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Lung deposition of budesonide in asthmatics: a comparison of different formulations

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Abstract

Lung deposition of budesonide administered from a pressurized metered dose inhaler (pMDI), with and without a large volume spacer (Nebuhaler®) attached, and from Turbuhaler®, were compared in an open, crossover, randomized study in eight asthmatic patients under optimum inhalation conditions using a ^{99m}Tc-tracer and scintigraphic imaging. The total and regional deposition of aerosol in the lungs as well as the oropharyngeal deposition was determined. The percentage of dose in the whole lung was $11.9 \pm 5.0\%$ (mean $\pm$ S.D.) from a pMDI, $38.4 \pm 10.2\%$ from a pMDI with Nebuhaler and $26.1 \pm 10.5\%$ from Turbuhaler. The mean lung deposition from Turbuhaler was significantly greater ($p = 0.0005$) than that from a pMDI alone, and a pMDI with Nebuhaler gave significantly greater lung deposition compared with a pMDI ($p < 0.0001$) and Turbuhaler ($p = 0.02$). No significant difference was observed in central lung deposition between Turbuhaler and Nebuhaler administrations, whereas Nebuhaler gave a greater intermediate and peripheral lung deposition. Administrations via pMDI and pMDI with Nebuhaler gave higher peripheral/central ratios (~ 1.2) vs 0.64 with Turbuhaler. The total lung deposition of budesonide via a pMDI and Turbuhaler in asthmatic patients in the present study was comparable with that previously found in healthy subjects.

Keywords: Asthma therapy; Gamma scintigraphy; Budesonide; Pressurized MDI; Turbuhaler®; Nebuhaler®

1. Introduction

Current guidelines for asthma treatment are based on inhalation therapy with glucocorticosteroids and β-agonists (British Asthma Guidelines Coordinating Committee, 1997). As the range of inhaler devices on the market increases, information about their delivery characteristics and lung deposition properties for each drug formulation will be needed. With marked differences in delivery characteristics, devices cannot be readily

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switched during treatment on the assumption that the same dose will be delivered to the lungs (Keeley and Rees, 1997). The clinical implications of any such differences have to be verified in additional studies on efficacy or safety.

The glucocorticosteroid budesonide was first developed for inhalation as a suspension aerosol in a conventional pressurized metered dose inhaler (pMDI). A large volume spacer, Nebuhaler® (Astra Draco AB, Sweden) was later developed to make the pMDI easier for the patients to use, since the patient avoids the need for coordination between actuation and inhalation. Spacers also increase the lung deposition due to the reduced velocity of the aerosol cloud (Newman, 1983). Additionally, spacers markedly reduce oropharyngeal deposition as larger particles are deposited on the walls of the spacer. Evaporation of the propellant from the droplets inside the chamber of the spacer device occurs, which may lead to delivery of smaller droplets to the lungs (Morén, 1978; Newman et al., 1991; Summers, 1991). The reduction of oropharyngeal deposition may be particularly important in the case of inhaled corticosteroids, as it may be associated with a reduction in the incidences of both local (Toogood et al., 1984) and systemic (Brown et al., 1993) side-effects, compared with a pMDI without a spacer.

Dry powder inhalers are today the most convenient alternative to pMDIs as they are breath-actuated and do not require CFC propellants (Dirksen and Groth, 1983; Engel et al., 1989; Crompton, 1990; Newman et al., 1991). Turbuhaler® (Astra Draco AB) is a multidose powder inhaler available with budesonide. Lung deposition of budesonide has previously been determined in healthy volunteers by plasma concentration vs time data and subtracting or masking the gastrointestinal contribution (Thorsson et al., 1994). In that study, it was found that about 15% of the metered dose reached the lung from a pMDI as compared with 32% from Turbuhaler (Thorsson et al., 1994). In an additional study, 13 of the healthy volunteers participating in the first study were given budesonide via a pMDI with Nebuhaler under optimum inhalation conditions. By attaching the spacer, lung deposition increased from 18 to 33% (Thorsson et al., submitted to *Eur. Respir. J.*).

