Eur Respir J 1998; 12: 1340–1345
DOI: 10.1183/09031936.98.12061340

European Respiratory Journal
ISSN 0903 - 1936

Lung deposition of budesonide from a pressurized metered-dose inhaler attached to a spacer

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Lung deposition of budesonide from a pressurized metered-dose inhaler attached to a spacer. L. Thorsson, S. Edsbäcker. ©ERS Journals Ltd 1998.

ABSTRACT: The absolute systemic availability and pulmonary deposition of budesonide inhaled from a pressurized metered-dose inhaler (pMDI) attached to a Nebuhaler® spacer was determined in 15 healthy subjects.

The study was of an open cross-over design. Each subject randomly received three single doses of budesonide on separate days: 0.5 mg given intravenously and 1.0 mg (0.2 mg × 5) by inhalation from a pMDI with a Nebuhaler®, with or without concomitant oral charcoal intake to prevent gastrointestinal absorption.

Charcoal intake did not significantly affect the systemic availability or deposition of budesonide. The systemic availability was 36±14% (metered dose, mean±SD) with charcoal and 35±10% without. The pulmonary deposition was 36±14% with charcoal and 34±11% without. Erroneous administration, in which the canister was shaken only before the first of the five actuations, halved the systemic availability.

In conclusion, the pulmonary deposition of budesonide from a pressurized metered-dose inhaler with Nebuhaler® is high under optimum conditions. The small discrepancy between the systemic availability and pulmonary deposition indicates that the contribution from deposition in the oropharynx and subsequent absorption from the gastrointestinal tract is negligible. The marked reduction in the systemic availability of budesonide with the unshaken canisters confirms that the performance of a pressurized metered-dose inhaler is very much dependent on proper handling.

Eur Respir J 1998; 12: 1340–1345.

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Keywords: Budesonide
lung deposition
Nebuhaler®
pressurized metered-dose inhaler

Received: July 9 1997
Accepted after revision July 10 1998

In the treatment of asthma, inhaled formulations are commonly used to direct drugs to the lungs. The inhaled drug is deposited either in the upper respiratory tract or in the lungs. Exhaled drug generally constitutes a negligible part of the dose. The fraction deposited extrapulmonarily is eventually swallowed and absorbed from the gastrointestinal (GI) tract and will thus contribute to the systemic availability of the inhaled drug.

Spacer devices between the actuator and the mouth are used to overcome the problem of co-ordinating actuation and inhalation from a pressurized metered-dose inhaler (pMDI). The particle size in the aerosol is reduced as evaporation of the propellant occurs [1–3]. Also, larger particles are preferentially deposited on the walls of the spacer. An increased fraction of small particles means that deposition in the oropharynx is decreased. In addition, lung deposition may be increased due to the fact that the velocity of the aerosol cloud is reduced before inhalation.

The Nebuhaler® is a large-volume (750 mL) spacer intended for pMDIs of budesonide and terbutaline sulphate. Studies with ^{99m}Tc-labelled Teflon™ particles, using γ-scintigraphic imaging techniques, have shown that the lung deposition, in asthmatic patients with airflow obstruction, increased from approximately 9% of the metered dose with a pMDI alone, to 21% after a single puff and 15% after multiple puffs when the pMDI was attached to a Nebuhaler® [4]. The lung deposition of ^{99m}Tc-labelled terbutaline sulphate from a pMDI with a Nebuhaler® was 32% compared with 11% from a pMDI alone [5].

Scintigraphic imaging is a commonly used technique to determine lung deposition after inhalation. Lung deposition can also be determined from urinary excretion of intact drug, provided that the contribution of orally deposited and subsequently swallowed drug can be accounted for, and that the drug is not metabolized in the lung [6]. One approach to accounting for swallowed drug is to prevent GI absorption by using concomitant oral administration of activated charcoal [7]. Another approach is to calculate the lung deposition from the systemic availability after inhalation by subtracting the estimated oral contribution [7].

