Differences in bronchodilating potency of salbutamol in Turbuhaler® as compared with a pressurized metered-dose inhaler formulation in patients with reversible airway obstruction


ABSTRACT: Two studies are presented, with the aim of establishing the dose potency ratio for salbutamol given via Turbuhaler® and via a pressurized metered-dose inhaler (pMDI). Both studies were of a double-blind, randomized design. Outpatients with mild-to-moderate chronic reversible airway obstruction were given single doses of salbutamol administered via Turbuhaler and via pMDI. Efficacy and safety variables were measured before and during 6 h after each dose.

The first study was a four-way crossover study including 12 patients. The salbutamol doses given were: 50, 100 and 200 μg via Turbuhaler and 2×100 μg via pMDI (Ventolin®). The study showed that 2×100 μg of salbutamol inhaled via Turbuhaler is more potent than 2×100 μg salbutamol inhaled via a pMDI, and that 100 μg salbutamol via Turbuhaler is at least as potent as 2×100 μg salbutamol inhaled via a pMDI.

The second study including 50 patients was a placebo-controlled five-way crossover, study. Two doses of salbutamol via Turbuhaler, 50 and 2×100 μg, and via pMDI, 100 and 2×200 μg, were given. There was a dose-dependent response in forced expiratory volume in one second (FEV1) for both inhalers. Adjusted for differences in baseline FEV1 values, the estimated relative dose potency for Turbuhaler versus pMDI was 1.98:1 (95% confidence interval 1.2–3.2).

These studies showed that the same bronchodilating effect can be achieved when half the dose of salbutamol given via a conventional pressurized metered-dose inhaler is given via Turbuhaler.


The pressurized metered-dose inhaler (pMDI) is the most widely used device for administering inhaled salbutamol, although dry-powder formulations dominate in a few countries. A substantial number of patients do not use their pMDIs optimally, the main problem being difficulties with co-ordination between the actuation of the dose and inhalation [1]. In addition, the chlorofluorocarbons (CFCs) used as propellants and lubricants are suspected of causing bronchoconstriction in some asthmatic individuals [2, 3]. Furthermore, CFC propellants are harmful to the environment. Restrictions on the use of pMDIs are currently being implemented in several countries.

To overcome co-ordination problems and other drawbacks with pMDIs, inspiratory flow-driven, dry-powder inhalers (DPIs), e.g. Rotahaler® and Diskhaler® (both GlaxoWellcome Operations, Greenford, Middlesex, UK), have been developed. Turbuhaler® (Astra Pharmaceutical Production AB, Södertälje, Sweden) is an inspiratory flow-driven multidose DPI [4]. Studies have shown that Turbuhaler deposits a higher fraction of the dose in the lung than do pMDIs or the earlier DPIs [5–9]. Results from a cumulative dose-response study indicated that salbutamol inhaled via Turbuhaler gives better bronchodilating effect than salbutamol inhaled via a pMDI [10].

The aim of the two single-dose studies presented here was to establish the dose potency ratio for salbutamol given via Turbuhaler compared with via a pMDI. In the first study, the lower dose of salbutamol Turbuhaler, 50 μg, was used for the first time. The relationship between Turbuhaler and pMDI was evaluated using three doses of salbutamol from Turbuhaler and one dose from pMDI. The second study was designed to be a single-dose study at two dose levels, that would show dose response for the bronchodilating effect of salbutamol when administered via either inhaler.
Materials and methods

Patients

Study No. 1. Twelve patients, seven males and five females, mean age 50 yrs (range: 24–68) and mean height 175 cm (range: 161–190) took part in the study. All patients had asthma with an average duration of 10 yrs (range: 3–24). Three patients were current smokers, six former smokers and three had never smoked. The patients had a mean basal forced expiratory volume in one second (FEV1), calculated as the mean of two consecutive measurements, of 2.43 L (range: 1.42–4.28), i.e. 71% (range: 46–109) of predicted normal value, and a mean reversibility of FEV1 of 24% (range: 15–40), 15 min after inhalation of two puffs of salbutamol pMDI (Ventolin®; Glaxo Wellcome Operations) 100 µg puff⁻¹.

Study No. 2. Fifty patients, 27 males and 23 females, mean age 46 yrs (range: 18–70) and mean height 173 cm (range: 153–190) took part in the study. All patients had asthma with an average duration of 22 yrs (range: 4–56). Ten patients were current smokers, 18 former smokers and 22 had never smoked. The patients’ asthma was characterized by a mean basal FEV1 of 2.22 L (range: 0.87–4.42), i.e. 65% pred (range: 35–102), and a mean reversibility of FEV1 of 24% (range: 15–62), 15 min after inhalation of two puffs of salbutamol pMDI (Ventolin) 100 µg puff⁻¹.