Most budesonide lung deposition studies, both scintigraphic and pharmacokinetic, have been performed in healthy volunteers. Depending on the severity of their disease, leading to altered ventilation, asthmatic patients may, however, have a different lung deposition pattern. In the present study, the objective was to use the scintigraphic imaging technique to compare lung deposition of budesonide inhaled via a pMDI, via a pMDI with Nebuhaler, and via Turbuhaler in asthmatic patients.

2. Methods

2.1. Patients

Eight asthmatic patients (two women) were recruited via local general practitioners. Mean age was 48 years (range 30–59 years), and mean body weight was 79 kg (range 66–90 kg). Forced expiratory volume in one second (FEV_1) ranged from 50–92% of predicted, and the patients had to have a documented reversibility of $>15\%$ within the previous 2 years. Each patient underwent a medical examination both prior to and following the completion of the study and was declared fit to participate in the study by a fully registered physician. The patients continued their normal medication throughout the study. Written informed consent was obtained from all patients before starting the study. The study was approved by the Quorn Research Review Committee UK, and approval to administer radioactive formulations was given by the Department of Health, UK. The study was conducted at Pharmaceutical Profiles, Nottingham, UK, in accordance with the Declaration of Helsinki guidelines.

2.2. Radiolabelling technique

Budesonide micronized powder was obtained in bulk from Astra Draco AB. The radionuclide ^{99m}Tc was obtained from the radiopharmacy in the Department of Medical Physics, Queen's Medical Centre. The radiotracer technique de-

scribed by Newman et al. (1989a) was used to label the pMDI formulation, and the technique described by Thorsson et al. (1993) was used to label budesonide powder. Briefly, ^{99m}Tc was extracted as pertechnetate into methyl-ethyl-ketone which was then evaporated to dryness. The radiolabel was redissolved in water and mixed with the budesonide powder. Finally the water was evaporated in a freeze dryer and the resulting powder was filled into an empty Turbuhaler.

2.3. In vitro validation

Prior to the clinical part of the investigation, in vitro particle size measurements were performed on the pMDI and on Turbuhaler to compare the distributions of unlabelled active drug (UAD) in different particle size fractions, using a high precision multistage liquid impinger (HPMLI). The measurements were performed at a continuous flow of 60 $l \cdot min^{-1}$, and a 90° bent glass tube was used as the inlet to the impinger. The data were compared with the corresponding measurements of labelled active drug (LAD) and radiolabel (RL). The relative distributions of drug and radiolabel in the actuator/mouthpiece, throat and the four stages of the HPMLI were measured.

2.4. In vivo deposition

The study was of an open, crossover, randomized design. Each patient received single-dose administrations of pMDI, pMDI plus Nebuhaler and Turbuhaler, as two metered doses (2×200 μg) of [^{99m}Tc]budesonide on each occasion, with the three study days separated by at least 48 h. A Vitalograph MDI-Compact spirometer (Vitalograph, UK) was used to measure the inhaled volume, the inhalation flow and the breath holding time. In order to achieve optimal conditions, a targeted inhalation mode was given for each device, and the patients were instructed and trained to do the inhalations accordingly. The pMDI was fired by an observer during the course of a deep slow inhalation with a targeted average inhalation flow of 30 $l \cdot min^{-1}$ (Dolovich et al., 1981). When attached to Nebuhaler, the pMDI was also fired by an observer. The patient then took a deep slow inhalation with a targeted flow of 15 $l \cdot min^{-1}$. When using Turbuhaler, patients were instructed to inhale deep and forcefully, at a targeted peak inhalation flow of 60 $l \cdot min^{-1}$ (Engel et al., 1990). All inhalations were followed by 10 s breath holding and exhalation through a filter (Pall Ultipor, UK). Each patient used a new Nebuhaler which had been primed by actuation of 20 doses of placebo pMDI 7 days before the study day, in order to reduce the electrostatic charge on the spacer walls (O'Callaghan, 1997).

