Vol. **95** (2001) 949–953

The efficacy of a new salbutamol metered-dose powder inhaler in comparison with two other inhaler devices

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Abstract An open cross-over and randomized study was carried out in order to compare the efficacy and safety of inhaled salbutamol delivered from a new 50 μg dose^{-1} metered-dose dry powder inhaler Taifun®, and a commercially available 50 μg dose^{-1} dry powder inhaler Turbuhaler®, and a conventional 100 μg dose^{-1} pressurized metered-dose inhaler with a spacer (pMDI+S). Twenty-one patients, aged 21–70 years, with stable asthma and with demonstrated reversibility upon inhalation of salbutamol were included in the study. On three separate study days, the patients received a total dose of 400 μg of salbutamol from the dry powder inhalers and a dose of 800 μg from the pMDI+S in a cumulative fashion: 1, 1, 2 and 4 doses at 30 min intervals. The per cent change in forced expiratory volume in 1 sec (FEV_1), was used as the primary efficacy variable. Salbutamol inhaled via the Taifun® produced greater bronchodilation than the other devices. The difference in percent change in FEV_1 between the Taifun® and the other devices was statistically significant at the two first dose levels, but diminished towards the higher doses when the plateau of the dose–response curve was reached. The estimated relative dose potency of the Taifun® was approximately 1·9- and 2·8-fold compared to the Turbuhaler® and the pMDI+S, respectively. The Taifun® caused a slight, but clinically insignificant, decrease in serum potassium concentration. There were no significant changes in the other safety parameters (blood pressure, heart rate and electrocardiogram recordings) with any of the used devices. In conclusion, this study indicates that salbutamol inhaled via the Taifun® is more potent than salbutamol inhaled from the other devices tested. In practise, a smaller total dose of salbutamol from the Taifun® is needed to produce a similar bronchodilatory response. All treatments were equally well tolerated.

doi:10.1053/rmed.2001.1189, available online at http://www.idealibrary.com on IDEAL®

Keywords asthma; salbutamol; bronchodilatron; dry powder inhaler.

INTRODUCTION

Inhaled, short-acting, selective β_2-adrenoceptor agonists, such as salbutamol, have played an important role in the treatment of asthma and other conditions associated with reversible airway obstruction. Their rapid onset of action makes them the medication of choice for the treatment of acute asthma attacks and for the prophylaxis of exercise- and allergen-induced bronchoconstriction (1).

The predominant formulation of inhaled medication has been the chlorofluorocarbon (CFC)-based pressurized metered-dose inhaler (pMDI), which was invented over 40 years ago and has remained practically unchanged since. In addition to the fact that CFC gases used in pMDIs deplete the ozone layer of our atmosphere (2), they may irritate the bronchial mucous membranes (3). Also, difficulties in co-ordinating the actuation of the pMDI and inhaling the drug (4) are frequently seen. These problems have led to the development of either alternative propellants or entirely different devices, metered dose powder inhalers (MDPI). With MDPIs all that described above can be avoided, and they are now generally considered as the devices of choice for future inhalation therapy of asthma.

Recently, Leiras Oy has developed a new breath-actuated MDPI, Taifun® (Fig. 1). It contains 200 doses of salbutamol (50 or 100 μg dose^{-1}) with lactose carrier, provides a high respirable fraction (40–45% of the

Received 8 January 2001, accepted in revised form 13 July 2001 and published online 22 October 2001.
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delivered dose) and with a mass median aerodynamic diameter of 2·5–2·7 μm, and is efficient in delivering the salbutamol dose into the lungs (5). In previous studies the Taifun® proved to be at least as effective in causing bronchodilation (6) as one of the pMDIs with a spacer device (S), and better in offering protection against methacholine-induced bronchoconstriction (7) than another conventional pMDI+S. The aim of this study was to compare the efficacy and relative potency of cumulative doses of salbutamol inhaled from the Taifun® (50 μg dose^{-1}) or via another MDPI (Turbuhaler®) or a pMDI+S.

