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International Journal of Pharmaceutics 180 (1999) 169–175

international journal of pharmaceutics

A comparison of the bronchodilatory effect of 50 and 100 μg salbutamol via Turbuhaler® and 100 μg salbutamol via pressurized metered dose inhaler in children with stable asthma

Hassan Razzouk [a], Lopes dos Santos [b], Jacques Giudicelli [c], Mário Queirós [d], Maria de Lurdes Chieira [e], Ana Castro [f], César Ramos [g], Christer Lindbladh [h,*]

[a] *Centre les Acacias, Briancon, France*
[b] *Centro Hospitalar de Vila Nova de Gaia, Portugal*
[c] *Centre Bellevue, Dieulefit, France*
[d] *Hospital de São João, Porto, Portugal*
[e] *Hospital Pediatrico de Coimbra, Coimbra, Portugal*
[f] *Hospital Distrital de Faro, Faro, Portugal*
[g] *Hospital de Santa Maria, Lisbon, Portugal*
[h] *Astra Draco AB, PO Box 34, 221-34 Lund, Sweden*

Received 14 August 1998; received in revised form 13 November 1998; accepted 4 December 1998

Abstract

Aim: The aim of the study was to compare the efficacy of single doses of salbutamol Turbuhaler® (50 and 100 μg), salbutamol pressurized metered dose inhaler (pMDI) (100 μg) and placebo in children with stable chronic reversible airway obstruction. Primary efficacy variable (FEV_1-av) was calculated as the area under the curve of forced expiratory volume in one second (FEV_1) (AUC, 0–4 h) and divided by the observed time. *Design:* The study was of a randomized, single-dose, crossover and double-blind design. Seven centres participated. FEV_1 was measured pre-dose and at 15 min, 0.5, 1, 1.5, 2, 3 and 4 h post study dose. *Patients:* Forty asthmatic children (9 girls) with a mean age of 9 years (range: 6–12), mean FEV_1 of 1.6 l (range: 0.9–2.4) and a mean FEV_1 in percentage of predicted normal value of 80% (range: 61–109) were randomized into the study. The mean reversibility 30 min after inhaling 2×100 μg salbutamol from pMDI was 20% (range: 9–45) or 15% (range: 8–27) in percentage of predicted normal value. *Results:* The mean FEV_1-av was 1.63 l for placebo, 1.71 l for 50 μg salbutamol Turbuhaler, 1.76 l for 100 μg salbutamol Turbuhaler and 1.76 for 100 μg salbutamol pMDI. Corresponding values for maximum FEV_1 were 1.76, 1.85, 1.87 and 1.87 l, respectively. There were no statistically significant differences between the active treatments in FEV_1-av or maximum FEV_1. All active treatments were significantly better than placebo. *Conclusion:* No significant differences in bronchodilating effect between 50, 100 μg salbutamol Turbuhaler and 100 μg salbutamol pMDI in

* Corresponding author. Tel.: +46-46-336000; fax: +46-46-336666.

PII: S0378-5173(98)00399-8

children, aged 6–12 years, with stable asthma could be demonstrated. All active treatments were significantly better than placebo.

Keywords: Children; Pressurized metered dose inhaler (pMDI); Salbutamol; Turbuhaler

1. Introduction

Salbutamol is the most widely used β_2-agonist in the world. It has been safely given to adults and children for approximately 30 years and today it is available in several presentations, the most common being pressurized metered dose inhaler (pMDI).

Besides the general problem with Freon® and lubricants in pMDIs, a major problem for children is the difficulty to coordinate inspiration with actuation of the aerosol. These problems can be avoided by using Turbuhaler®, an inspiratory flow driven multi-dose dry powder inhaler which does not require any propellants. Previous studies and clinical practice with terbutaline Turbuhaler have shown that Turbuhaler can be used by children from the age of 3 to 4 years (Ahlström et al., 1989; Goren et al., 1994). It has also been demonstrated that a majority of school children, 6–18 years, prefer to use Turbuhaler rather than pMDI (Hultquist et al., 1989).