Gamma scintigraphic images of the chest, stomach and oropharynx were recorded immediately following inhalation, using a General Electric Maxicamera. In addition, images of the actuator/mouthpiece, the exhalation filter and Nebuhaler were obtained. The gamma camera was coupled to a Bartec Micas V data processing system, and images were stored on optical disk for subsequent analysis. Regions of interest were drawn around the oropharynx, oesophagus and stomach. Counts were corrected for background radioactivity, radioactive decay and attenuation by body tissue (Fleming, 1979). In regions where both anterior and posterior images were recorded, the geometric mean of counts in both images was calculated prior to correcting for tissue attenuation. The relative deposition in the oropharynx included activity adhering to the mouth and pharynx together with any swallowed activity detected in the oesophagus, stomach and intestine. In addition, radioactivity adhering to the cardboard mouthpiece leading to the exhalation filter was judged to represent a portion of the oropharyngeal dose. The metered dose was fractioned into percentages in (i) lungs, (ii) oropharynx, (iii) pMDI actuator/Turbuhaler mouthpiece/Nebuhaler, and (iv) exhalation filter. The lung outlines were obtained from a posterior lung ventilation image using an inert gas (^{81m}Kr) which was used to define the edges of the lung fields on the aerosol views. The lungs were subdivided into central, intermediate and peripheral regions of interest (Newman et al., 1989b).

2.5. Statistical considerations

Lung deposition data were log-transformed before analysis using an ANOVA model with factors patient, visit and treatment. Pairwise comparisons were made using appropriate linear

3. Results

The particle size distributions of unlabelled and labelled budesonide, and of radiolabel are given in Fig. 1a for the pMDI formulation and in Fig. 1b for the formulation for Turbuhaler. The fine particle fractions, defined as particles trapped in the third and fourth stages of the HPMLI, of unlabelled active drug, labelled active drug and radiolabel from the pMDI formulation were 30.8, 27.3 and 25.6%, respectively. The corresponding data for the formulation for Turbuhaler was 31.1, 30.0 and 32.0%. The ratio of radiolabel fine particle fraction to unlabelled active drug fine particle fraction was 0.83 for pMDI and 1.03 for Turbuhaler.

Lung function determined as FEV_1, immediately before inhalation of radiolabelled budesonide on the second and third study days, was within 15% of that of the first study day. Lung function measurements were also performed 30 min post-dosing in order to check that no one bronchoconstricted. The mean inhalation flow recorded for pMDI was 28 $l \cdot min^{-1}$ (range 14.7–40.5 $l \cdot min^{-1}$) with a mean inhaled volume of 2.9 l, and 16 $l \cdot min^{-1}$ (6.7–23.7 $l \cdot min^{-1}$) for pMDI with Nebuhaler with a mean inhaled volume of 1.9 l. With Turbuhaler, a mean peak inspiratory flow of 67 $l \cdot min^{-1}$ (49–88 $l \cdot min^{-1}$) was achieved, with a mean inhaled volume of 3.4 l.

Gamma scintigraphic images of the chest and oropharynx following inhalation from a pMDI, a pMDI plus Nebuhaler and Turbuhaler are shown in Fig. 2a–c. The relative deposition in the lungs, the oropharynx, the actuator/mouthpiece and Nebuhaler, and on the exhalation filter, expressed as percentages of the metered dose, are shown in Table 1. The mean whole lung deposition for the pMDI alone was $11.9 \pm 5.0\%$ (mean $\pm$ S.D.) of the metered dose. The effect of attaching a Nebuhaler spacer device between the actuator and the patient, and reducing the inhalation flow to 15 $l \cdot min^{-1}$, resulted in an increase in lung deposition to $38.4 \pm 10.2\%$. The mean lung deposition from Turbuhaler was $26.1 \pm 10.5\%$, which was significantly greater ($p = 0.0005$) than that from a pMDI alone, and significantly less ($p = 0.02$) than that from a pMDI with Nebuhaler. The pMDI administration resulted in a high oropharyngeal deposition (80.6%) compared with Turbuhaler (56.6%). As a consequence of the high device retention in Nebuhaler (31.4%) and the low inhalation flow, the oropharyngeal deposition was low (23.1%).

