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

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Differences in bronchodilating potency of salbutamol in Turbuhaler® as compared with a pressurized metered-dose inhaler formulation in patients with reversible airway obstruction. C-G. Löfdahl, L. Andersson, E. Bondesson, L-G. Carlsson, K. Friberg, J. Hedner, Y. Hörnblad, P. Jemsby, A. Källén, A. Ullman, S. Werner, N. Svedmyr. ©ERS Journals Ltd 1997.

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 2×100 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 (FEV_1) for both inhalers. Adjusted for differences in baseline FEV_1 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.

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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 Glaxo Wellcome Operations, Greenford, Middlesex, UK), have been developed. Turbuhaler® (Astra Pharmaceutical Production AB, Södertalje, 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 (FEV_1), 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 FEV_1 of 24% (range: 15–40), 15 min after inhalation of two puffs of salbutamol pMDI (Ventolin®; Glaxo Wellcome Operations) 100 $\mu g \cdot puff^{-1}$.

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 FEV_1 of 2.22 L (range: 0.87–4.42), *i.e.* 65% pred (range: 35–102), and a mean reversibility of FEV_1 of 24% (range: 15–62), 15 min after inhalation of two puffs of salbutamol pMDI (Ventolin) 100 $\mu g \cdot puff^{-1}$.

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.

Study design

The studies were of a randomized, single-dose, crossover and double-blind design. The patients were examined at the same time of day (±30 min) on nonconsecutive days on which they received a single dose of salbutamol *via* Turbuhaler, *via* a pMDI, or placebo (the second study only). In the first study, the salbutamol Turbuhaler doses were 50, 100 or 2×100 μg and the pMDI dose was 2×100 μg. In the second study, the Turbuhaler doses were 50 or 2×100 μg and the pMDI doses were 100 or 2×200 μg salbutamol. Inhaled and nasal glucocorticosteroids, cromolyn sodium, maintenance immunotherapy and acetylcysteine were allowed throughout the study if kept at a constant dosage. Oral and long-acting inhaled β_2-agonists, xanthines and short-acting antihistamines were allowed during the study but were prohibited and washed out before each study day. Xanthines were withdrawn 24 h, oral controlled release β_2-agonists 36 h, and long-acting inhaled β_2-agonists 48 h (24 h in the first study) prior to each study day. Patients were instructed not to inhale short-acting β_2-agonists, ingest caffeine or perform any strenuous activities within 8 h before performance of study procedures.

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 $L \cdot min^{-1}$ through Turbuhaler, and approximately 30 $L \cdot min^{-1}$ 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, FEV_1 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 FEV_1 was not allowed to vary more than ±15% from FEV_1 at the enrolment visit. If it did vary more, the patient was rescheduled for a new study day (baseline measurement) after 1–7 days. Postdose recordings of FEV_1 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 (E_{av}), defined as Area Under the Curve (AUC) of effect *versus* time divided by observational time (~6 h). The primary lung function measurement was FEV_1. The log-transformed values of

*E*av 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 *E*av. 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, *E*av 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 ($p<0.01$).

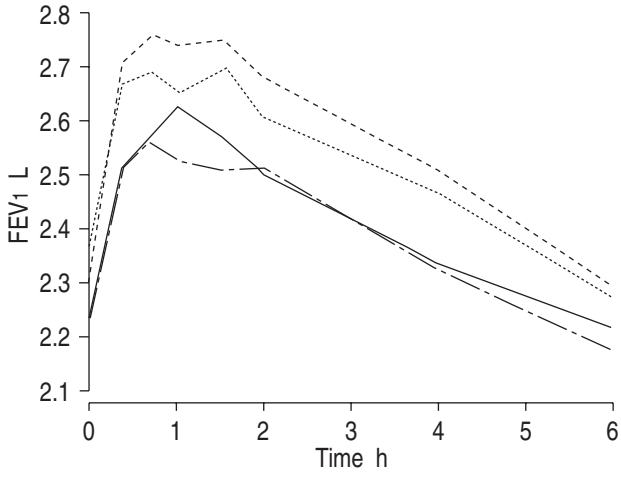

Fig. 1. – Forced expiratory volume in one second (FEV1) mean value curves, study No. 1. —·—: salbutamol Turbuhaler (TBH) 50 μg; ·····: salbutamol TBH 100 μg; - - - - -: salbutamol TBH 2×100 μg; ——: salbutamol pressurized metered-dose inhaler (pMDI) 2×100 μg.