All patients gave their signed informed consent. The studies were approved by the Ethics Committees of the universities of Göteborg and Malmö (in the second study only). They were also approved by the Swedish Medical Products Agency and were carried out according to the principles of Good Clinical Practice adopted by the European Community. The studies were performed in accordance with principles stated in the Declaration of Helsinki.

Methods

The technique used for inhalation of study drugs was standardized in accordance with the manufacturers’ recommendations. The patients were trained in the correct usage of both inhalers. Training was repeated on the morning of each study day and inhalations were supervised by trained technicians or nurses. Turbuhaler and pMDI were connected one by one in series to a Vitalograph MDI modified Compact spirometer (Vitalograph Ltd, Ennis Co., Clare, Republic of Ireland). By using this technique, peak inspiratory flow (PIF) could be obtained. When patients inhaled salbutamol, a PIF of at least 50 L·min⁻¹ through Turbuhaler, and approximately 30 L·min⁻¹ through pMDI was aimed for. Blindness was obtained with a double-dummy technique using placebo for both pMDI and Turbuhaler, which meant that four inhalations in the first study and six inhalations in the second study, had to be performed on each study day. The order in which pMDI and Turbuhaler inhalations were performed was randomized. Active treatment was always given with the first or second inhalation.

Clinical and laboratory assessments were performed before and during 6 h after study drug administration. Baseline assessments on each study day were performed following a rest of at least 30 min duration. Lung function measurements, FEV1 and forced vital capacity (FVC), were conducted using a Vitalograph Compact in the first study and a Vitalograph Alpha in the second study (Vitalograph Ltd) and performed according to recommendations by the American Thoracic Society. On each of the study days, baseline FEV1 was not allowed to vary more than ±15% from FEV1 at the enrollment visit. If it did vary more, the patient was rescheduled for a new study day (baseline measurement) after 1–7 days. Postdose recordings of FEV1 and FVC were performed at 20, 40, 60, 90, 120, 180 (the second study only), 240, 300 (the second study only) and 360 min. Patients were asked for adverse events pre- and at 360 min postdose on each study day.

In the second study, pulse and blood pressure measurements were performed predose and at 20, 40, 60, 90, 120, 180, 240, 300 and 360 min postdose. A 12-lead electrocardiogram (ECG) and a blood sample for determination of serum potassium concentration were taken predose and at 90 min postdose. The serum potassium concentration was analysed using a direct ion-selective electrode. The patients were asked to grade tremor following a four-point scale predose and at 20 min postdose. Patient data were entered directly into a computer at the investigational site using the Remote Study Monitoring (RSM) system, a data entry system from Onsite Systems Inc (Augsburg, Germany).

Data analysis

All patients who had performed more than one study day were included in the analysis. The key pharmacodynamic parameter for lung function measurement data was the average effect (Eav), defined as Area Under the Curve (AUC) of effect versus time divided by observational time (~6 h). The primary lung function measurement was FEV1. The log-transformed values of
Eav for FEV1 were analysed with an analysis of variance (ANOVA) model with factors patient, visit and treatment. In the second study, relative dose potency of Turbuhaler versus pMDI and its 95% confidence interval were also estimated. This was done by fitting parallel lines to the four mean values of log Eav. Mean values for FEV1 are antilogs of those obtained from the ANOVA analysis, and thus adjusted geometric mean values.

In the second study, pulse, blood pressure, the 90 min value of serum potassium and cardiac frequency from the ECG recording were analysed with the same ANOVA model, but without log transformation.

With 12 patients in the first study, a pairwise comparison of two treatments was assumed to give a significant result (p<0.05) in 80% of trials provided that the actual mean difference was 90% of the standard deviation of differences. The choice of 40 evaluable patients in the second study was based on recommendations by the US Food and Drug Administration (FDA) [11]. Differences were considered significant at the p<0.05 level.

Results

Study No. 1

Inhalation technique. Mean PIFs through Turbuhaler were 60 (range: 44–74), 62 (range: 51–72) and 63 (range: 46–78) L·min⁻¹, when inhaling 50, 100 and 2×100 µg of salbutamol, respectively. When pMDI was studied, mean PIF was 39 (range: 19–71) L·min⁻¹.

FEV1. Mean (±sd) basal value for FEV1 was 2.40 (±1.03), 2.51 (±0.97) and 2.46 (±1.01) L, respectively, on the study days with 50, 100 and 2×100 µg of salbutamol inhaled via Turbuhaler, and 2.40 (±0.99) L with 2×100 µg salbutamol inhaled via pMDI. Corresponding geometric means were 2.22, 2.37, 2.29 and 2.15, respectively.