The regional distribution within the lungs, shown in Table 2, was calculated as the fraction of the dose deposited in the peripheral zone relative to that in the central zone. The increase in total lung deposition with Nebuhaler as compared to pMDI without spacer was reflected in approximately equal, and statistically significant ($p < 0.0001$) increases in central, intermediate and peripheral deposition. No significant difference was observed in central deposition between Turbuhaler and Nebuhaler administrations, whereas Nebuhaler gave a greater intermediate and peripheral deposition. With a mean peripheral/central zone deposition ratio of 1.24 for pMDI and 1.22 for pMDI with Nebuhaler, a more even distribution was obtained than with Turbuhaler. The latter had a P/C ratio of 0.64, which indicates a more central deposition.

4. Discussion

In this study, the lung deposition of budesonide has been compared between three different combinations of drug and inhaler. The in vitro validation of the radiolabelling procedure showed that the match between radiolabel and unlabelled active drug was within acceptable limits. The slight mismatch for the pMDI suggests that the lung deposition data for this device when used either alone, or in conjunction with Nebuhaler in this study, may have been underestimated.

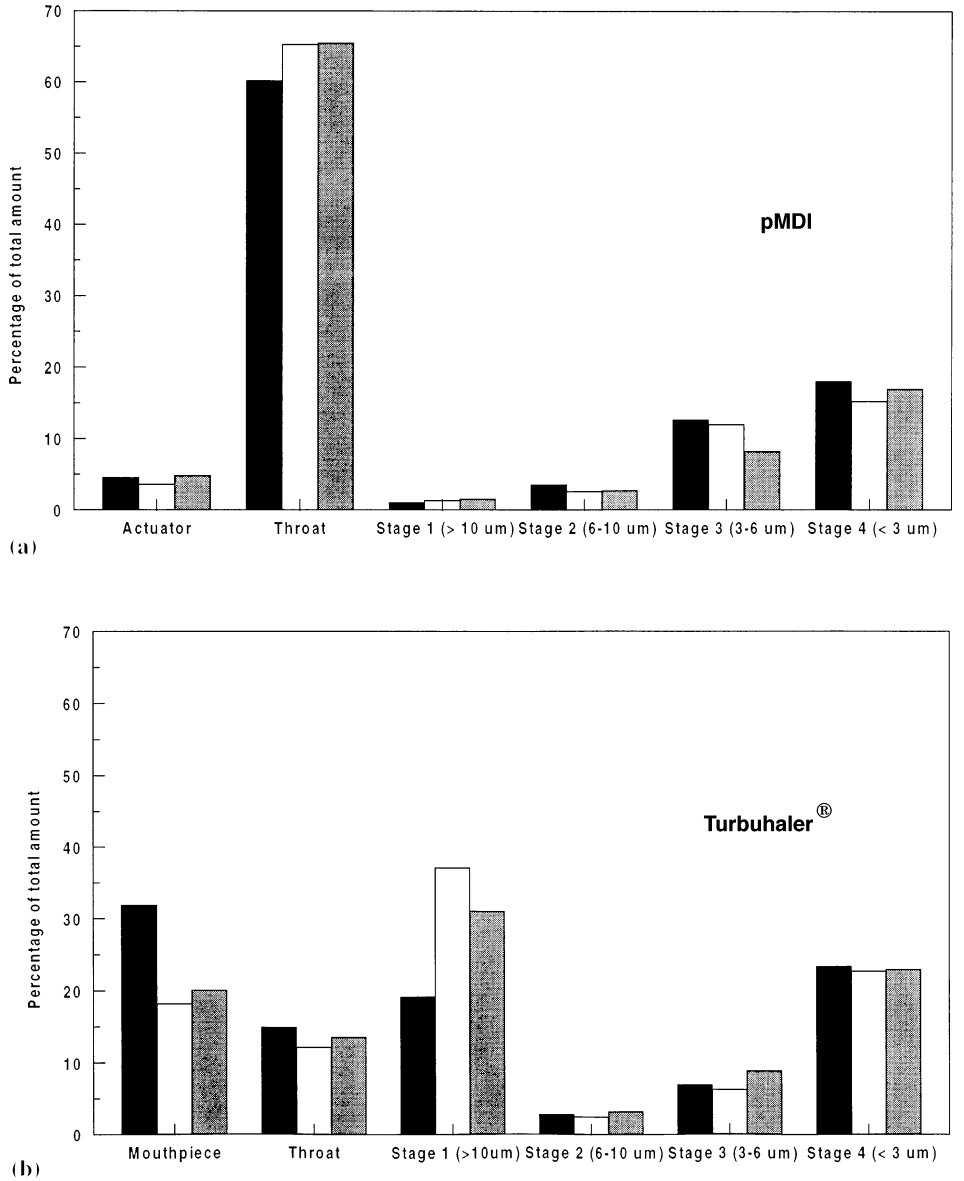

Fig. 1. (a) Percentage of unlabelled budesonide (black), labelled budesonide (white) and radiolabel (grey) from pMDI in the actuator, throat and the four stages of multistage liquid impinger. (b) Percentage of unlabelled budesonide (black), labelled budesonide (white) and radiolabel (grey) from Turbuhaler in the actuator, throat and the four stages of multistage liquid impinger.

