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Deposition and pharmacokinetics of budesonide from the Miat Monodose inhaler, a simple dry powder device

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Abstract

Dry powder inhalers (DPIs) are used to deliver asthma drugs to patients, but lung deposition may depend upon the degree of inspiratory effort. The pulmonary deposition of the glucocorticosteroid budesonide (SMB-Galephar) has been assessed in 12 asthmatic patients when delivered by the Monodose inhaler (Miat, Milan, Italy); the Pulmicort Turbuhaler DPI (AstraZeneca, Lund, Sweden) was used as a comparator product. Patients inhaled from each device with maximal or sub-maximal inspiratory effort: Monodose inhaler 90 vs 45 l/min; Turbuhaler DPI 60 vs 30 l/min. The formulations were radiolabelled with ^{99m}Tc, and deposition of budesonide was quantified by gamma scintigraphy. Mean (SD) whole lung deposition for the Monodose inhaler (% capsule dose), was independent of inspiratory effort (maximal: 21.4 (4.3)%; sub-maximal: 21.4 (7.5)%), while lung deposition for the Turbuhaler DPI (% metered dose) fell significantly with decreasing inspiratory effort (maximal: 25.1 (6.1)%; sub-maximal: 18.5 (6.5)%; $P < 0.05$). The plasma concentrations of budesonide showed the same trends as the whole lung deposition data. The Monodose inhaler showed inspiratory effort-independent drug delivery characteristics, and could prove be a valuable low-cost alternative to more complex devices such as the Turbuhaler DPI. The Monodose inhaler may be especially useful in groups of patients unable to inhale maximally through DPIs, including young children and adult patients with severe respiratory impairment.

Keywords: Asthma; Drug deposition; Pharmacokinetics; Corticosteroids; Dry powder inhalers

1. Introduction

International agreement to phase out the use of chlorofluorocarbon (CFC) propellants has led to the development of many new inhaler devices and formulations for asthma therapy. The CFC ban also provided an opportunity to overcome some of the other limitations of the pressurized metered

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dose inhaler (pMDI), including the need to press the pMDI and breathe in simultaneously (Clark, 1995), and the low lung deposition together with high oropharyngeal deposition (Farr et al., 2000) which most pMDIs bring about. Many pMDIs have been reformulated with non-CFC propellants, sometimes targeting drug to the lungs better than their CFC counterparts (Leach et al., 1998). Some companies have developed breath-actuated pMDIs, to overcome coordination difficulties. However, other companies have taken the opportunity to develop powder formulations of asthma drugs, delivered via a range of dry powder inhalers (DPIs). These devices are generally breath-actuated since the patient's inspired air is used to disperse the powder during inhalation, and no propellants are required. Some DPIs deposit drugs more efficiently in the lungs than pMDIs, thereby improving pulmonary targeting (Newman, 1997).

The Turbuhaler DPI (AstraZeneca, Lund, Sweden) was introduced in the late 1980s in many European countries, and has proved very effective in delivering both inhaled bronchodilators and corticosteroids to asthmatic patients (Pauwels et al., 1996). However, many other DPIs have been introduced or are being developed, some of which may be equally effective. The Monodose inhaler (Miat, Milan, Italy) is a simple DPI in which the drug is contained in gelatine or hypromellose capsules, and potentially offers a low-cost alternative to more complex devices such as the Turbuhaler DPI. In breath-actuated DPIs, drug delivery generally depends upon the degree of inspiratory effort, often quantified in terms of the inhaled flow rate generated through the device. In this study, the lung deposition of the glucocorticosteroid budesonide (SMB-Galephar, Brussels, Belgium), when delivered by the Monodose inhaler and by the Turbuhaler DPI, has been determined by the radionuclide imaging technique of gamma scintigraphy (Newman, 1993, 1998). In order to assess the flow rate dependence of each device, deposition was assessed with maximal inspiratory effort and also with sub-maximal effort. In addition, the pharmacokinetic profiles of budesonide from each device, and at each flow rate, were determined.