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, 2.05 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, *E*av 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, *E*av 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

Table 1. – Average effect (FEV1) comparison between treatments, study No. 1

Comparison	Ratio %	95% CI	p-value
TBH 50 μg/pMDI 2×100 μg	99.2	95.2–103.3	NS
TBH 100 μg/pMDI 2×100 μg	104.7	100.5–109.0	0.03
TBH 2×100 μg/pMDI 2×100 μg	106.4	102.1–110.9	0.004
Baseline adjusted TBH 100 μg/pMDI 2×100 μg+	101.4	97.6–105.3	NS

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.

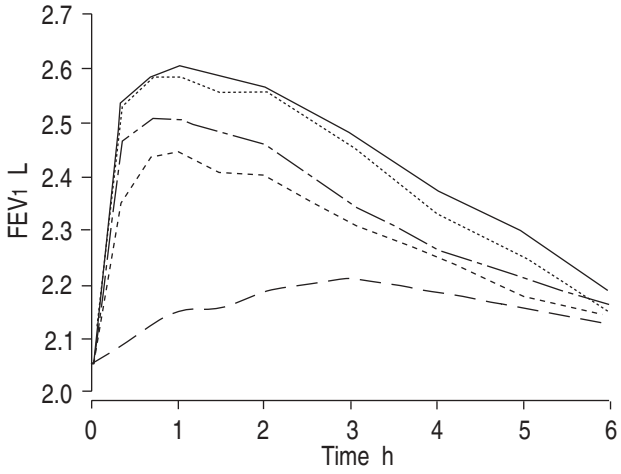

Fig. 2. – FEV1 mean value curves, study no. 2. — - - — : salbutamol TBH 50 μg; ····· : salbutamol TBH 2×100 μg; - - - - - : salbutamol pMDI 100 μg; ——— : salbutamol pMDI 2×200 μg; — — : placebo. For definitions, see legend to figure 1.

Table 2. – Average effect (FEV_1) comparison between treatments, study No. 2

Comparison	Ratio %	95% CI	p-value
pMDI 100 μg/placebo	106.2	103.8–108.6	<0.0001
TBH 50 μg/pMDI 100 μg	102.0	99.7–104.3	NS
TBH 2×100 μg/pMDI 2×200 μg	99.0	96.8–101.3	NS
TBH 2×100 μg/TBH 50 μg	102.8	100.5–105.2	0.02
pMDI 2×200 μg/pMDI 100 μg	105.9	103.6–108.3	<0.0001
Baseline adjusted TBH 50 μg/pMDI 100 μg+	101.0	98.9–103.1	NS

+: adjusted for the higher baseline value for Turbuhaler 50 μg. For definitions see legend to table 1.

1.2–3.2 (fig. 3). Without the adjustment, the potency ratio was 2.36:1.

The number of patients responding with at least a 15% increase in FEV_1 at 40 min after dosing was 3, 32, 44, 30 and 44 for placebo, Turbuhaler 50 μg, Turbuhaler 2×100 μg, pMDI 100 μg and pMDI 2×200 μg, respectively. Forty minutes was judged to be a relevant time-point by which a short-acting β_2-agonist should have executed a substantial improvement in lung function.

