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Assessment of the systemic effects of budesonide inhaled from Easyhaler® and from Turbuhaler® in healthy male volunteers

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Abstract The main objective of this study was to show dose-dependent equivalence in the systemic activity of budesonide 800 μg day^{-1} and 1600 μg day^{-1} delivered from either Easyhaler® or Turbuhaler® in healthy male subjects.

This single-centre study was carried out according to a randomized, double-blind, double-dummy, five-way cross-over design over a 9-week period. All subjects received 1 week of treatment with the following, in randomized order, with a washout week between each treatment: budesonide Easyhaler® 800 μg day^{-1} plus placebo Turbuhaler®; budesonide Easyhaler® 1600 μg day^{-1} plus placebo Turbuhaler®; placebo Easyhaler® plus Pulmicort® Turbuhaler® 800 μg day^{-1}; placebo Easyhaler® plus Pulmicort® Turbuhaler® 1600 μg day^{-1}; placebo Easyhaler® plus placebo Turbuhaler®. The final inhalation of study drug was performed at the study centre, where blood and urine samples were collected.

Fifteen subjects were recruited and all completed the study. Mean serum cortisol AUC_{0-20} values (the primary outcome variable) were comparable for each device at the two dose levels, and met the defined criteria for equivalence (90% CI 0·8–1·25 for between-treatment difference). Budesonide 800 μg day^{-1} caused minimal suppression of serum cortisol AUC_{0-20} values. Budesonide 1600 μg day^{-1} statistically significantly suppressed serum cortisol AUC_{0-20} values compared with placebo. Mean morning serum cortisol values were within the reference range in all treatment groups. At a budesonide dose of 800 μg day^{-1} mean urine cortisol/creatinine ratio was statistically significantly higher with Easyhaler® than with Turbuhaler®, but there was no significant difference between the devices at the 1600 μg day^{-1} dose. Serum budesonide concentrations were equivalent for each device at both dose levels. Adverse drug reactions were infrequent and mild in nature and there were no clinically significant changes in laboratory safety variables.

In conclusion, in healthy male volunteers, budesonide 800 μg day^{-1} and 1600 μg day^{-1} inhaled from Easyhaler® had comparable systemic effects to the same doses inhaled via Turbuhaler®.

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Keywords budesonide; easyhaler®; turbuhaler®; systemic safety; healthy volunteers.

INTRODUCTION

Budesonide is a potent glucocorticosteroid, with well-documented efficacy in the treatment of asthmatic patients (1). When inhaled, the systemic bioavailability of budesonide results primarily from absorption across the lung vascular bed, while any swallowed drug undergoes extensive first-pass metabolism in the liver (2,3). Pharmacokinetic studies of budesonide have demonstrated that about 30% of the inhaled dose is bioavailable (4).

Dose-related suppressive effects on HPA axis function have been observed with budesonide (5,6). The systemic markers most commonly used to monitor these effects in humans are serum and/or urinary cortisol (7). These measures can be made more sensitive by determining integrated area under the curve (AUC) for repeated serum cortisol measurements, and by correcting urinary cortisol excretion for creatinine [urinary cortisol/creatinine (UCC) ratio].

A key element in determining the systemic bioavailability of an inhaled corticosteroid is the delivery device (8). Hence, it is important to document the systemic effects of an agent in relation to the particular devices from which it will be inhaled. One of the most widely used devices for the delivery of corticosteroids in most of Europe is the pressurized metered-dose inhaler (pMDI) (9). However, these devices are associated with a number of problems, including under-dosing due to poor hand–breath coordination (10) and airway irritation from the lubricants or propellants used (11).

In order to overcome the drawbacks of pMDIs, breath-actuated multi-dose dry powder inhalers were developed, of which Turbuhaler® was one of the first, and is well documented for the delivery of budesonide

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(12–15). Easyhaler® is a new-generation dry powder inhaler currently documented and registered for the delivery of salbutamol (16) and beclometasone dipropionate (17).