2. Materials and methods

2.1. Study design

The study was a four-way randomized cross-over study in 12 patients with a clinical diagnosis of mild to moderate asthma (10 males, two females, age range 18–62 years). The forced expiratory volume in 1 s (FEV_1) ranged from 60 to 111% of the value predicted on the basis of each subject's age, sex and height (Quanjer et al., 1993).

A dose of 400 μg budesonide was given on each of 4 study days as follows:

i) Monodose inhaler; targeted peak inhaled flow rate (PIFR) 90 l/min;
ii) Monodose inhaler; targeted PIFR 45 l/min;
iii) Turbuhaler DPI; targeted PIFR 60 l/min;
iv) Turbuhaler DPI; targeted PIFR 30 l/min.

The Monodose inhaler has a lower resistance to airflow than the Turbuhaler DPI, and hence PIFRs of 90 and 60 l/min represented maximal inspiratory effort through the Monodose inhaler and the Turbuhaler DPI, respectively.

The objectives and methods used in the study were approved by the Quorn Research Review Committee (Leicestershire, UK), and each subject provided informed consent in writing. The administration of radioactivity to the subjects was approved by the Department of Health, UK.

2.2. Preparation of inhalers

In order to prepare a radiolabelled Monodose inhaler, ^{99m}Tc pertechnetate from a radionuclide generator (Nycomed Amersham, Amersham, UK) was extracted into methyl ethyl ketone (MEK) and the MEK evaporated with gentle heating under a continual stream of air in a glass vial. The radiolabel was then re-suspended in HPLC grade water and mixed thoroughly with a small amount of micronised budesonide (SMB-Galephar, Brussels, Belgium) until all of the powder was wet. The water was removed by freeze drying and the radiolabelled drug passed through a sieve (300 μm) before being blended with a fine/coarse lactose mixture using a Turbula T2C mixer.

Capsules were then filled with the radiolabelled formulation, so that each capsule contained 200 μg budesonide plus 24 mg lactose.

The radiolabelling technique used for the Turbuhaler DPI formulation has been described previously elsewhere (Thorsson et al., 1993). The radiolabel (^{99m}Tc pertechnetate) was extracted into MEK which was evaporated with gentle heating under a continual stream of air. HPLC grade water (1 ml) was added to the vial containing the radiolabel, which was sonicated for 10 min. A commercial budesonide Pulmicort Turbuhaler DPI (AstraZeneca, Lund, Sweden) was emptied and the spheres were placed into a glass beaker together with the water and radiolabel mixture. Using a needle, the spheres were mixed until they were completely wet, and the water removed by freeze-drying. The previously emptied device was re-filled with the radiolabelled powder and primed by firing 10 shots to waste.

2.3. Validation of radiolabelling methods

A radiolabelling method is considered to be validated and suitable for use in an in vivo study provided that two criteria are met; first that the size distribution of the drug is not changed significantly by the labelling process, and second that the radiolabel acts as a valid marker for the drug across an appropriate range of particle size fractions (Farr, 1996). Prior to starting the clinical phase of the study, a series of experiments was performed using a High Precision Multistage Liquid Impinger (HPMLI) to assess whether the radiolabelling process had any effect on the particle size distribution of budesonide from the two DPIs, and to determine whether the radiolabel would reflect the distribution of the drug substance. The HPMLI comprised an inlet (a United States Pharmacopeia (USP) induction port (United States Pharmacopeia, 1996)), and five impaction stages (stages 1–5, the fifth stage being an absolute filter). The particle size distribution of budesonide before labelling was compared with that after labelling, and also with the particle size distribution of the ^{99m}Tc radiolabel. The HPMLI was operated at 60 l/min for both devices, for a duration of 4 s per dose.