METHODS

Design

This was a randomized, open, cross-over, cumulative dose study, which was carried out in three clinics of pulmonary diseases in Finland. Each subject attended the laboratory three times after the screening visit. The sessions were at least 24 h apart, and the subjects completed the study within 2 weeks from the screening visit.

Subjects

Twenty-one outpatients (nine males) with chronic asthma, and a reversibility of forced expiratory volume in 1 sec (FEV_1) of at least 15% measured 20 min after inhalation of 200 μg of salbutamol from a Ventoline® pMDI connected to a Volumatic® spacer were enrolled. The patients fulfilled the American Thoracic Society criteria for asthma. The detailed demographic characteristics of the enrolled patients are listed in Table 1. All patients were of Caucasian origin. Nine of them were ex-smokers, the others had never smoked. Seventeen of the patients used inhaled glucocorticosteroids, 13 inhaled short-acting and six long-acting β_2-adrenoceptor agonists. One patient used a combination product of an inhaled anticholinergic and β_2-adrenoceptor agonist. Two patients had inhaled chromones, and one was on antihistamine medication due to allergic rhinitis. Additionally, six patients were on regular medication for other than respiratory or allergic conditions; one patient took an oestrogen supplement for menopausal symptoms, two patients zopiclone for insomnia, two paracetamol for musculoskeletal pains, one thyroxin for hypothyreosis, and one patient isosorbide-5-mononitrate and diltiazem for coronary artery disease.

Further, concomitant medication was withheld as follows: inhaled short-acting β_2-adrenoceptor agonists for 12 h, oral and inhaled long-acting β_2-adrenoceptor agonists for 48 h, inhaled anti-cholinergics for 24 h, oral anti-cholinergics for 7 days, and theophylline and its derivatives for 72 h, prior to each study visit. Concomitant medication with nasal, inhaled or oral glucocorticosteroids, or inhaled nedocromil or sodium cromoglycate, with a constant dose for at least 1 month prior to and during the study was allowed.

Table 1. Summary of demographic characteristics of the recruited patients (n=21)

Characteristic	Mean ±SD	Range
Age (years)	50·4 ±13·4	21–70
Weight (kg)	81·2 ±17·3	60–136
Height (cm)	170 ±9	156–191
FEV_1 (l)*	2·13 ±0·59	1·05–3·36
FEV_1 of predicted (%)	62·5 ±13·2	37–96
Reversibility in FEV_1 after salbutamol (%)*	23·3 ±10·4	15·1–51·2

*Measured at the screening visit.

The study was performed in accordance with the principles stated in the Declaration of Helsinki and the principles of Good Clinical Practice adopted by the European Community. The Finnish National Agency for Medicines was notified of the study, and the study was approved by the ethics committees of each hospital. All subjects gave their signed informed consent before they were enrolled in the study.

Instruments and drugs

Pulmonary function was measured with Vitalograph Compact II® spirometers (Vitalograph Ltd., Buckingham, U.K.) calibrated prior to the study. The calibration was checked daily before any study measurements. The equipment was used only for the present study.

The reversibility test was performed with an inhalation of 200 μg of salbutamol from Ventoline® pMDI connected to a Volumatic® spacer (both from GlaxoWellcome, Uxbridge, U.K.). The studied inhalers were Taifun® (Leiras Oy, Turku, Finland) giving 50 μg of salbutamol per dose with lactose carrier, salbutamol 50 μg dose^{-1} Turbuhaler® (Astra AB, Sōdertâlje, Sweden), and 100 μg dose^{-1} Ventoline®+ Volumatic® (pMDI+S). In order to optimize the function of the devices, inhalation techniques recommended by the manufacturers were followed. When using the Taifun® the patients after having loaded the device exhaled normally to functional capacity (FRC) and then took a normal, slow tidal volume inhalation through the device. With the Turbuhaler® the procedure was similar, except that the inhalation through the device was deep and forceful. When the pMDI+S was used, after shaking the canister the patients exhaled to FRC, placed the mouthpiece firmly between their lips and actuated the device, and after a wait of 2–4 sec took a slow and deep inhalation. In order to maximize lung deposition all inhalation procedures were followed by a breath holding period of 10 sec.