The main purpose of the present study was to compare the systemic activity of budesonide, at clinically recommended dose levels (800 μg day^{-1} and 1600 μg day^{-1}), delivered from Easyhaler® and Turbuhaler® in healthy male subjects. Three measures were used to assess the potential effect of budesonide on HPA axis function: morning (08·00 h) serum cortisol, area under the curve (AUC) for repeated serum cortisol measurements and urinary cortisol/creatinine (UCC) ratio. Serum budesonide concentrations were also determined.

MATERIALS AND METHODS

Subjects

Healthy male volunteers, aged 18–40 years, were recruited into the study. In order to be included in the study, they had to be non-smokers (for at least 6 months) with a body mass index of 19–26 kg m^{-2}, and to have normal health as determined by previous medical history and both physical and laboratory examinations performed within 30 days before study entry.

Study design

The study was carried out at a single centre (the Pharmacokinetic Unit of the Department of Medical Product Maintenance and Pharmacokinetics, Orion Pharma, Kuopio, Finland) according to a randomized, placebo-controlled, double-blind, double-dummy, five-way cross-over design. Both of the dry powder inhalers used in the study, budesonide Easyhaler® (Orion Pharma, Espoo, Finland) and Pulmicort® Turbuhaler® (AstraZeneca, Lund, Sweden), delivered budesonide at a dose of 400 μg per inhalation. After careful instruction in the technique for each device, all subjects received the following treatment regimens for 1 week each, in randomized order, with a 1-week washout period between each treatment:

- budesonide Easyhaler®, 400 μg dose^{-1}, one inhalation twice daily (800 μg day^{-1}) plus placebo Turbuhaler® one inhalation twice daily;
- budesonide Easyhaler®, 400 μg dose^{-1}, two inhalations twice daily (1600 μg day^{-1}) plus placebo Turbuhaler® two inhalations twice daily;
- placebo Easyhaler®, one inhalation twice daily plus Pulmicort® Turbuhaler® 400 μg dose^{-1}, one inhalation twice daily (800 μg day^{-1});
- placebo Easyhaler®, two inhalations twice daily plus Pulmicort® Turbuhaler® 400 μg dose^{-1}, two inhalations twice daily (1600 μg day^{-1});
- placebo Easyhaler®, one inhalation twice daily plus placebo Turbuhaler®, one inhalation twice daily.

Thus, the total study period lasted for 9 weeks, comprising five treatment weeks with 4 washout weeks in between each treatment week. Subjects were instructed to perform inhalation(s) at 08·00 h and 20·00 h from the devices. After each inhalation, subjects were instructed to hold their breath for 5–10 sec before exhaling, and to rinse their mouth with water and spit it out after each inhalation. Before the study days, all subjects learned to inhale with an optimal inspiratory flow rate using a peak inspiratory flow (PIF) meter, designed for Easyhaler®.

Of the 14 inhalations in each treatment week, 13 were performed at home and the last was performed at 20·00 h at the Pharmacokinetic Unit under the supervision of the study personnel. Blood samples (5 ml) were drawn in the week before starting treatment (baseline) and on the last day of each treatment week at multiple time points: before inhaling the last dose (time 0), and every 2 h up to 20 h after it. For 24 h prior to each study visit, subjects were instructed to avoid strenuous exercise, eat normal meals and to avoid cold air (-20°C for several h), alcohol and sauna. They were also instructed to fast from 16·00 h. onwards on the day of the study visit and to stay in bed from 00·00 h until 07·00 h the following morning.

The blood samples were allowed to clot (approximately 30 min) and the serum was separated by centrifugation and stored at -20°C until analysed. Serum cortisol analysis was performed using a radioimmunoassay method at Oy Medix Ab, Helsinki, Finland. The AUC_{0-20} was calculated using BIOPAK software (Statistical Consultants, Inc., Lexington, Kentucky, U.S.A.) according to the trapezoidal rule. Mean single morning serum cortisol concentrations at 08·00 h were also calculated. For each blood sample (0 – 20 h), serum budesonide concentrations were also determined using a combination of high performance liquid chromatography (HPLC) and mass spectrometry at the Department of Bioanalytics and Pharmacokinetics of Orion Pharma, Espoo, Finland. The pharmacokinetic parameters AUC_{0-20}, C_{max} and t_{max} for budesonide were calculated using BIOPAK software.