Budesonide is a potent glucocorticosteroid effective in the treatment of asthma. When given by inhalation, its antiasthmatic effect may be explained by a local pulmonary action [8]. No oxidative or reductive metabolism of budesonide has been noted in human lung homogenates [9]. The drug is rapidly and extensively absorbed [10]. Pharmacokinetic studies, performed in healthy subjects and asthmatic children, have shown that budesonide undergoes a high first-pass metabolism and has a low systemic availability (about 10%) after oral dosing [10, 11]. Inhaled budesonide undergoes a rapid systemic uptake, with a time of maximum concentration of about 20 min. The systemic availability was found to be 26% from a pMDI and 38%

from a Turbuhaler® (a breath-actuated dry powder inhaler), with reference to metered doses [7]. In the same study, it was found that approximately 15% of the metered dose reached the lung from a pMDI as compared with 32% from a Turbuhaler®.

The aim of the present study was to determine the absolute systemic availability and the pulmonary deposition, in healthy volunteers, of budesonide inhaled as a suspension aerosol from a pMDI attached to a Nebuhaler® spacer.

Materials and methods

Study subjects

Fifteen healthy subjects (seven males) with a mean age of 42 yrs (range 26–56) and a mean body weight of 68 kg (range 49–88) participated in the study. All subjects were healthy, as judged by routine physical examination, including haematology, blood chemistry tests and urinalysis. All subjects were moderate consumers of alcohol. One subject was a current smoker, and five subjects were exsmokers. One of the exsmokers was a current user of snuff tobacco. The study was approved by the Ethics Committee of the University of Lund, Sweden and by the Medical Products Agency, Uppsala, Sweden, and was in accordance with the Declaration of Helsinki. The subjects were informed about the study, verbally and in writing, and gave their written consent to participation.

Study design

The study was of an open cross-over design. Each subject randomly received three single doses of budesonide on separate days with at least 6-week intervals: one dose given as an intravenous infusion, another as a single dose inhalation from a pMDI with a Nebuhaler®, and a third one as a single dose inhalation from a pMDI with a Nebuhaler® plus concomitant oral charcoal administration. An additional intravenous administration with concomitant oral charcoal was given at the end of the study to six of the subjects in order to investigate whether or not charcoal would affect the disposition kinetics of budesonide.

Methods

A nominal dose of 1 mg Pulmicort® was administered by inhalation from a pMDI with a Nebuhaler®, and 0.5 mg by intravenous infusion. The intravenous formulation was manufactured by the Department of Pharmaceutical Development at Astra Draco. Carbomix (Norit, Holland) charcoal suspension (200 mg·mL^{-1}) was used for charcoal administration.

During administrations in which oral charcoal was used, the mouth was thoroughly rinsed with 2×25 mL (10 g) charcoal suspension, which was then swallowed. The charcoal administrations were performed immediately before, and at 5 min, 1 and 2 h after drug administration. Following administrations without charcoal, the mouth was rinsed with water (200 mL) and the water was then swallowed.

On the treatment days, the subjects arrived at the clinic after an overnight fast and were served a standardized breakfast 30 min before the start of administration. No alcohol was allowed for 24 h before each treatment. The subjects had to abstain from eating for 4 h and from drinking for 2 h after each drug administration.

The subjects were trained to exhale and then to inhale from the Nebuhaler® at a flow of 15 L·min^{-1}, hold their breath for 5 s and then to slowly exhale through a Respirgard® filter. A total dose of 1.0 mg was administered in five doses of 200 µg, taken at intervals of 30 s. The pMDI was thoroughly shaken immediately before each actuation, and the subjects had to inhale twice after each actuation. A pneumotachygraph (Vitalograph Compact; Vitalograph, Buckingham, UK) was used to record the inspiratory flow and volume, and a noseclip prevented breathing through the nose.

The lung deposition of budesonide was assessed by two different methods, previously described in a study in which the budesonide pMDI and Turbuhaler® formulations were compared [7]: 1) calculated from the systemic availability corrected for an assumed oral availability of 13%; and 2) determined directly after blocking of the GI contribution by an oral charcoal suspension.

