ELSEVIER

International Journal of Pharmaceutics 190 (1999) 57–62

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

A comparison of the bronchodilator effect of salbutamol inhaled via Turbuhaler® as two consecutive doses or as two divided doses at different time intervals

Christer Lindbladh [a,*], Paula Smith [b], Linda Jackson [b], Bachi Begishvilli [b], Audrey Jamieson [c], Stephen T. Holgate [b]

[a] *AstraZeneca R&D Lund, S-221 87 Lund, Sweden*
[b] *Southampton General Hospital, Southhampton, UK*
[c] *AstraZeneca Clinical Research Unit, 10, Loggie Mill, Beaverbrook Office Park, Logie Green Road, Edinburgh EH7 4HG, UK*

Received 17 February 1999; received in revised form 12 July 1999; accepted 27 July 1999

Abstract

The aim of the study was to compare the bronchodilatory effect of 2 × 50 μg salbutamol inhaled via Turbuhaler® as two consecutive doses compared with two divided doses (50 + 50 μg) at different time intervals. The study was of a randomized, double-blind, crossover design. The patients inhaled two doses of 50 μg salbutamol immediately after each other and with a time interval between the doses of 1.5, 3, 5, or 10 mins. Forced expiratory volume in 1 s (FEV_1) was measured before the first inhalation and at 1, 2.5, 4.5, 9.5, 15, 20, 30, and 60 min after the first inhalation. Seventeen asthmatic patients (8 men) with a mean age of 32 years (range: 19–49 years), mean FEV_1 of 2.9 l (range: 1.7–3.9 l) and a mean FEV_1 in percentage of predicted normal value of 77% (range: 63–91%) participated. The mean reversibility 15 min after inhaling 100 μg salbutamol from pMDI was 23% (range: 16–35%). The mean maximum increase in FEV_1 from baseline ranged between 18.6% (consecutive doses) and 21.2% (1.5 min between doses), corresponding to a difference between the treatments of 0.06 l. There were no significant differences in maximum FEV_1 or time to reach maximum FEV_1 between the treatments. We were not able to show any clinically relevant differences in maximal bronchodilating effect, assessed as FEV_1, in stable asthmatics, when therapeutic doses of salbutamol were given via Turbuhaler® either as two consecutive doses or as two divided doses separated by different time intervals.

Keywords: Salbutamol; Turbuhaler®; Dose response; Divided doses; Consecutive doses; Time interval

1. Introduction

It has been suggested that inhalation of β_2-agonists with a time interval between the doses results in greater bronchodilatation than if the same

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

0378-5173/99/$ - see front matter
PII: S0378-5173(99)00264-1

Table 1
Demographic data of the randomized patients ($n = 17$)[a]

	Mean	Range
Duration of asthma (years)	17	0.2–37
Age (years)	32	19–49
Weight (kg)	77	57–116
Height (cm)	172	162–182
FVC (l)	3.4	2.0–4.9
PEF (l min^{-1})	474	350–600
PIF (l min^{-1})	72	51–88
FEV_1 (l)	2.9	1.7–3.9
FEV_1 (% pred)	77	63–91
FEV_1 rev (%)	23	16–35

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

Table 2
Geometric mean treatment ratios of maximum FEV_1-values[a]

Comparison[b]	Treatment ratio	95% CI	p-Value
Consecutive versus 1.5 min	0.991	0.967–1.015	0.47
Consecutive versus 3 min	0.998	0.974–1.022	0.88
Consecutive versus 5 min	0.985	0.962–1.009	0.23
Consecutive versus 10 min	1.002	0.979–1.026	0.87

[a] Adjusted for visit and baseline at each visit.
[b] Consecutive doses versus two doses separated by different time intervals.

doses are given as a single dose. An argument for this hypothesis has been that the 'opening effect' of the first dose facilitates better penetration of the succeeding doses into the lower airways, as has been demonstrated when terbutaline is inhaled before inhalation of budesonide (Santolicandro et al., 1994). However, the results from previous studies are conflicting, some studies supporting the hypothesis (Britton and Tattersfield, 1984), while others do not (Dulfano et al., 1977; Lawford and McKenzie, 1983).