Urine was collected at the study site in one 12-h fraction. Subjects were instructed to empty their bladder immediately before the last inhalation(s) of study drugs. Thereafter, urine was collected and stored in a refrigerator at +4°C until completion of the 12-h period. Samples (5 ml and 10 ml) were then transferred to test tubes and stored at -20°C until analysed. Urine cortisol values were analysed with HPLC (18), and creatinine determinations were performed by spectrophotometry at Helsinki University Hospital.

Safety was also determined by measuring standard laboratory parameters before and after study. In addition, subjects recorded all adverse events in their treatment diaries. At each study visit, the investigators also performed oropharyngeal swabs to determine the presence of *Candida albicans*; use of any anti-mycotic medication was recorded in the diaries.

Compliance with study treatment was assessed by subjects' daily diary records and by the return of all used Easyhalers® and Turbuhalers®.

The study protocol and amendments were reviewed and approved by the Ethics Committee of Orion Pharma, Finland. All subjects were required to give written informed consent and the study was conducted according to the principles of the current revision of the Declaration of Helsinki (19).

Outcome variables

The primary outcome variable was serum cortisol AUC_{0-20}. For each dose/device comparison, the following variables were also analysed: morning (08·00 h) serum cortisol, serum budesonide values (AUC_{0-20}, C_{max} and t_{max}) and UCC ratio. Finally, laboratory values and adverse events (whether related to study drug or not) were recorded in each case.

Statistical analysis

The primary hypothesis of the study was that, at equal daily doses, Budesonide Easyhaler® and Pulmicort® Turbuhaler® would have an equivalent effect on serum cortisol AUC_{0-20}. Equivalence was defined as 90% CI 0·8—1·25 for test/reference ratio at each dose level. Treatment differences for other outcome variables (as described above) were analyzed in a similar way.

Mixed analysis of variance (ANOVA) models were used in the analysis of serum cortisol AUC_{0-20}, morning serum cortisol, UCC ratio and serum budesonide concentrations. For serum budesonide concentrations, 95% CI was estimated; for all other variables, 90% CI was estimated.

It was estimated that the 0·9 power needed to assess equivalence using 0·8—1·25 criterion for test/reference ratios would be attained with 12 subjects. In order to allow discontinuations or protocol violations, 15 subjects were recruited into the study.

RESULTS

Subjects

Demographic and baseline characteristics of the 15 subjects recruited into the study are shown in Table 1. All subjects completed the study and were evaluable for safety.

TABLE 1. Demographic and baseline subject information (n=15)

Parameter	Mean (SD)
Age (years)	25 (2)
Height (cm)	177 (4)
Weight (kg)	73 (6)
BMI (kg m^{-2})	23 (1)
Heart rate (beats min^{-1})	61 (13)
Blood pressure (mmHg)	
Systolic	130 (8)
Diastolic	80 (7)

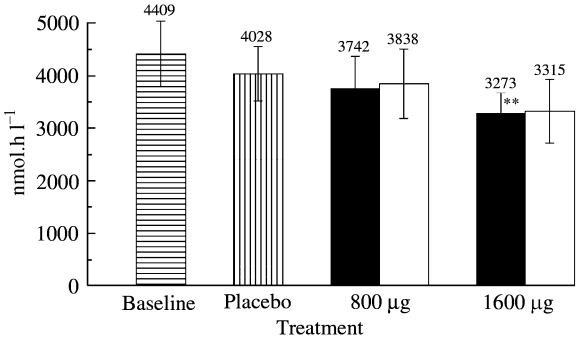

FIG. 1. Mean (SD) serum cortisol AUC_{0-20} values (nmol·h l^{-1}). (■) Easyhaler® and (□) Turbuhaler®. **P<0·01 *vs.* placebo and 800 µg Easyhaler®.