The higher lung deposition of budesonide via Turbuhaler than via a pMDI in the present study in asthmatic patients is in good agreement with the data from a previous study using a nonradioactive method in healthy volunteers, in which the lung deposition of budesonide via Turbuhaler was found to be about twice that from a pMDI (Thorsson et al., 1994). In addition, variability in drug delivery, measured as relative coefficient of variation (CV%), was twice as high with pMDI as

Table 1
Deposition of [^{99m}Tc]budesonide (Bud) at various sites after inhalation via pMDI, pMDI with Nebuhaler and Turbuhaler as percent of metered dose

Subject no.	Lung			Oropharynx			Device			Exhaled		
	pMDI	pMDI + Nebuhaler	Turbuhaler	pMDI	pMDI + Nebuhaler	Turbuhaler	pMDI actuator	pMDI actuator + Nebuhaler	Turbuhaler mouthpiece	pMDI	pMDI + Nebuhaler	Turbuhaler
1	13.8	52.1	16.0	76.5	16.7	78.0	9.2	5.1 + 25.2	6.0	0.6	0.9	0.1
2	10.5	37.0	41.4	81.9	21.7	33.0	7.0	6.6 + 33.9	25.2	0.7	0.9	0.4
3	7.0	16.9	16.4	89.6	37.0	71.0	3.1	9.7 + 35.4	12.4	0.3	1.0	0.2
4	18.2	36.9	28.7	75.8	29.4	40.8	5.2	4.6 + 28.0	30.4	0.9	1.1	0.1
5	18.3	44.4	39.8	73.5	22.9	41.6	6.6	4.5 + 27.0	18.2	1.7	1.2	0.4
6	9.2	36.2	14.3	83.1	31.6	72.0	6.7	4.6 + 26.8	13.8	1.0	0.8	0.0
7	4.6	41.0	23.6	88.3	17.0	65.3	6.8	8.0 + 33.8	10.8	0.3	0.2	0.2
9	13.6	42.9	28.2	76.3	8.4	50.8	8.9	6.5 + 41.0	17.7	1.2	1.0	3.2
Mean	11.9	38.4	26.1	80.6	23.1	56.6	6.7	6.2 31.4	16.8	0.8	0.9	0.6
S.D.	5.0	10.2	10.5	6.1	9.3	17.1	1.9	1.9 5.5	7.9	0.5	0.3	1.1