The efficacy and safety of single doses (Löfdahl et al., 1997) and regular use (Chapman et al., 1994) of salbutamol Turbuhaler and salbutamol pMDI have been compared in recent studies on adult patients with stable asthma. The result showed that half the dose of salbutamol via Turbuhaler compared to pMDI was enough to control the disease. Turbuhaler has also been shown to give a higher pulmonary deposition of terbutaline, compared with pMDI, which was also reflected in pulmonary effects (Borgström et al., 1996). To date, no clinical study have compared the efficacy of commercially available doses of salbutamol Turbuhaler and salbutamol pMDI in children. The aim of the present study was to make a placebo-controlled comparison of the efficacy of single doses of salbutamol Turbuhaler (50 and 100 μg) with salbutamol pMDI (100 μg), in children with chronic reversible asthma.

Spacers are often recommended when the patient has problems with coordination of inhalation and actuation of the pMDI. However, in comparative studies of drugs and dosages, it is important to note that the amount of drug delivered to the patient, using a spacer, varies greatly depending on the choice of spacer (Barry and O'Callaghan, 1994, 1996). Therefore, the pMDI was used without a spacer when the relationship between Turbuhaler and pMDI was studied.

2. Patients and methods

2.1. Patients

Forty out-patients (9 girls) were randomized into the study. All children had diagnosed asthma, with a mean duration of 7 years (range: 2–12). Baseline forced expiratory volume in one second (FEV_1) was to be $\geq 60\%$ of predicted normal value, according to Polgar's predicted normal value (Polgar and Promadhat, 1971). FEV_1 reversibility compared to baseline should be $\geq 15\%$ or an increase in percentage of predicted normal FEV_1 of $\geq 9\%$, 30 min after inhaling 2×100 μg salbutamol from pMDI, without spacer. The children had to have a history of perennial symptoms and be willing and able to utilize Turbuhaler and pMDI.

Before each study day inhaled short-acting β_2-agonists were withdrawn 8 h prior to the visit; long-acting β_2-agonists, 72 h; oral β_2-agonists, 12 h; long-acting oral β_2-agonists, 48 h; xanthines, 48 h; anticholinergics, 12 h; oral and parenteral corticosteroids, 1 month and astemizole 6 weeks prior to visit. Patients using inhaled steroids, sodium cromoglycate and ketotifen continued to use these at a constant dose.

The study was performed according to the principles stated in the Declaration of Helsinki. Signed informed consent from the parent/legal

guardian and witnessed verbal informed assent from the child was obtained prior to conducting any study-related procedures. The study was approved by the ethics committees in France and Portugal.

2.2. Study design

The study was of a four-way cross-over, single-dose, randomized and double-blind design, and performed at two centers in France and five centers in Portugal. The patients visited the clinic five times. Reversibility test was performed on the enrollment day. The four following study days were separated by at least 20 h and maximally 14 days.

The children arrived at the clinic between 07:00 and 10:00 h. After registration of pulse, blood pressure and baseline FEV_1 the children practiced the inhalation technique with an empty Turbuhaler or a placebo pMDI, connected to a Vitalograph MDI modified Compact spirometer (Vitalograpg, UK) (measurement of peak inspiratory flow, PIF). FEV_1 baseline was not to vary more than $\pm 15\%$ from the value obtained at visit 1. Each child received a single dose of either 50 or 100 μg of salbutamol Turbuhaler, 100 μg of salbutamol pMDI or placebo (double-dummy technique) on each study day. Assessment of FEV_1 was performed pre-dose and 15, 30 min, 1, 1.5, 2, 3 and 4 h post-dose.

Salbutamol Turbuhaler, 50 and 100 μg/dose, containing 75% lactose, and placebo for salbutamol Turbuhaler, containing lactose, were manufactured by Astra Draco AB, Sweden. Salbutamol pMDI, 100 μg/dose, was manufactured by Glaxo-Wellcome, UK. Placebo for salbutamol pMDI was manufactured by 3M Health Care Limited, UK

2.3. Statistical calculations

The number of patients was estimated assuming a coefficient of variation of 7% for the primary variable. The primary variable was calculated as the area under the curve of FEV_1 (AUC, 0–4 h) and divided with the observed time. This variable represents an average FEV_1 during the period (FEV_1-av). Using a pairwise comparison of 40 patients, this results in an 80% chance of demonstrating a treatment difference of at least 3%, calculated as the ration between the different FEV_1-av values. Maximum FEV_1 was analysed in addition to FEV_1-av. The efficacy variables were analysed using a multiplicative ANOVA model in combination with a two-sided test at the 5% level.