The pMDI was primed, prior to the study administration, by actuating 10 doses into a plastic bag, using a separate actuator. The pMDIs were individually characterized with regard to drug output; the metered dose was calculated as a mean of the doses leaving the valve stem (standard *in vitro* measurement using a mean of 2×5 doses). The Nebuhaler® was primed with a placebo pMDI, in order to reduce the electrostatic charge on the spacer walls. In the priming procedure, two actuations of placebo were fired into the Nebuhaler®. After 5 s, the spacer was emptied by vacuum for 5–10 s. This procedure was repeated for a total of 20 actuations, at least 12 h before drug inhalation. The amount of drug retained in the actuator, spacer and exhalation filter was determined by through rinsing with ethanol (99.5%) containing an internal standard, followed by liquid chromatography.

The intravenous dose was administered as an infusion, over 10 min, into an antecubital vein. The dose was estimated by weighing the syringe before and after infusion.

Blood samples were obtained from an indwelling catheter inserted into an antecubital vein in the arm not used for drug administration. The plasma was separated by centrifugation (1500×*g*) for 10 min and was then imme-diately frozen at -20°C until analysis. The assay of budesonide in plasma was based on a combination of liquid chromatography and mass spectrometry [12].

Analysis

Pharmacokinetic parameters were calculated according to routine methods. The individual systemic availability data were log-transformed, and means were expressed as geometric means with 95% confidence limits. For all other parameters, means are expressed as arithmetic means.

The fraction of the metered dose of budesonide deposited and absorbed in the lung ($f_{L,mtd}$) was calculated from the systemic availability ($F_{syst,mtd}$) on the assumption that oral availability (F_O) was 13% and that no metabolism of budesonide occurred locally in the lungs, using the equa-

tion: $f_{L,mtd} = (F_{syst,mtd} - F_O \cdot (1-f_{ret}))/(1-F_O)$, where f_{ret} is the fraction of the metered dose retained in the device [7]. An oral availability of 13%, the highest mean value found in earlier studies in healthy subjects, was used in order not to underestimate the oral contribution to the systemic availability [7]. Pulmonary deposition ($F_{L,mtd}$) was calculated as a percentage of the metered dose: $f_{L,mtd} \times 100$.

When calculating the pulmonary deposition from the administration with charcoal, the values found were adjusted for drug still being absorbed from the GI tract, with an assumed oral availability of 2.5%, as charcoal adsorbs only about 80% of the budesonide deposited in the GI tract [7].

Results

All of the 15 subjects randomized into the study completed all visits and were considered eligible for pharmacokinetic evaluation. One of the 6 subjects, who received the additional intravenous administration with concomitant oral charcoal, was excluded from the analysis due to a technical error during the infusion.

Dosing

Analysis of individual inhalers revealed that, of the nominal dose of 1,000 µg (5×200 µg), a mean (±SD) of 888± 60 µg left the canister (metered dose), 62±34 µg was retained in the actuator, 435±119 µg in the Nebuhaler®, and 2 µg (0–6 µg range) was exhaled. The dose delivered from the pMDI with a Nebuhaler® was thus approximately 45% of the metered dose, with the major fraction (90%) of the nondelivered amount being retained in the Nebuhaler®. The oropharyngeal deposition of budesonide was on average <10%.

Plasma concentrations

The mean plasma concentrations of budesonide after intravenous infusion, with and without concomitant oral charcoal, are illustrated in figure 1 and, after inhalation, in figure 2. The terminal phases were considered log-linear, and the slopes were similar for the two routes of administration.

Intravenous kinetics

Kinetic parameters are listed in table 1 for the intravenous administrations without and with oral charcoal.