Study procedure

The patients were randomized for the sequence of the three inhalers, and inhaled salbutamol on three separate days. On each study visit the baseline pulmonary function was established by having the patients do repeated spirometric efforts at intervals of 1 min until obtaining three FEV_1 values from consecutive measurements, of which at least two were within a range of 0·1–l. The better of these two values was recorded as the baseline FEV_1 which was required to be within $\pm$12% from the baseline values of all other study days. All the baseline measurements were performed at the same time between 07·00 and 11·00 hours. Immediately after them, cumulative doses of salbutamol were inhaled at 30 min intervals as follows: from the Taifun® and Turbuhaler® 1+1+2+4 inhalations with cumulative doses of 50, 100, 200 and 400 μg of salbutamol; from the pMDI+S 1+1+2+4 inhalations with doses of 100, 200, 400 and 800 μg of salbutamol. Pulmonary function was measured 25 min after each drug dose, and the FEV_1 from the best technically valid spirometric effort of three was recorded.

As safety precautions, every patient's electrocardiogram (ECG), blood pressure (BP) and heart rate (HR) were recorded during the study. ECG was recorded before and after the study procedures. BP and HR were recorded before the first drug inhalation and 20 min after each dose. Also blood samples for analysing serum potassium (S-K) levels were collected before the first, and 30 min after the last, drug inhalation.

Data analysis

The results are presented as means and standard deviations (SD), unless otherwise indicated. All analyses were based on the intent-to-treat population. Per cent change in FEV_1 from the baseline was used as the primary efficacy variable. A one-sided 95% confidence interval (95% CI), corresponding to a two-sided 90% CI (90% CI), based on the least square of means was calculated to test the non-inferiority of the Taifun® in comparison with the other devices. If Taifun® was detected to be at least as effective as the other devices, analysis of variance (ANOVA) with a 3×3 cross-over design or corresponding non-parametric method was performed. ANOVA was performed also for numerical safety parameters. A P-value of less than 0·05 was considered statistically significant. Also, to support the results of the primary efficacy parameter, the relative dose potency of the devices was calculated by estimating the parallel shift of the dose-response curves by applying a linear model: effect = subject+ device+period+log-dose. A normal two-sided 95% confidence interval (95% CI) was calculated for this parameter.

RESULTS

All but two of the recruited patients completed the study according to the protocol. Both discontinuations were due to exacerbation of asthma. The mean (SD) baseline FEV_1 values of the Taifun®, Turbuhaler® and pMDI+S periods were 2·12 (0·59) l, 2·11 (0·62) l and 2·17 (0·58) l, respectively. The cumulative salbutamol doses caused bronchodilation increasing dose by dose, which at the first two doses was most prominent with the Taifun®, followed by the Turbuhaler® and then the pMDI+S (Fig. 2). At the first two dose steps the Taifun® differed significantly from the other devices, the Turbuhaler® ($P = 0·037$ for the first and $P = 0·007$ for the second dose) and the pMDI+S ($P = 0·019$ for the first and $P = 0·028$ for the second dose) (Table 2). At higher dose levels (200 and 400 μg for the Taifun® and the Turbuhaler®, 400 and 800 μg for the pMDI+S) the difference between the devices diminished, being no longer significant, but the order of efficacy remained (Fig. 2, Table 2). The estimated relative dose potency (95% CI) of the Taifun® was 1·9 (1·4–2·6) and 2·8 (2·1–3·8) when compared to the Turbuhaler® and pMDI+S, respectively. The relative potency of the

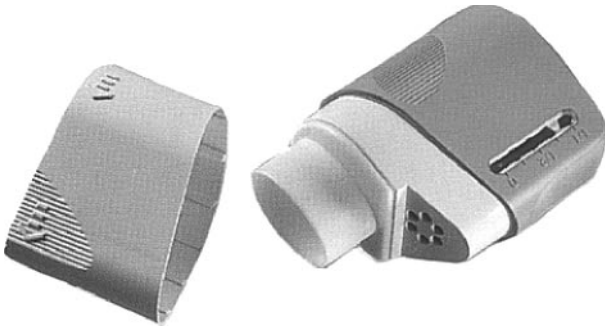

FIG. 1. The Taifun® inhaler.