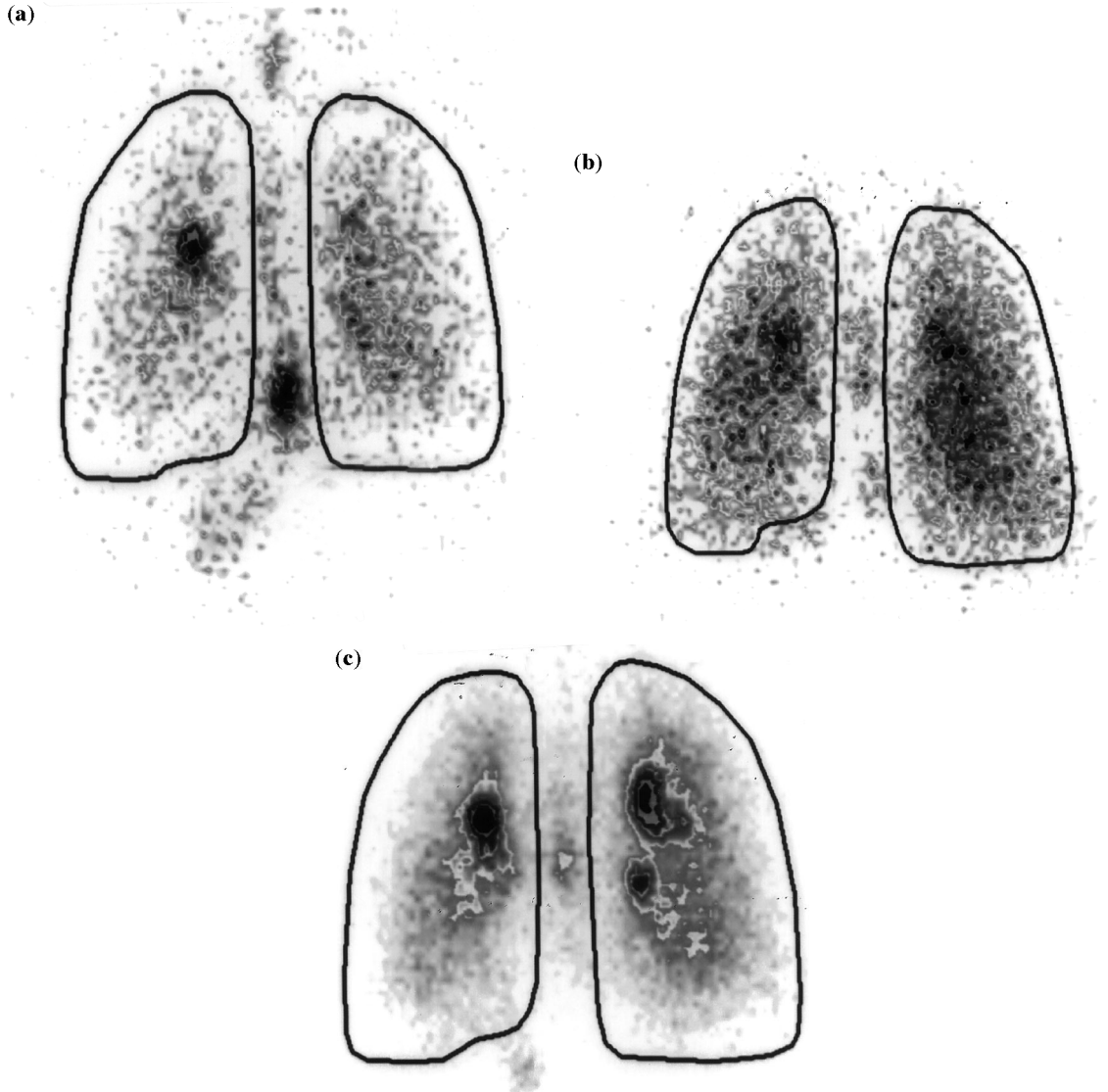

Fig. 2. Gamma scintigraphic images of deposition of ^{99m}Tc-labelled budesonide in the lungs and oropharynx of an asthmatic patient after inhalation via a pMDI (a), a pMDI plus Nebuhaler (b) and Turbuhaler (c).

compared with Turbuhaler. Budesonide Turbuhaler delivers a higher fine particle dose than budesonide pMDI in vitro (Olsson, 1995), and has shown evidence of a better clinical effect (Agertoft and Pedersen, 1993). There is also strong evidence of a good correlation between deposition data and clinical effect for other anti-asthma drugs with an approximate 2:1 relationship to the corresponding pMDI formulation for terbutaline Turbuhaler, salbutamol Turbuhaler and ipratropium bromide Turbuhaler (Löfdahl et al., 1994; Matusiewicz et al., 1995; Borgström et al., 1996).