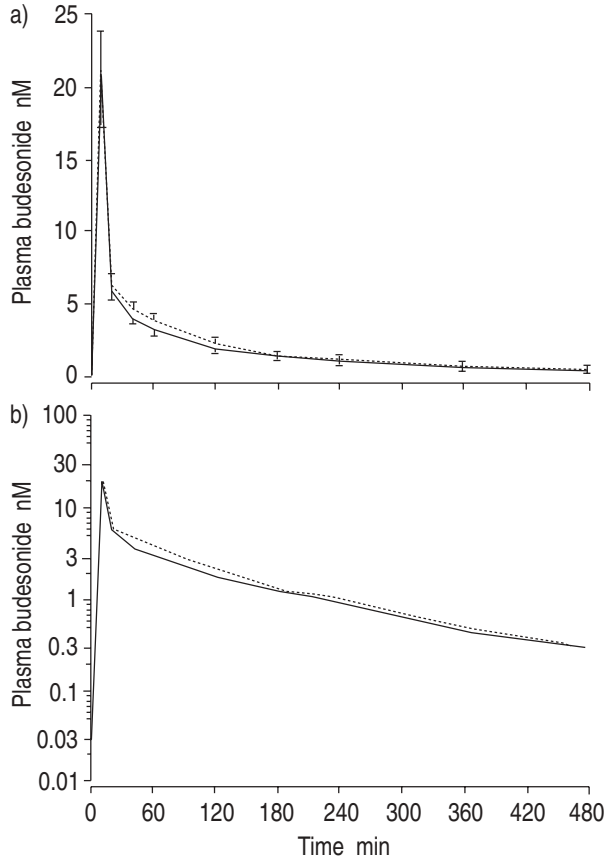

Fig. 1. – a) Mean (±SEM) plasma concentrations of budesonide after intravenous administration (0.5 mg) without (——; n=15) or with (·····; n=5) concomitant oral charcoal administration; and b) same data shown on a semi-logarithmic scale.

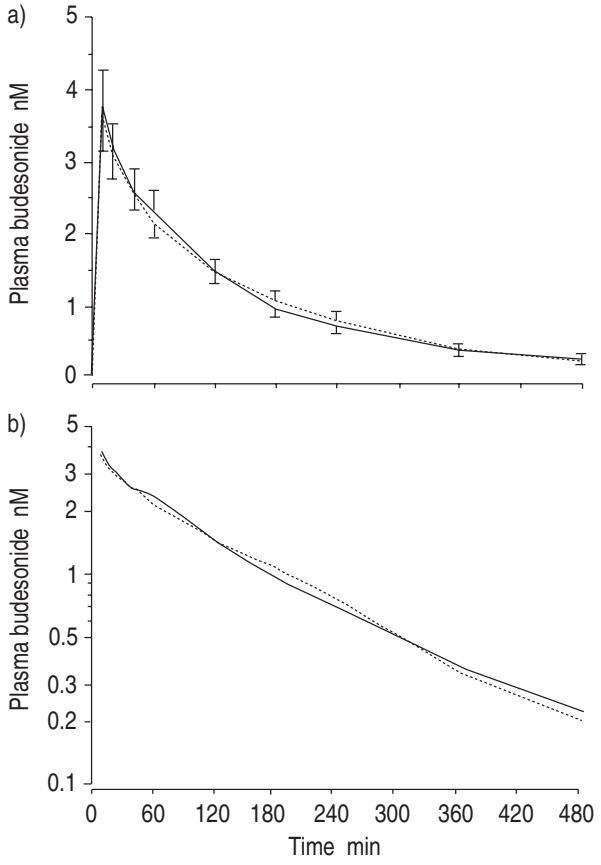

Fig. 2. – a) Mean (±SEM) plasma concentrations of budesonide after inhalation (1 mg) from a pressurized metered-dose inhaler with a Nebuhaler® without (——) or with (·····) concomitant oral charcoal administration, in 15 healthy volunteers; and b) same data shown on a semi-logarithmic scale.

Table 1. – Pharmacokinetic parameters from intravenous administrations of 0.5 mg budesonide, with and without concomitant oral charcoal

Parameter	Intravenous administration	
	Without charcoal (n=15)	With charcoal (n=5)
Dose nmol*	1173±2.1	1173±3.2
AUC mnol·h·L^{-1}	14.8±2.6	16.5±3.3
Half-life h	2.2±0.3	2.2±0.3
Mean residence time h	2.3±0.4	2.2±0.4
Clearance mL·min^{-1}	1366±294	1228±267
V_{ss} L	265±65	227±47

Values are means±SD. *: 1 µg budesonide is equivalent to 2.32 nmol. AUC: area under the curve (fig. 1a); V_{ss}: volume of distribution at steady state.