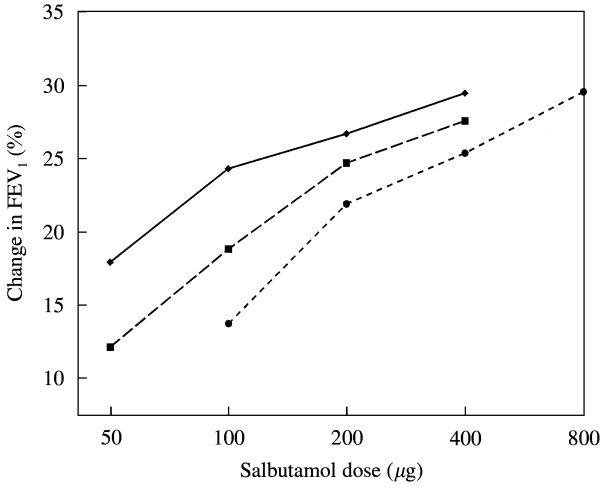

FIG. 2. The increase in FEV_1 after each salbutamol dose. Taifun® (-◆-), Turbuhaler® (-■), pMDI+S(●).

Table 2. The difference in per cent changes between the Taifun® and other studied devices presented as % units and two-sided 90% confidence intervals in brackets (90% CI)

	Dose from the Taifun®			
	50 μg	100 μg	200 μg	400 μg
Turbuhaler® 50 μg	5·2 (1.1–9·4)			
100 μg		4·9 (1·9–7·9)		
200 μg			1·5 (−1·8–4·8)	
400 μg				1·5 (−2·7–5·6)
PMDI+S 100 μg	5·9 (1·7–10·0)			
200 μg		4·0 (1·0–6·9)		
400 μg			2·9 (−0·4–6·3)	
800 μg				1·6 (−2·5–5·8)

Turbuhaler® was estimated to be 1·5 (1·1–2·0) of that of the pMDI+S.

All S-K concentrations measured during the study were within the normal range (3·5–5·1 mmol $^{-1}$). The mean (SD) baseline S-K levels were 4·22 (0·19), 4·12 (0·28) and 4·25 (0·24) mmol l^{-1} at the Taifun®, Turbuhaler® and pMDI+S periods, respectively. After the salbutamol inhalations the corresponding values were 4·12 (0·22), 4·21 (0·22) and 4·15 (0·30) mmol l^{-1}. The difference between the Taifun® and the Turbuhaler® was statistically significant, −0·19 (95% CI −0·33 to 0·05). The Taifun® and the pMDI+S did not differ in this respect from each other; the difference in S-K values was 0·01 (95% CI −0·15 to 0·12). The baseline BP, HR or ECG did not differ between medications and there were no significant changes in these parameters during the different treatments.

There were 10 reported AEs, altogether, in five patients during the study: two after the Taifun®, three after the Turbuhaler® and four after the pMDI+S period. Of these only four AEs in two patients were probably drug-related: one event of tremor after each treatment and one report of dizziness after Turbuhaler® treatment.

DISCUSSION

The development of new inhalation devices raises the question of their relative efficacy. This investigation was carried out in order to compare the efficacy of a new salbutamol MDPI, Taifun®, with that of another MDPI and a conventional pMDI with a spacer containing the same active drug substance. When comparing different inhalers, it would have been preferable to employ a double-blind and double-dummy technique. However, for reasons of simplicity and feasibility it was decided not to utilize this technique in the study design. For the same reason also placebo control was left out of the study. The lack of blindness in comparing the devices may slightly reduce the value of this study since this allows, at least theoretically, some bias to occur in the measurements. The differences in the efficacy measurements between devices were, however, consistent and clear, and also there were no difference in the safety parameters between the devices, which indicates that this fault in the study design had probably no major effect on the results. Since most patients inhaled the first dose quite early in the morning, in the absence of a placebo it cannot be precluded that natural increase in pulmonary function due to the circadian rhythm (8) might also have contributed to the bronchodilation seen. This, however, has no effect on the between-device comparison and the main results of this study.