The total lung deposition of budesonide was found to be high via a pMDI with Nebuhaler in the present study. This is in agreement with an in vitro comparison, in which the fine particle dose of budesonide was higher from a pMDI with Nebuhaler than from a pMDI alone, using an

anatomical throat as an inlet to an Andersen sampler (Berg, 1995). A number of 'user' variables have, however, been shown to affect the in vitro performance of spacer devices; single dose actuations, slow inhalation flow and minimum delay time between actuation and inhalation were required to maximize the fine particle fraction delivered (Clark, 1992). This has also been confirmed in a specific study on the in vitro delivery of budesonide from Nebuhaler (Barry and O'Callaghan, 1995). In addition, electrostatic charge on the walls of a spacer may be one of the major determinants of the performance of the device with respect to the dose delivered. Taken together, all these 'user' variables will further increase variability in drug delivery as compared to pMDI alone. In the present study, the inner surface of Nebuhaler was coated with placebo pMDI before use. By this, electrostatic charge is reduced, which should maximize drug delivery.

When used under clinically relevant conditions in asthmatic children, where 'user' variables may not be optimal, the lung deposition of budesonide was approximately twice as high after Turbuhaler treatment as after pMDI with Nebuhaler (Pedersen et al., 1993). In another study in children, budesonide via Turbuhaler was shown to be equally effective at half the dose as budesonide via pMDI with Nebuhaler (Agertoft and Pedersen, 1993).

Table 2
The percentages of the metered dose of budesonide deposited into central, intermediate and peripheral zones of the lung after administration via a pMDI, a pMDI with Nebuhaler and Turbuhaler in eight asthmatic patients

Region	pMDI	pMDI + Nebuhaler	Turbuhaler
Central lung	3.6 ± 1.5	11.1 ± 2.8	10.2 ± 3.2
Intermediate lung	4.2 ± 1.8	14.1 ± 4.1	9.2 ± 4.0
Peripheral lung	4.1 ± 2.1	13.2 ± 4.9	6.7 ± 4.0
Total lung	11.9 ± 5.0	38.4 ± 10.2	26.1 ± 10.5
P/C ratio	1.24	1.22	0.64

Values are mean $\pm$ S.D. P/C-ratio has been calculated as the fraction of dose deposited in the peripheral zone relative to that in the central zone.

The regional lung deposition of budesonide via Turbuhaler has only been examined in one previous study in healthy volunteers, in which a P/C ratio of 1.72 was determined (Borgström et al., 1994). The more central deposition found in the present study, with a P/C ratio of 0.64, suggests that peripheral aerosol penetration of budesonide via Turbuhaler is lower in asthmatic patients. However, the total lung deposition appears more or less unaffected by the disease, with 28% in the previous study in healthy and 26% in the present study in asthmatics.

Total lung deposition of budesonide was significantly higher from pMDI with Nebuhaler than with Turbuhaler. This difference was mainly due to a higher peripheral deposition with pMDI with Nebuhaler, compared with Turbuhaler, while the central deposition was similar for the two devices. Though the fine particle fraction has been suggested to relate to deposition in the peripheral parts of the lung (Fuller et al., 1995), the present results together with in vitro data, showing that Turbuhaler and pMDI with Nebuhaler delivers a similar fine particle fraction in vitro (Berg, 1995; Olsson, 1995), indicates a more complex picture. The reason for the difference between in vitro and in vivo results probably involves other factors like the interaction of the inhaled aerosol cloud with the oropharynx and lungs, in healthy and diseased state. Whether this difference between total and also regional deposition between Turbuhaler and pMDI with Nebuhaler is maintained also in the clinical and less optimal setting remains to be elucidated.

The development of more efficient inhalers, directing more drug to the lungs, may enable asthma to be treated with a lower daily dose of drug. Any difference in lung deposition between formulations should, however, be verified on clinical outcome before any recommendations of possible dose reduction are made.

In summary, this study has compared the total and regional lung deposition of budesonide from a pMDI, a pMDI with Nebuhaler and from Turbuhaler in asthmatic patients. Nebuhaler, used under optimum conditions, was found to give the highest lung deposition, and Turbuhaler gave about twice the lung deposition as from a pMDI

alone. The deposition in the central regions of the lung was similar for Nebuhaler and Turbuhaler, whereas peripheral lung deposition was higher for pMDI with Nebuhaler.

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