Plasma concentration *versus* time curves were almost identical for the two administrations. Comparing the dose-adjusted areas under the curves, for the five evaluable subjects receiving both administrations, gave a relative ratio of 103% (95% confidence limits: 94.8–113.9%) for administration with charcoal: without charcoal. Thus, no effect of charcoal was detected in the distribution or elimination of budesonide.

Inhalation kinetics

The systemic availability of budesonide after inhalation *via* the Nebuhaler® was 36±14% (mean±SD) with charcoal and 35±10% without charcoal with reference to the metered dose. Individual figures are listed in table 2. The pulmonary deposition with reference to the metered dose was 36±14% when administered with concomitant administration of charcoal and compensated for the contribution of drug still being absorbed from the GI tract. The pulmonary deposition was found to be 34±11%, based on the systemic availability of the metered dose after inhalation without concomitant charcoal and assuming an oral availability of 13%. There was no significant difference between the two modes of estimating the pulmonary deposition. Due to a large variability in the amount of budesonide retained in the Nebuhaler®, the adapter and on the exhalation filter, the pulmonary deposition was slightly higher than the systemic availability for some individual subjects.

The absolute systemic availability of budesonide was only marginally higher than the pulmonary availability, indicating that the contribution from deposition in the oropharynx and subsequent absorption from the GI tract was negligible.

Inhalation kinetics (unshaken canisters)

Twelve subjects (six subjects with charcoal, and six subjects without) received their first administration as an inhalation where the canisters were, erroneously, shaken only before the first puff, and not between each of the four following puffs. This unintended mistake was due to insufficient instruction of laboratory personnel and was not included in the protocol. By this means, the systemic availability of budesonide was reduced and was 19.0±7.2% and 17.6±6.5% with reference to the metered dose for the charcoal and noncharcoal treated groups, respectively. The mean systemic availability of budesonide for the 12 subjects who received this nonoptimal administration, with the unshaken canisters, was 52.1% (95% confidence interval 39.5–70.1) relative to that obtained when the administration was repeated with shaken canisters. Again, the charcoal and noncharcoal-treated groups did not differ in this respect.

Table 2. – The absolute systemic availability ($F_{syst,mtd}$) and the pulmonary availability ($F_{L,mtd}$) of budesonide with reference to the metered dose, with and without concomitant oral administration of charcoal, after inhalation of 1 mg from a pressurized metered-dose inhaler with a Nebuhaler®

Subject No.	$F_{syst,mtd}$ %		$F_{L,mtd}$ %	
	With charcoal	Without charcoal	With charcoal	Without charcoal
1	22.4	30.8	21.9	28.8
2	36.2	26.8	36.0	24.2
3	50.8	43.1	51.0	43.0
4	40.4	33.4	40.3	31.8
5	31.8	49.1	31.5	49.9
6	32.3	28.4	32.1	26.1
7	24.6	29.9	24.1	27.8
8	27.9	42.1	27.5	41.8
9	75.9	27.7	76.7	25.3
10	26.7	20.4	26.2	16.8
11	26.1	26.4	25.7	23.8
12	30.2	48.8	29.8	49.5
13	28.7	29.1	28.4	26.9
14	48.7	49.2	48.8	50.0
15	40.7	41.1	40.6	40.6
Mean	36.2	35.1	36.0	33.8
SD	13.9	9.5	14.2	11.0

Discussion

The Nebuhaler® has been suggested to be useful for controlling both local [13] and systemic [14] side-effects associated with high-dose inhaled steroids. A markedly reduced oropharyngeal deposition with the Nebuhaler® (<10% (mean value) of the metered dose) was observed in the present study, as compared with previous data on a pMDI without a spacer (70% (mean value) of the metered dose) [7]. This is reflected in the close agreement between systemic availability and lung deposition for a Nebuhaler®, whereas a larger discrepancy is seen with a pMDI alone [7].