This is the first time the Taifun® was compared to any other MDPI. It is considered that the clinical efficacy of inhaled β_2-adrenoceptor agonist drugs is directly related to their lung deposition (9,10). There is no published data available of pulmonary deposition of salbutamol inhaled from the Turbuhaler®. However, with terbutaline Turbuhaler® previous deposition studies show approximately similar lung drug deposition (21–28%) as with salbutamol Taifun® (24%) (5,11,12). There are some previous studies comparing the relative efficacy of salbutamol Turbuhaler® to various other inhalation devices. The Turbuhaler® has proven to be a very efficient inhaler since in these studies it has been shown to be about twice as effective as Diskhaler® or Rotahaler® (13,14), and about two to three times as effective as a pMDI (15). When comparing the Taifun® and the pMDI+S, the results of this study are in accordance with an earlier study (7) where ability of a single dose of 100 μg of salbutamol inhaled via the Taifun® to protect against methacholine-induced bronchoconstriction was found to be clearly better

compared to that of an equal dose of salbutamol via the pMDI+S ($PD_{20}FEV_1$ 1737 μg *vs.* 622 μg). However, there are no previous studies where the Taifun® has been compared with other powder inhalers, or with a wide range of different salbutamol doses with any other inhaler devices.

When planning the present study it was assumed that the salbutamol Taifun® and Tubuhaler® would have approximately the same level of performance. Bearing in mind the results of a previous study (7), it was expected that higher salbutamol doses from the pMDI+S would be needed to gain a similar level of performance as with the Taifun®. Consequently, the doses of salbutamol were selected to start from the smallest available dose from each device and range up to 400 μg for the MDPIs and to 800 μg for the pMDI+S. The hypothesis was that at each dose level salbutamol inhaled via the Taifun® would be at least as effective as salbutamol inhaled via the Turbuhaler® or the pMDI+S.

Salbutamol inhaled via the Taifun® produced at each dose level greater bronchodilation than equal doses of salbutamol inhaled via the Turbuhaler® or twice as high nominal doses from the pMDI+S. At the two lowest doses levels the resulted bronchodilation was significantly greater with the Taifun® than with the Turbuhaler® or the pMDI+S, respectively. Thereafter, towards the higher doses, the differences between the devices diminished, being no longer statistically significant as the plateau of the dose–response curve was achieved. On the basis of these results it can be estimated that the relative dose potency of salbutamol from the Taifun® is about twice that of the Turbuhaler® and about three times that of the pMDI+S.

The overall safety of the tested devices seemed to be similar. The reported drug-related adverse effects were mild and were distributed rather evenly between the devices. In previous studies (16,17) the hypokalaemic effect of inhaled salbutamol (via a pMDI and a spacer) became evident at a dose level of 500 μg or higher. Consequently, some changes in potassium concentrations were expected in the present study. Indeed, potassium concentrations seemed to decrease slightly after the usage of the Taifun® and the pMDI+S, as expected. On the contrary, an unexplained increase was seen after the Turbuhaler®. Although the actual changes in serum potassium concentrations with all the devices were small and clinically insignificant, this resulted in a statistically significant difference in potassium concentrations after salbutamol dosing between the Taifun® and the Turbuhaler®.

In conclusion, the salbutamol Taifun® was found to be more potent in producing bronchodilaton in asthmatic patients than the salbutamol Turbuhaler® or salbutamol pMDI connected to a Volumatic® spacer. Approximately two doses from the Turbuhaler® and three doses from the pMDI+Volumatic® were needed to produce bronchodilation of similar magnitude than a single dose from the Taifun®. It is always an advantage if the patient can be burdened with as small as possible total dose, inhaled and swallowed, of the drug, and still get relief to the symptoms of asthma. All treatments were equally well tolerated.

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