 4.08 and 3.8 mmol/l, respectively, with minimum values of 3.5 and 3.0 mmol/l, respectively. The mean values of the two highest doses, 400 and 800 µg, of salbutamol Turbuhaler were 4.3 and 4.2 mmol/l, respectively, with minimum values of 3.7 and 3.7 mmol/l, respectively. The mean serum potassium value after the last dose of salbutamol Turbuhaler, 800 µg, was the same as after 800 µg salbutamol Diskhaler and almost the same as the value before treatment.

Tremor

Statistically significant ($P < 0.05$) differences in objective and subjective tremor were seen for the two highest doses of salbutamol Diskhaler compared with the two highest doses of salbutamol Turbuhaler.

Blood pressure and heart rate

When the cardiovascular data were compared, the differences between the inhalers were small but statistically significant ($P=0.05$) for all three high doses for diastolic blood pressure and heart rate, and after the highest dose only for systolic blood pressure, thus showing a pronounced systemic effect with salbutamol Diskhaler in comparison with salbutamol Turbuhaler.

No unexpected adverse events were seen for either of the two inhalers.

Discussion

The development of new inhalation devices raises the question of their relative efficacy. Earlier studies have shown that the same bronchodilating effect can be achieved when half of the dose of salbutamol given via conventional pMDI is given via Turbuhaler (4, 5). Studies comparing salbutamol Diskhaler and salbutamol Rotahaler with salbutamol pMDI have shown that an equal dose or twice the dose has to be administered from Diskhaler and Rotahaler as with a pMDI for the same bronchodilating effect (6–9). These results indicated a ratio of 4:1 for the relative bronchodilating potency of Turbuhaler compared with that of Diskhaler, and this was also our hypothesis when we designed the present study. In most countries, dose recommendations suggest that twice the dose is needed from the Rotahaler and Diskhaler as from the pMDI.

Several studies have shown that Turbuhaler deposits a higher fraction of the dose in the lung than both pMDIs and other DPIs (14–17), but there are no comparative studies for lung deposition of salbutamol from Diskhaler and Turbuhaler. Firm conclusions regarding the efficacy of different inhalers can be drawn only from direct comparisons, so the aim of our study was to estimate the dose potency of salbutamol inhaled via Turbuhaler and Diskhaler.

As 0.2 mg was the lowest dose of salbutamol in Diskhaler available on the market, this had to be the lowest dose from Diskhaler in the study, compared with a fourfold lower dose of salbutamol from Turbuhaler.

For estimation of what dose of salbutamol from Turbuhaler corresponds to a given dose from Diskhaler, parallel lines were fitted to mean values as a function of dose on a log-scale (Fig. 1). On the basis of FEV₁, about half a given dose via Turbuhaler gives about the same effect as the full dose via Diskhaler.

There were effects on serum potassium, blood pressure, tremor, and heart rate with the highest doses from salbutamol Diskhaler, but not with the highest doses from salbutamol Turbuhaler. Since we did not observe any significant systemic effects

with salbutamol Turbuhaler, it was impossible to establish any true potency ratio of Turbuhaler to Diskhaler for systemic effects.

In summary, this study indicates that only half the dose of salbutamol is required via Turbuhaler as with Diskhaler for the same bronchodilating effect.

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