Compliance

According to the daily diary records, 100% of the prescribed dose of study drug was used in each treatment course.

Safety

Serum cortisol AUC_{0-20}

Mean serum cortisol AUC_{0-20} values were similar in subjects using budesonide Easyhaler® 800 µg day^{-1} and Pulmicort® Turbuhaler® 800 µg day^{-1} (90% CI for ratio 0·89–1·04), and in those using budesonide Easyhaler® 1600 µg day^{-1} and Pulmicort® Turbuhaler® 1600 µg day^{-1} (90% CI for ratio 0·87–1·03) (Fig. 1, Table 2). Thus, 90% CIs at each dose level were within the predefined criteria for equivalence. There was no statistically significant difference between budesonide Easyhaler® 800 µg day^{-1} and placebo. Mean serum cortisol AUC_{0-20} values were statistically significantly lower for budesonide Easyhaler® 1600 µg day^{-1} compared with placebo (P=0·008) and compared with budesonide Easyhaler® 800 µg day^{-1} (P=0·005).

Table 2. Mean (SD) values for serum cortisol AUC_{0-20} (nmol·h l^{-1}), morning (08·00 h) serum cortisol (nmol l^{-1}) and UCC ratio nmol $mmol^{-1}$ (n=15 in each case)

			Budesonide 800 μg day^{-1} from		Budesonide 1600 μg day^{-1} from	
	Baseline	Placebo	Easyhaler®	Turbuhaler®	Easyhaler®	Turbuhaler®
Serum cortisol AUC_{0-20}	4408·6 (621·6)	4027·6 (518·1)	3741·7 (619·2)	3837·9 (659·7)	3272·9 (397·2)*,†	3315·5 (608·3)
Morning serum cortisol	460·0 (64·7)	407·3 (117·0)	358·0 (120·8)	358·7 (145·0)	287·2 (158·5)	291·5 (132·3)
UCC ratio	2·01 (1·27)	1·56 (0·99)	1·53 (0·99)‡	1·05 (0·46)	1·30 (0·60)	1·11 (0·42)

*P=0·008 *vs.* placebo.
†P=0·005 *vs.* Easyhaler® 800 μg day^{-1}.
‡P=0·046 *vs.* Turbuhaler® 800 μg day^{-1}.

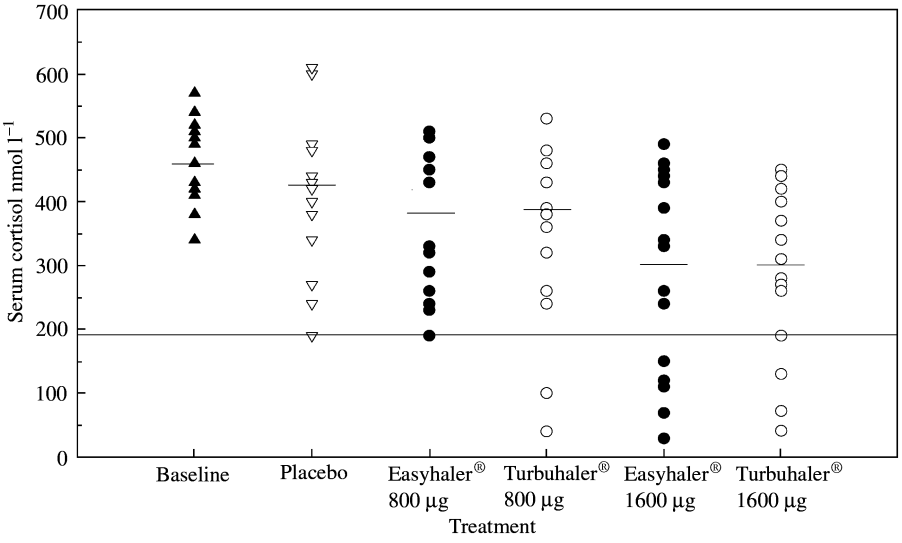

Fig. 2. Individual morning (08·00 h) serum cortisol concentrations and mean (indicated by bar). The line indicates the lower reference limit (190 nmol l^{-1}).