3. Results

A total of 40 patients were randomized in the study. Thirty-eight patients fulfilled the reversibility criteria based on a 9% increase in percentage of predicted FEV_1 and 28 patients fulfilled the criteria of at least a 15% increase in FEV_1 from baseline. Thirty-seven patients received 50 μg salbutamol via Turbuhaler, 37 patients 100 μg salbutamol via Turbuhaler, 38 patients 100 μg salbutamol via pMDI and 40 patients placebo. Thirty-seven children were included in the statistical analysis of the efficacy variable. Of these, one patient had been incorrectly included and had a reversibility in FEV_1 of 9 and 8% in predicted normal value. Demographic data of the children is shown in Table 1.

Table 1
Demographic data of the randomized patients[a]

	Mean	Range
Age (years)	9	6–12
Weight (kg)	34	21–52
Height (cm)	137	113–162
PEF (l/min)	219	102–324
FVC (l)	2.2	1.2–3.5
FEV_1 (l)	1.6	0.9–2.4
FEV_1 (% pred.)	80	61–109
FEV_1 rev (%)	20	9–45
FEV_1 rev (% pred.)	15	8–27

[a] PEF, peak expiratory flow; FVC, forced vital capacity; FEV_1 (% pred.), FEV_1 in percentages of predicted normal value; FEV_1 rev (%), reversibility in FEV_1; FEV_1 rev (% pred), reversibility in percentage of predicted normal FEV_1.

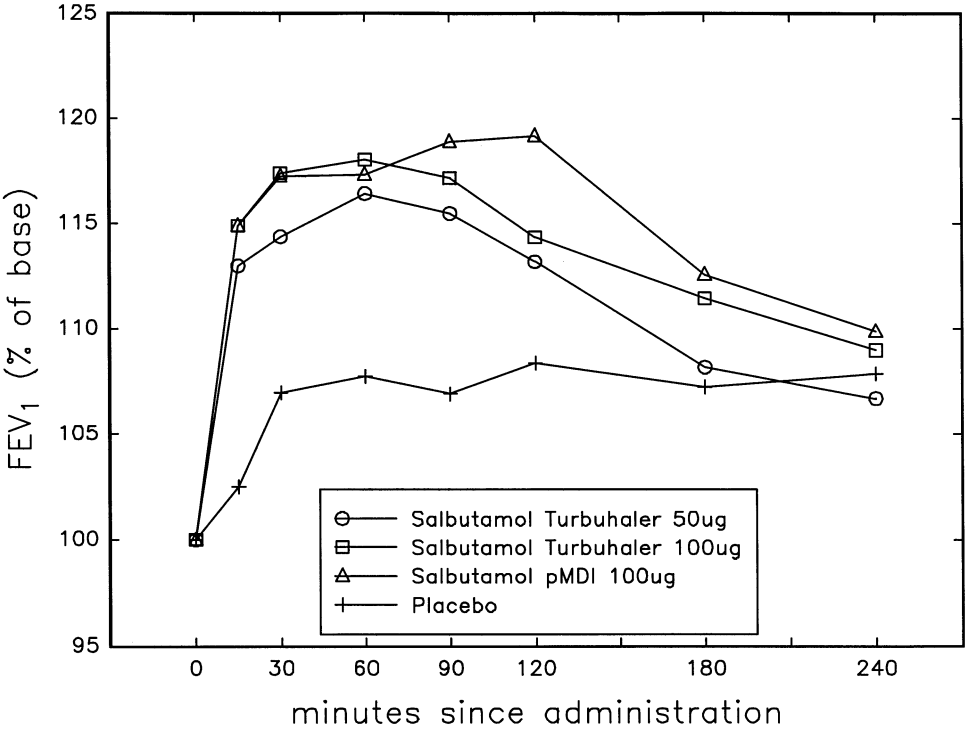

Fig. 1. Baseline adjusted geometric mean FEV_1 as a function of time.

The most common drugs used by the children before being included in the study were Pulmicort® (budesonide) (15 children), Bronchodual® (fenoterol and ipratropium bromide) (9 children), Bricanyl® (terbutaline) (8 children) and Intal® (disodium cromoglycate) (7 children). The most common additional diagnosis was allergic rhinitis (17 children).