In clinical practise it may be more adequate to recommend a simple dosing regimen to the patient rather than trying to optimize the clinical effect by specific dosing schedules. However, to preserve the blinding of a clinical study sometimes complex dosing schedules have to be used. Therefore, when designing and evaluating clinical studies it may be of importance to know what impact a time interval between doses may have on the clinical effect, compared to that of a single dose. The clinical effect of interval administration of β_2-agonists has mostly been evaluated using drug delivery via pressurized metered dose inhaler (pMDI). Since the inhalation technique as well as the in vivo variability in the delivered dose is different using a pMDI and Turbuhaler® (Borgström, 1997), it is important to also assess how Turbuhaler® behaves in these circumstances.

The purpose of this study was to compare the bronchodilator effect of therapeutic doses of salbutamol inhaled via Turbuhaler® as two consecutive doses or as two divided doses separated by different time intervals. Previous experiments have shown that 0.25 mg terbutaline sulphate inhaled from Turbuhaler® gives about 65% of the maximum effect after 1 min (Jackson et al., 1994). Since salbutamol and terbutaline are similar in onset of action, it was assumed that possible interval effects would be obtained if there were 1–10 min between the doses. The selected dose intervals were 0, 1.5, 3, 5, and 10 min.

2. Patients and methods

2.1. Patients

A total of 17 out-patients (8 men) were randomized into the study. All patients suffered from confirmed asthma disease and had at least 15% increase in forced expiratory volume in 1 s (FEV_1) after inhalation of 100 μg salbutamol via pMDI. None of the patients had had a respiratory infection within 4 weeks of the start of the study. Demographic data and lung function at baseline are shown in Table 1. Eight patients had never smoked and nine patients were former smokers. The lowest peak inspiratory flow (PIF) through

Turbuhaler® was 51 l min^{-1}, which is well above the 30 l min^{-1} when satisfactory clinical efficacy is obtained (Pedersen et al., 1990). All randomized patients completed all visits and there were no protocol deviations. All patients were using a short-acting β_2-agonist. Twelve patients were on inhaled steroids and one patient was using long-acting β_2-agonist. Before each study day inhaled short-acting β_2 agonists were withdrawn 8 h and long-acting β_2-agonists, 72 h before visit. Patients using inhaled sterioids continued to use these at a constant dose. The study was performed in accordance with the principles stated in the Declaration of Helsinki. Signed informed consent was obtained prior to conducting any study-related procedures. The study was approved by the Southampton and South West Hampshire Health Authority and University of Southampton Faculty of Medicine Joint Ethics Committee.

2.2. Study design

The study was of a 5-way cross-over, single-dose, randomized, double-blind design, and was performed at one center. The patients visited the clinic six times. A reversibility test was performed on the enrollment day. The five following study days were separated by at least 20 h and maximally 7 days. Patients arrived at the clinic between 8:00 and 11:00 h. At all visits FEV_1 at baseline was not to vary more than $\pm 15\%$ from the value obtained at the first visit. Patients practiced the inhalation technique (peak inspiratory flow) with an empty Turbuhaler®, connected to a Vitalograph MDI modified compact spirometer (Vitalograph, UK). On each study day the patient received 100 μg of salbutamol via Turbuhaler® as two consecutive doses (2×50 μg) or as divided doses ($50 + 50$ μg) separated by 1.5, 3, 5, or 10 mins. Placebo Turbuhaler® was used in the dosing schedule to preserve the double-blind nature of the study. Assessment of FEV_1 (Vitalograph Spirometer, Maids Morten) was performed in triplicate pre-dose and at 1, 2.5, 4.5, 9.5, 15, 20, 30 and 60 min after inhalation of the first dose (time 0 min). The highest FEV_1 value was recorded from each assessment. Salbutamol Turbuhaler®, 50 μg per dose, containing 75% lactose, and placebo for salbutamol Turbuhaler®, containing lactose, were manufactured by Astra Draco AB, Sweden.