The FEV1 mean value curves are shown in figure 1. After correcting for baseline differences (Turbuhaler 100 µg), the FEV1, Eav values, did not differ significantly between salbutamol Turbuhaler 50 or 100 µg and salbutamol pMDI 2×100 µg (table 1). The highest dose inhaled via Turbuhaler, 2×100 µg, produced a statistically significantly higher response than did 2×100 µg inhaled via the pMDI (p<0.01).

Other variables. No unexpected adverse events were seen with either of the treatments.

Study No. 2

Inhalation technique. The recorded mean PIF through Turbuhaler was 67 L·min⁻¹ (range: 40–124) for the 50 µg dose and 66 L·min⁻¹ (range: 47–97) and 66 L·min⁻¹ (range: 50–100) for the 2×100 µg dose. The recorded mean PIF through pMDI was 41 L·min⁻¹ (range: 10–99) for the 100 µg dose and 53 L·min⁻¹ (range: 25–114) and 48 L·min⁻¹ (range: 12–90) for the 2×200 µg dose.

Each patient’s sd for PIF through Turbuhaler and pMDI was calculated for inhalations containing active substance. The mean value of the sds for PIF was 6.5 L·min⁻¹ for Turbuhaler and 11.9 L·min⁻¹ for pMDI. This difference was statistically significant (p=0.0002).

FEV1. Mean basal value for FEV1 was 2.27 (±0.96) L before inhalation of placebo, 2.28 (±0.92) L before Turbuhaler 50 µg, 2.28 (±0.95) L before Turbuhaler 2×100 µg, 2.22 (±0.91) L before pMDI 100 µg and 2.23 (±0.93) L before pMDI 2×200 µg. Corresponding geometric means were 2.06, 2.09, 2.06 and 2.06, respectively.

The FEV1 mean value curves for the active treatments came in two groups, a low and a high dose group (fig. 2). The mean value for Turbuhaler 50 µg was slightly higher than for pMDI 100 µg, but without any significant difference. However, it should be noted that the predose value was somewhat higher for Turbuhaler 50 µg than for the other doses.

An analysis of the FEV1, Eav values showed that all treatments gave a significantly better effect compared with placebo (p<0.0001) (table 2). The high dose had a better effect than the low dose for both Turbuhaler (p<0.02) and pMDI (p<0.0001). No difference between Turbuhaler and pMDI could be detected, either for the low doses or for the high doses. The coefficient of variation for FEV1, Eav was 5.7%. Relative dose potency of Turbuhaler versus pMDI was estimated adjusting for differences in baseline values. The estimated relative dose potency was 1.98:1 with 95% confidence interval

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95% CI: 95% confidence interval. +: adjusted for the higher baseline value for Turbuhaler 100 µg; ns: nonsignificant; TBH: Turbuhaler; pMDI: pressurized metered-dose inhaler; FEV1: forced expiratory volume in one second.

Fig. 1. – Forced expiratory volume in one second (FEV1) mean value curves, study No. 1. –––: salbutamol Turbuhaler (TBH) 50 µg; ––––: salbutamol TBH 100 µg; -•-•-•: salbutamol TBH 2×100 µg; -: salbutamol pressurized metered-dose inhaler (pMDI) 2×100 µg.
The ideal comparison of dose-response curves is performed on the steep part of the curve. A problem is that pathological ECG findings. Mean and maximum changes from baseline to 90 min after dose are presented in Table 4. There were no other relevant pathological ECG findings.

No unexpected adverse events were seen with either of the treatments.

**Discussion**

The present studies showed an approximate mean 2:1 dose potency ratio for salbutamol given via Turbuhaler as compared with salbutamol given via pMDI.

**For definitions, see legend to figure 1.**

![Fig. 2. – FEV1 mean value curves, study no. 2.](image)

![Fig. 3. – Relative dose potency of salbutamol administered via Turbuhaler and via pMDI, study No. 2. Eav: average effect; ln: natural logarithm. For further definitions, see legend to figure 1.](image)
with the pMDI [10], three doses were given with Turbuhaler and one with pMDI.

In the second study, the lowest possible dose with each equipment was given together with a fourfold higher dose. These doses showed a dose-response relationship for bronchodilation of salbutamol inhaled via either of the inhalers.

In the second study, the highest dose of each equipment may be at the top of the dose-response curve, in which case these mean values can not be used as an argument for the 1.98:1 ratio. However, the similar mean values on the lower part of the curve, i.e. 50 µg salbutamol via Turbuhaler and 100 µg via pMDI favour a 1.98:1 ratio. The 95% confidence interval for this ratio was 1.2–3.2.

Clearly, an effective inhalation technique is mandatory for optimum delivery of inhaled study drug. Specific training sessions were therefore undertaken in these studies. Inhalations were supervised and actual airflow was monitored. The mean PIF through Turbuhaler was 1.98:1 ratio. The 95% confidence interval for this ratio was 1.2–3.2.

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References