3.1. FEV_1

The geometric mean FEV_1 measured 20 min before inhalation of the study drug was similar for each treatment group, 1.52 l (50 μg salbutamol Turbuhaler), 1.55 l (100 μg salbutamol Turbuhaler and pMDI) and 1.54 l (Placebo). After inhalation of the study drug, FEV_1 was monitored as described above. Fig. 1 shows the baseline adjusted geometric mean FEV_1 (% of baseline) as a function of time. The maximum mean increase for the active treatments with Turbuhaler was 17–18% after 60 min. The pMDI group showed a further slight increase after 120 min. The mean increase for placebo was approximately 7–8%, after 30 min. This placebo response was the same throughout the whole study period (4 h).

3.2. FEV_1-av and FEV_1 max

Table 2 shows the geometric mean FEV_1-av, geometric mean maximum FEV_1 (FEV_1 max) and corresponding ratios between the treatments. All active treatments were significantly better than placebo and there were no significant differences between the active treatments, in any of the two variables ($P > 0.05$). Therefore, a dose potency relationship between salbutamol Turbuhaler and salbutamol pMDI could not be estimated. The coefficient of variation was 7.6%.

The difference in mean FEV_1 max values between placebo and 50 μg Turbuhaler was 0.09 l ($P = 0.001$). The difference between placebo and

100 μg Turbuhaler and placebo and 100 μg pMDI was 0.11 l ($P < 0.001$). The coefficient of variation was 6.4%.

A sensitivity test (Cook's D) (Weisberg, 1985) of the primary variable (FEV_1-av) revealed no major influence on the results of any single individual, meaning that there were no extreme 'outliers' among the children.

3.3. Patients with 15% increase in FEV_1 from baseline

Fig. 2 shows the percentage of patients whose FEV_1 increased more than 15% from baseline. On average 50% of the patients on active treatment had responded after 30 min and at the end of the study period 25–30% of the patients were still above 15%, compared to baseline. There were no significant differences between the active treatments. About 20% of the patients on placebo showed an increase of more than 15%.

3.4. Adverse events

In total, four patients discontinued the study due to non-drug related adverse events between the visits. All active doses were well tolerated by the children.

4. Discussion

The results showed that there were no statistically significant differences in FEV_1-av or in FEV_1 max when any of the active doses from Turbuhaler or pMDI were given to the children. All treatments were clinically effective and significantly better than placebo. Since no dose-response curve could be shown for the Turbuhaler doses, it was not possible to estimate a relative dose relationship between salbutamol Turbuhaler and salbutamol pMDI.

Previously, a number of studies on adult patients have shown that the dose-relationship between salbutamol Turbuhaler and pMDI is around 2:1 (Chapman et al., 1994; Löfdahl et al., 1997). This is also supported by a study where the relationship between lung deposition and fine particle dose of salbutamol from pMDI and Turbuhaler was investigated (Olsson et al., 1996). The results showed that both the fine particle dose and the lung deposition from pMDI was lower compared with Turbuhaler, thus making Turbuhaler more efficient (Borgström et al., 1996). A possible explanation for the result obtained in this study is that children have smaller airways compared to adults, thus making it easier to reach near maximum effect of a single dose. Therefore, it is

Table 2
Geometric mean values and ratios for FEV_1-av and FEV_1 max[a]

Treatment	g-mean (l)	Turbuhaler 100 μg			pMDI 100 μg			Placebo		
		Ratio[b]	95% CI	*P*	Ratio	95% CI	*P*	Ratio	95% CI	*P*
FEV_1-av										
TBH 50 μg	1.71	0.97	(0.94, 1.01)	0.10	0.97	(0.94, 1.01)	0.09	1.04	(1.01,1.08)	0.02
TBH 100 μg	1.76				1.00	(0.96, 1.04)	0.93	1.08	(1.04, 1.12)	<0.001
pMDI 100 μg	1.76							1.08	(1.04, 1.12)	<0.001
Placebo	1.63									
FEV_1 max										
TBH 50 μg	1.85	0.99	(0.96, 1.02)	0.34	0.99	(0.96, 1.02)	0.36	1.05	(1.02,1.08)	0.001
TBH 100 μg	1.87				1.00	(0.97, 1.03)	0.98	1.07	1.03, 1.10)	<0.001
pMDI 100 μg	1.87							1.07	(1.03, 1.10)	<0.001
Placebo	1.76									

[a] g-mean = geometric mean; 95% CI = 95% confidence intervals; $P = P$-value.