2.3. Analysis of results

The primary variable was log (maximum FEV_1). Assuming a mean maximum FEV_1 of 3.1 l and an intra-individual standard deviation for log maximum FEV_1 of 0.052 (0.4 l), 20 patients were required to detect a treatment difference of at least 4.7% in FEV_1 (i.e. 0.15 l) with 80% power at a 5% significance level. The time to reach maximum FEV_1 was analysed in addition to maximum FEV_1. The efficacy variables were analysed using an additive ANOVA model. Confidence intervals of 95% were calculated for treatment ratios.

3. Results

Geometric mean baseline FEV_1 for each treatment was: 2.92 l (consecutive doses); 2.81 l (1.5 min between doses); 2.82 l (3 min); 2.90 l (5 min); and 2.89 l (10 min), respectively. Fig. 1 present the

Table 3
Difference in time to reach maximum FEV_1

Comparison[a]	Difference (min)	95% CI (min)	*p*-Value
Consecutive versus 1 min 30 s	−.21	−15.3–11.1	0.76
Consecutive versus 3 min	−10.3	−23.4–2.89	0.13
Consecutive versus 5 min	−7.8	−20.9–5.4	0.25
Consecutive versus 10 min	−2.4	−15.6–10.8	0.72

[a] Consecutive doses versus two doses at different time intervals.

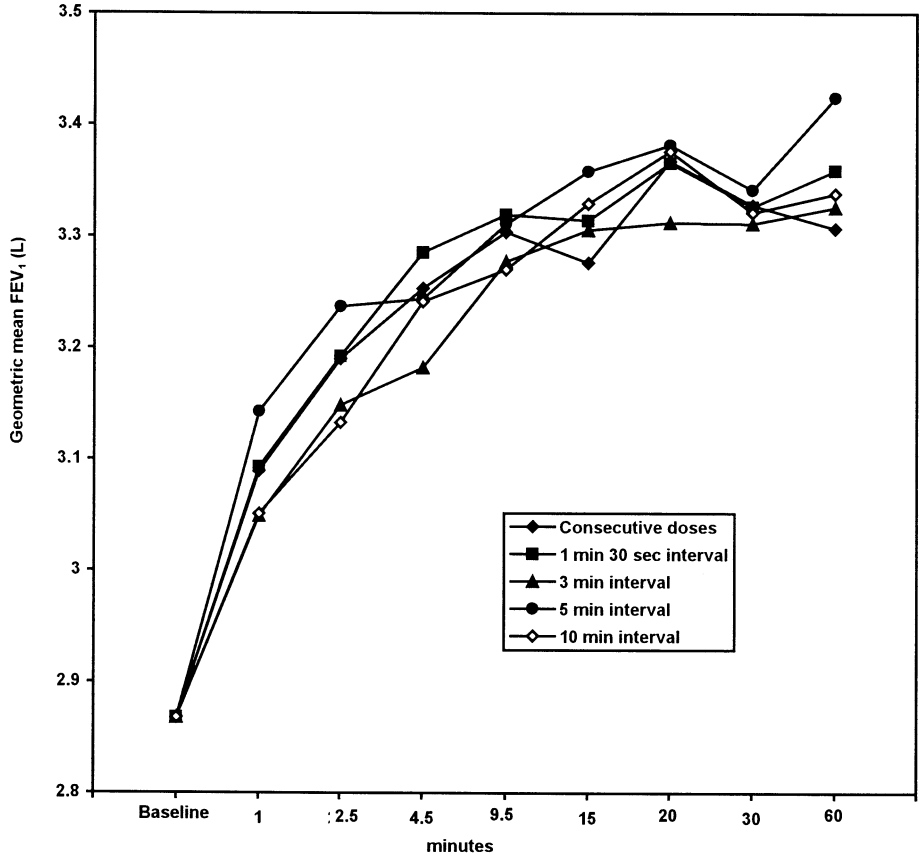

Fig. 1. Geometric means of FEV_1 over time adjusted for differences in baseline.

baseline adjusted geometric mean FEV_1 for the five treatments, measured during 1 h after inhalation of the first dose. The mean percentage increase in maximum FEV_1 from mean baseline ranged between 18.6 and 21.2%, corresponding to 0.56 and 0.62 l, respectively. Table 2 shows the treatment ratios between consecutive doses versus divided doses. The largest difference in maximum FEV_1 between consecutive and divided doses was 1.5%. None of the differences were statistically significant. The intra-individual standard deviation for log (maximum FEV_1) was 0.051. The mean time to reach maximum FEV_1 ranged from 24 to 34 min depending on the treatment. The shortest mean time was obtained when the doses were given consecutively, however, this was not statistically significant (Table 3).