Morning serum cortisol

Mean morning (08·00 h) serum cortisol values were above the lower limit of the normal reference range (190 nmol l^{-1}) in all treatment groups, and there were no statistically significant differences between any of the groups (Fig. 2, Table 2). Analysis of individual values showed that two subjects in the Turbuhaler® 800 μg day^{-1} group but none in the Easyhaler® 800 μg day^{-1} group had values $<$190 nmol l^{-1} (Fig. 2). At the 1600 μg day^{-1} dose of budesonide, five subjects in the Easyhaler® group and three subjects in the Turbuhaler® group had values below the lower reference limit.

UCC ratio

The mean UCC ratio was statistically significantly higher for Easyhaler® 800 μg day^{-1} than Turbuhaler® 800 μg day^{-1} (P=0·046, ratio 1·38, 90% CI 1·06–1·80). However, there was no significant difference between the devices at the 1600 μg day^{-1} dose, nor between either of the Easyhaler® groups and placebo (Table 2).

Serum budesonide concentrations

In terms of serum budesonide concentrations (AUC_{0-20} and C_{max}), there were no statistically significant differences between Easyhaler® and Turbuhaler® at 800 μg day^{-1}, nor at 1600 μg day^{-1} (Table 3). However, as expected, there were significant differences in serum budesonide values between the 800 μg day^{-1} and 1600 μg day^{-1} dose levels for each device. Serum budesonide concentration/time curves are shown in Fig. 3. Lack of samples between 0 and 2 h, and 2 and 4 h has an effect on the concentration/time curves, showing a C_{max} at 2 h (t_{max}) after the last inhalation of the study drugs.

TABLE 3. Mean (SD) values for serum budesonide AUC_{0-20} (pg·h ml^{-1}) and C_{max} (pg ml^{-1}) (n=15 in each case)

	Budesonide 800 μg day^{-1} from		Budesonide 1600 μg day^{-1} from	
	Easyhaler®	Turbuhaler®	Easyhaler®	Turbuhaler®
Serum budesonide AUC_{0-20}	1461·7 (903·8)	1252·3 (633·2)	2904·3 (1379·4)*	2992·3 (795·2)†
Serum budesonide C_{max}	289·3 (140·3)	284·9 (91·6)	545·2 (189·6)‡	587·5 (114·1)§

*P=0·0002 *vs.* Turbuhaler® 800 μg day^{-1}.
†P=0·0001 *vs.* Easyhaler® 800 μg day^{-1}.
‡P=0·0001 *vs.* Turbuhaler® 800 μg day^{-1}.
§P<0·0001 *vs.* Easyhaler® 800 μg day^{-1}.

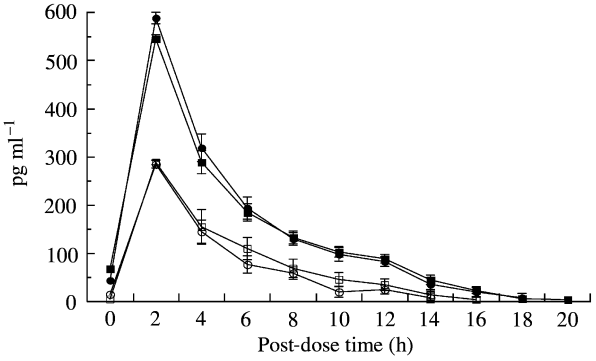

FIG. 3. Serum budesonide concentration/time curves. Means ± SD. (□) Easyhaler® 800 μg, (○) Turbuhaler® 800 μg, (■) Easyhaler® 1600 μg and (●) Turbuhaler® 1600 μg.