Charcoal does not affect the distribution and elimination of budesonide, since it did not affect the intravenous pharmacokinetics of the drug. If oral uptake is efficiently blocked, the method should be valid for assessment of pulmonary availability. Also, there was no significant difference between the charcoal-block method and the method using an assumed GI availability for estimating the pulmonary availability. This is in agreement with a pre-vious study where the pulmonary availability from the pMDI and from the Turbuhaler® was investigated using the same two methods [7]. By use of the charcoal-block method, and similar inhalation modes, as in the present study, lung deposition values for terbutaline sulphate from a pMDI with a Nebuhaler® were 34% compared with

11% from a pMDI, and 32% and 11%, respectively, from γ-scintigraphic imaging in the same study [5].

In the present study, the Nebuhaler® was used under optimum conditions with regard to the dose delivered to the subject, thus minimizing any variability. In clinical practice, the variability may be anticipated to be larger. *In vitro*, the effects on device performance of a number of "user" variables have shown that single-dose actuations, slow inhalation flow and minimum delay time between actuation and inhalation were required to maximize the fine-particle fraction delivered, and hence to maximize lung delivery from spacers and reservoir devices [15]. It has been suggested that a high respirable fraction is achievable by lining a spacer with antistatic spray [16] or by wiping a spacer with an antistatic cloth prior to use [17]. The amount of small (<5 μm) particles of budesonide from the Nebuhaler® was more than doubled with a low-static spacer [18]. In the same *in vitro* study, a 20-s delay between actuation and inhalation reduced the amount delivered significantly, as did multiple actuations into the spacer before sampling. In the present study, optimum conditions were provided by priming the Nebuhaler® with a placebo pMDI prior to use in order to reduce electrostatic effects, shaking the canister before each actuation, using single-dose actuations, and by allowing only minimum delay between actuation and inhalation.

The marked reduction in the systemic availability of budesonide when using the unshaken canisters, in the present study, indicates that suboptimum conditions may have a profound effect on drug delivery from a pMDI. This is also in agreement with *in vitro* data showing that failure to shake a pMDI canister has a marked effect on the doses delivered consecutively [19]. The difficulty in properly shaking the bulky combination of a pMDI with a spacer attached, or, alternatively, in disconnecting and reconnecting the pMDI and the spacer for each shaking, probably makes the phenomenon with unshaken canisters more likely to happen with a spacer than without. Different pMDI and spacer combinations are subject to suboptimum performance as a general characteristic [16–21].

The pulmonary deposition of budesonide was about twice as high from a pMDI with a Nebuhaler® (32.6%, geometric mean), used under optimum conditions, in the present study, as from a pMDI (18.3%) in a previous study [7], whereas no difference could be detected when compared with the Turbuhaler® (34.2%), using data from 13 subjects participating in both studies. Budesonide administered *via* a Turbuhaler® has also been shown to be as effective as twice the dose from a pMDI with a Nebuhaler® in a clinical comparison in asthmatic children [22]. Using γ-scintigraphy, in asthmatic patients, the lung deposition was found to be 38.4% from a pMDI with a Nebuhaler® under optimum conditions, similar to those in the present study [23]. Thus, the lung deposition of budesonide from a pMDI with a Nebuhaler® is comparable in healthy subjects and in asthmatics. In routine every-day use, where the combination of pMDI plus Nebuhaler® is likely to perform suboptimally, the Turbuhaler® may perform in a more efficient and reproducible fashion than a pMDI with a Nebuhaler®. This could be one explanation for the results seen in the study of AGERTOFT and PEDERSEN [22].

Conclusion

The pulmonary deposition of budesonide administered from a pressurized metered-dose inhaler with a Nebuhaler® is high under optimum conditions. Approximately half of the metered dose is retained within the spacer. The absolute systemic availability of budesonide is only marginally higher than the pulmonary deposition, thus indicating that the contribution from deposition in the oropharynx and subsequent absorption from the gastrointestinal tract is negligible. The marked reduction in the systemic availability of budesonide with the unshaken canisters indicates, however, that an optimum performance of a pressurized metered-dose inhaler attached to a Nebuhaler® may not always be achieved.

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