4. Discussion

In this study there were no statistically significant differences in maximum bronchodilating effect, assessed by FEV_1, or time to reach maximum effect when a total dose of 100 μg salbutamol via Turbuhaler® was given as two consecutive doses or as two doses separated by different time intervals, from 1.5 to 10 min. The clinical relevance of interval administration has been investigated in several previous trials, mostly involving pMDIs. These include the administration of β_2-agonists before glucocorticosteroids (Muers and Dawkins, 1983), relief of asthma symptoms in adult patients (Dulfano et al., 1977) and children (Pedersen, 1986), and in acute situations of asthma (Pedersen, 1986; Phanichyakarn et al., 1992). In these studies no significant effects have been

found in stable asthmatics. For instance, when a total dose of 0.5 mg terbutaline sulphate was administered as a single dose, two consecutive doses of 0.25 mg or four consecutive doses of 0.125 mg, over a 2-min period, no significant differences in maximum FEV_1 were observed (Dulfano et al., 1977). In a study on children with stable asthma it was not possible to detect any significant differences when the doses were delayed by up to 10 min (Pedersen, 1986). However, during attacks of acute wheeze, a pause between the doses significantly improved dilatation of the airways, compared to when given as a single dose (Pedersen, 1986). A second study on children with acute asthma showed a similar result, but failed to reach significance (Phanichyakarn et al., 1992). Two possibilities could explain the obtained results found in stable asthma and acute attacks. Firstly, it could be that it is only in the acute situation when the airways are tightly constricted that there is a clinically relevant 'opening' effect with the first dose. Secondly, at the onset of an attack the inhalation technique with pMDI may deteriorate. A pause between the doses may give some symptomatic relief and some time for the patient to concentrate more on the inhalation technique when the next dose is taken, thus favouring a pause between the doses (Pedersen, 1986). In contrast to these results, using therapeutical doses, it has been demonstrated that four cumulative doses of isoprenaline, of increasing strength (10, 20, 80, 400 μg) given 5 min apart, give a significantly greater response, measured as the area under the FEV_1 curve, than when given as a single dose (Britton and Tattersfield, 1984). This was further demonstrated for peak expiratory flow (PEF), where a plateau was observed after a single dose of 20 μg, while the PEF continued to increase when additional cumulative doses were given, although non-significantly. This 'bonus effect' of a time interval between the doses has also been seen in other studies on stable asthmatics, where the relative dose potency between different inhalers has been estimated from cumulative dose–response curves (Ekström et al., 1995; Mahadewsingh et al., 1996). In these studies, the total cumulative dose was high and the doses were given with a 30 min interval. Collectively, the results suggest that a pause between succeeding doses may be of importance in acute situations of bronchoconstriction and in stable conditions when the total dose far exceeds normal therapeutical doses, as in cumulative dose–response studies, while it is of less importance at normal therapeutic dose-ranges.