Adverse events

The overall incidence of adverse events during the study was low. Sixteen ADRs were reported. All were mild in nature and were considered only possibly related to study drug. There were no cases of oropharyngeal candidiasis and no serious adverse events occurred during the study.

DISCUSSION

The purpose of this study was to investigate the systemic activity of inhaled budesonide at a daily dose of 800 μg and 1600 μg from Easyhaler® or Turbuhaler® measured as the effect on HPA-axis function. Healthy male volunteers were selected for this study because they have shown to be more sensitive than asthmatic patients to the systemic effects of inhaled steroids (6).

A study period of 1 week was established to reach the maximum systemic effect of budesonide. The washout period of 1 week was used on the basis of an earlier study (20) as well as prior reports that a washout period of at least 48 h is necessary when assessing the systemic effects of different inhaled corticosteroids (21). In addition, the degree of adrenal suppression seen with repeated twice daily dosing reflects more accurately what may be expected in clinical practice (22). It has been reported that even single dosing may be used with budesonide when systemic effects are determined (23). A crossover design was used so that the subjects could serve as their own controls, which reduced error variance as well as the number of subjects needed for statistical analysis.

The two dose levels of budesonide to be tested were chosen because 800 μg day^{-1} is an average dose for maintenance treatment in asthmatic patients, and 1600 μg day^{-1} is the maximum recommended daily dose in asthma. A placebo week was included in the study because it has previously been reported that stress factors associated with having blood drawn can increase serum cortisol values.

The results of this study showed that budesonide at a daily dose of 800 μg day^{-1} from both Easyhaler® and Turbuhaler® caused no statistically significant decrease in serum cortisol AUC_{0-20} values, the primary study variable, compared with placebo. At a daily dose of budesonide 1600 μg day^{-1}, serum cortisol values were suppressed to a comparable and statistically significant extent compared with placebo for both inhalers. At the 1600 μg daily dose of budesonide, the highest per cent suppression compared with placebo was 19% for serum cortisol AUC_{0-20}.

The results of this study are consistent with those of earlier studies with inhaled budesonide. Multiple dosing for 7 days with budesonide from Turbuhaler® in healthy male volunteers resulted in 19% plasma cortisol suppression in AUC_{0-24} at a dose of 800 μg day^{-1} and 47% suppression at a dose of 1600 μg day^{-1} (24). In addition, Lönnebo *et al.* noticed that multiple dosing with budesonide from Turbuhaler® at 1600 μg day^{-1} resulted in a 34% suppression of plasma cortisol (measured as AUC_{0-20}) (25).

It has been suggested that suppression of plasma or serum cortisol AUC values only becomes clinically significant when it exceeds 50% (24,26). Even at the higher daily dose of budesonide used in the present study, serum

cortisol AUC_{0-20} suppression was only 19% compared with placebo. The systemic effects of budesonide on morning serum cortisol and UCC ratios were in accordance with the effects on serum cortisol AUC_{0-20}.

In this study, serum budesonide concentrations were also well matched at each dose of budesonide for each inhaler used. After inhalation, budesonide is absorbed rapidly and peak concentration is achieved within 20 min (27). Therefore, in further studies, in order to identify peak budesonide values more precisely, it may be of value to increase the frequency of blood sampling between 0 and 4 h after inhalation.

The overall incidence of adverse events in the study was low, and all those considered possibly related to study drug were mild in nature. There were no differences in the frequency of ADRs between the placebo and active treatments at either dose level.

CONCLUSIONS

In conclusion, 800 μg day^{-1} of budesonide via Easyhaler® or Turbuhaler® had no statistically significant effect on serum cortisol AUC_{0-20} compared with placebo. At a dose of 1600 μg day^{-1} the decrease in serum cortisol AUC_{0-20} was statistically significant and comparable with both devices. Serum budesonide concentrations at both budesonide dose levels were comparable for the two devices. There were no differences in the tolerability of budesonide with either Easyhaler® or Turbuhaler®.

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