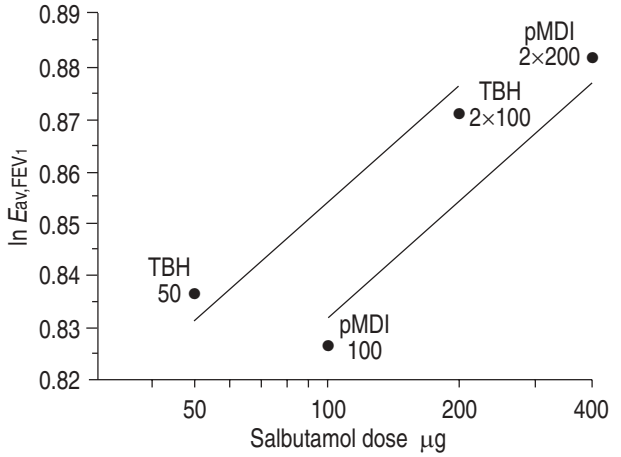

Fig. 3. – Relative dose potency of salbutamol administered *via* Turbuhaler and *via* pMDI, study No. 2. E_{av}: average effect; ln: natural logarithm. For further definitions, see legend to figure 1.

Table 3. – Mean and minimum serum potassium values at baseline and 90 min after dose, study No. 2

Treatment	Serum potassium mmol·L^{-1}			
	Mean		Minimum	
	Baseline	90 min	Baseline	90 min
Placebo	4.33	4.57	3.8	4.0
TBH 50 μg	4.38	4.53	3.9	3.7
TBH 2×100 μg	4.36	4.48	3.8	3.9
pMDI 100 μg	4.41	4.54	3.9	3.8
pMDI 2×200 μg	4.34	4.46	3.9	4.0

For definitions, see legend to table 1.

Table 4. – Mean and maximum change in cardiac frequency from baseline to 90 min after dose, study No. 2

Treatment	Cardiac frequency mean change bpm	Maximum change bpm
Placebo	-4	35
TBH 50 μg	-6	7
TBH 2×100 μg	-4	1
pMDI 100 μg	-6	7
pMDI 2×200 μg	-6	8

bpm: beats per minute. For further definitions, see legend to table 1.

Serum Potassium. Potassium was little affected by the treatments. In comparison with placebo, the only statistically significant effect was seen with the highest pMDI dose (p=0.01). Arithmetic mean and minimum values at baseline and at 90 min after dose are presented in table 3.

Tremor. A total of 14 positive scores (score 1=mild) was given by eight different patients. Only on eight of these 14 occasions was tremor reported after dose administration, four occasions concerned placebo treatment, one Turbuhaler 50 μg, one Turbuhaler 2×100 μg and two pMDI 2×200 μg.

Other safety variables. No treatment effect could be demonstrated on E_{av} for pulse and blood pressure or on the mean change in cardiac frequency counted from ECG. Mean and maximum changes from baseline to 90 min after dose in cardiac frequency and blood pressure 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.

The ideal comparison of dose-response curves is performed on the steep part of the curve. A problem is that the doses given with the currently used β_2-agonist inhalation devices often give an almost maximum effect when given as single doses.

In the first study, which was performed after a cumulative dose-response study indicating a higher dose potency ratio for salbutamol Turbuhaler in comparison

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 about 60 $L \cdot min^{-1}$, which represents a typical inhalation flow through Turbuhaler for asthmatic patients [12, 13]. At a lower inhalation flow of around 30 $L \cdot min^{-1}$, the fraction delivered to the patient is decreased, but it has been shown that some efficacy is still maintained [14, 15]. In the second study, when PIF data was analysed, it was seen that patients had some difficulty in performing a slow inhalation, which is optimal with the pMDI [16]; the mean inspiratory flow was 47 $L \cdot min^{-1}$. This is also indicated in the same study by the PIF values being more widely spread for inhalation *via* pMDI than *via* Turbuhaler.

The 1.98:1 dose potency ratio is well in accordance with lung deposition data from studies performed with other substances. The ratio for terbutaline administered *via* Turbuhaler and *via* pMDI was 2:1 both for bronchodilating potency and lung deposition [8]. For budesonide, the lung deposition was also twice as high with Turbuhaler than with pMDI [7]. Data also indicate that patients may be controlled by half the dose when switched from pMDI to Turbuhaler formulations of budesonide [17].

The present studies did not show any important sign of systemic drug effect and there was no difference between inhalers. This is well in accordance with the previous cumulative dose-response study (maximum total dose 1600 μg) which did not show any difference in side-effects when comparing salbutamol Turbuhaler and pMDI at equal bronchodilating effect [10].

In conclusion, 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.

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