In this study we were not able to demonstrate any significant differences between the treatments. We are aware of the fact that there are only small differences in bronchodilatation between the single dose and the consecutive doses, as seen after 10 min. However, the design has been made using the lowest commercially available doses, which is also of interest from a clinical perspective. In previous studies with salbutamol Turbuhaler®, dose–response has been demonstrated up to 200 μg with single doses (Löfdahl et al., 1997) and up to 400 μg with cumulative doses (Mahadewsingh et al., 1996). The study was dimensioned to detect treatment differences larger than 4.7% (0.15 l) in maximum FEV_1, which in many previous trials is considered as a clinically relevant difference. This means that if a difference of $\geq 4.7\%$ exists we would have had an 80% chance to detect this, since the conditions behind the power calculation were fulfilled. The maximum difference between consecutive doses and divided doses was 1.5% (non-significant), as shown by the treatment ratios in Table 2. Thus, even if it can not be excluded that small treatment differences exist, using Turbuhaler® in this category of stable asthmatics, it is unlikely that they are of clinical relevance (i.e. ≥ 0.15 l). The study thus supports previous findings, based on pMDI, indicating that asthmatic patients under stable conditions do not benefit from delaying their second dose. In conclusion, we have not been able to show any clinically relevant differences in maximum bronchodilating effect in stable asthmatics, when therapeutic doses of salbutamol were given via Turbuhaler® either as two consecutive doses or as two doses at various time intervals.

References

Borgström, L., 1997. Performance characteristics of pMDI and Turbuhaler® in vitro and in vivo. J. Aerosol Med. 10 (suppl 1), 9–12.

Britton, J., Tattersfield, A., 1984. Comparison of cumulative and non-cumulative techniques to measure dose–response curves for β_2-agonists in patients with asthma. Thorax 39, 597–599.

Dulfano, M.J., Glass, P., McPhillips, J.J., 1977. A comparison of the bronchodilator effects on the same amounts of terbutaline aerosol given as a single or divided doses. Ann. Allergy 39, 266–271.

Ekström, T., Andersson, A.-C., Skedinger, M., Lindbladh, C., Ståhl, E., 1995. Dose potency relationship of terbutaline inhaled via Turbuhaler® or via a pressurized metered dose inhaler. Ann. Allergy Asthma Immunol. 74, 328–332.

Jackson, L., Ståhl, E., Holgate, S.T., 1994. Terbutaline via pressurized metered dose inhaled (pMDI) and Turbuhaler® in highly reactive asthmatic patients. Eur. Respir. J. 7, 1598–1601.

Lawford, P., McKenzie, D., 1983. Pressurized aerosol inhaler technique: how important are inhalation from residual volume, inspiratory flowrate and the time interval between puffs? Br. J. Dis. Chest 77, 276–281.

Löfdahl, C.-G., Andersson, L., Bondesson, E., Carlsson, L.-G., Friberg, K., Hedner, J., Hörnblad, Y., Jemsby, P., Källen, A., Ullman, A., Werner, S., Svedmyr, N., 1997. Differences in bronchodilating potency of salbutamol in Turbuhaler® as compared with pressurized metered dose inhaler formulation in patients with reversible airwayobstruction. Eur. Respir. J. 10, 2474–2478.

Mahadewsingh, J.V., Hamersma, W.B.G.J., Schreurs, A.J.M., 1996. Relative efficacy of three different inhalers containing salbutamol in patients with asthma. Eur. J. Clin. Pharmacol. 50, 467–469.

Muers, M., Dawkins, K., 1983. Effect of a timed interval between inhalation of β2-agonist and corticosteroid aerosols on the control of chronic asthma. Thorax 38, 378–382.

Pedersen, S., 1986. The importance of a pause between the inhalation of two puffs of terbutaline from a pressurized aerosol with a tube spacer. J. Allergy Clin. Immunol. 77, 505–509.

Pedersen, S., Hansen, O.R., Fuglsang, G., 1990. Influence of inspiratory flow rate upon the effect of a Turbuhaler®. Arch. Dis. Child. 65, 308–310.

Phanichyakarn, P., Kraisarin, C., Sasisakulporn, C., Kittikool, J., 1992. A comparison of different intervals of administration of inhaled terbutaline in children with acute asthma. Asian Pac. J. Allergy Immunol. 10, 89–94.

Santolicandro, A., Di Mauro, M., Sorti, S., Buzzigoli, G., Marelli, C., Borgström, L., Giuntini, C., 1994. Lung deposition of budesonide inhaled through Turbuhaler® in asthmatic patients before and after bronchodilation. Am. J. Respir. Crit. Care Med. 149 (4pt2), A220.