[b] These ratios was calculated as the g-mean of TBH 50 μg/ g-mean of Turbuhaler 100 μg. The other ratios were calculated in a similar way.

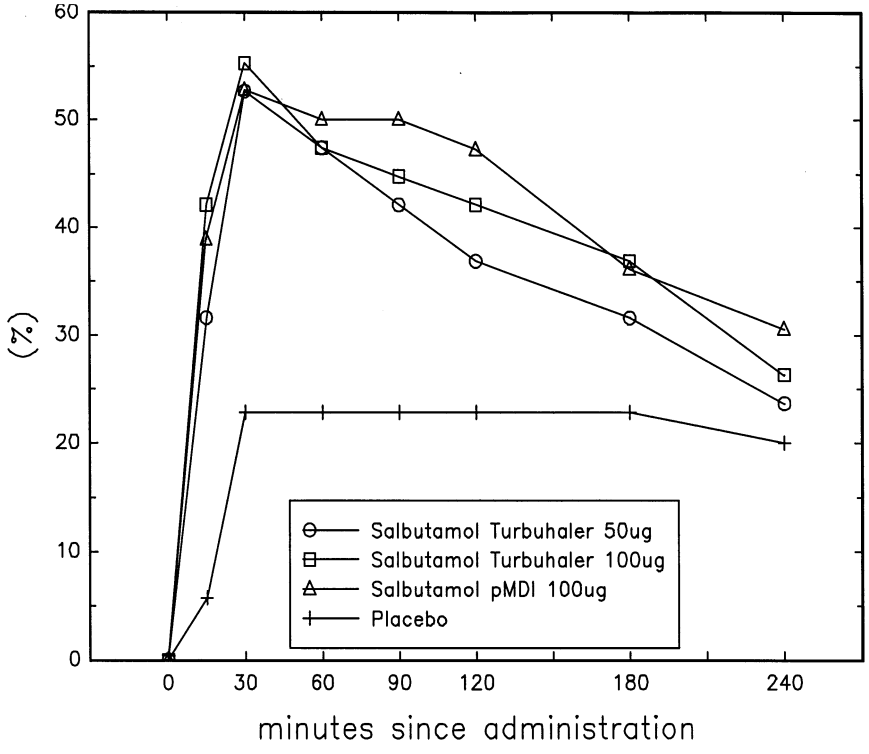

Fig. 2. Percentage of the patients who responded more than 15% in FEV_1 over baseline.

reasonable to assume that most of the children were on or near the top of the dose-response curve already after inhalation of 50 μg salbutamol via Turbuhaler. This indicates that this dose is sufficient to induce a clinically adequate bronchodilation in this age group. Similar results have been shown in another study in children in which no clinically relevant differences in PEF were found when 0.25, 0.5 and 1.0 mg terbutaline sulphate was inhaled from Turbuhaler (Ståhl et al., 1996). Moreover, a recent investigation of the protective effect against exercise-induced asthma in children showed that there were no differences between 50 and 100 μg salbutamol inhaled via Turbuhaler (Nordvall et al., 1996).

When children use inspiratory flow driven inhalers, there has been concern that the PIF may be insufficient to deliver the required dose to the lungs. However, studies have demonstrated that even young children with moderately severe asthma or patients with an acute asthma attack are capable of producing sufficient PIF to achieve adequate drug delivery and effect with Turbuhaler (Brown et al., 1995; Ståhl et al., 1996). With an inspiratory flow through Turbuhaler of 30 l/min or more, satisfactory clinical efficacy is guaranteed (Pedersen et al., 1990). In this study the lowest PIF through Turbuhaler was 46 l/min.

In conclusion, no significant differences in bronchodilating effect between 50, 100 μg salbutamol Turbuhaler and 100 μg salbutamol pMDI in children, aged 6–12 years, with stable asthma could be demonstrated. All active treatments were significantly better than placebo.

Acknowledgements

The following co-investigators are gratefully acknowledged for excellent technical assistance. Drs Libério Ribeiro, Natália Ferreira, Costa Trindade, Maria Amélia Aguílar, Dulce Zamite,

Jusé António Pinheiro, Bonito Victor, Maria Luisa Vaz, Isabel Tavares, Teresa Nunes, Maria de Fátima Matos, Eva Maria Gomes, Mario Antonio Santos Cardoso, Abilio Oliveira.

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