For the Monodose inhaler, each particle size distribution of drug or radiolabel was determined by firing five capsules into the HPMLI. The capsules, device, induction port, and stages were then washed quantitatively with methanol into separate volumetric flasks. To determine the particle size distributions of both drug and radiolabel from the Turbuhaler DPI, 10 doses from a primed device were fired into the HPMLI. The mouthpiece, induction port and stages were then washed quantitatively with methanol into separate volumetric flasks. Drug and radiolabel content of the washes were determined by UV spectrophotometry at 243 nm, and by gamma counting, respectively. The dose was fractionated into the percentages of both drug and radiolabel recovered from the device and capsule (for Monodose inhaler), mouthpiece (for Turbuhaler DPI), induction port, and five impaction stages. The fraction of the drug or radiolabel recovered from stages 3, 4 and 5 (representing particles smaller than 6.8 μm diameter) was defined as the Fine Particle Fraction (FPF). The Fine Particle Mass (FPM) was defined as the total amount of drug (μg) deposited on stages 3, 4 and 5, and represented the mass of drug contained in particles with an aerodynamic diameter < 6.8 μm. Study day inhalers were checked subsequently before dosing in order to ensure that their radiolabel FPFs came within the range of values seen in the pre-study validation tests.

2.4. Administration of radiolabelled aerosols

Inhalations were performed with the devices connected in series with a Vitalograph MDI-Compact Spirometer (Vitalograph, Buckingham, UK). Each patient was given detailed instruction on inhaler use, and practiced with a placebo device until the desired inhalation manoeuvre had been mastered. Patients could see the inhaled flow rate trace on a screen, and were instructed to keep the flow rate signal between a set of tram-lines. In addition to inhaling at the required PIFR, patients were also instructed to inhale deeply, hold the breath for 10 s, and then exhale via a filter. Each patient received two radiolabelled doses on each study day, each dose containing 200 μg budesonide plus 5 MBq ^{99m}Tc (total 400 μg budesonide, 10

MBq ^{99m}Tc, from each device). For each dose, two breaths were taken from the Monodose inhaler, to ensure complete capsule emptying. In order to minimize the total duration of the inhalation manoeuvre, only the inhalation details of the second dose from the Turbuhaler DPI, and the second breath for the second dose from the Monodose inhaler, were recorded.

2.5. Scintigraphic and pharmacokinetic data

Scintigraphic images of the chest (posterior and anterior, duration 100 s), and lateral oropharynx (duration 30 s), were recorded immediately after dosing (General Electric Maxicamera, Milwaukee, WI, USA). The empty device and capsule (Monodose inhaler), mouthpiece (Turbuhaler DPI) and exhalation filter were also counted. Each patient underwent a posterior ventilation scan using the radioactive inert gas ^{81m}Kr in order to delineate the lung edges. All images were recorded on a Park Medical Micas Xplus computer system (Park Medical, Farnborough, Hampshire, UK) for subsequent analysis.

Venous blood samples were taken pre-dose, and then at 15, 30 min, 1, 2, 3, 4 and 6 h post-dose in order to quantify plasma levels of budesonide. After centrifugation, plasma concentrations of budesonide epimers A and B were determined using an on-line LC-MS/MS method with an atmospheric pressure chemical ionisation interface. This determination was preceded by purification of each plasma sample using an off-line solid-phase extraction on disposable extraction cartridges, performed automatically by a robotic system (ASPEC). The collected eluate was then evaporated to dryness before being dissolved in the mobile phase. The plasma budesonide concentrations were expressed as the sum of budesonide epimers A and B. Maximal plasma concentration (C_{max}) and time to maximal plasma concentration (T_{max}) were taken directly from the plasma concentration vs time curve. Area under the curve (AUC) was calculated by the linear trapezoidal rule from measured data points from time of administration until the time of the last quantifiable concentration.

2.6. Lung function measurements

FEV_1 was measured by Microloop Spirometer (Micro Medical, Rochester, UK) before dosing and then 30 min later, in order to check whether the inhaled formulations had led to any significant bronchoconstriction.

2.7. Data analysis

During data analysis, regions of interest were drawn around the lungs, oropharynx, oesophagus and stomach. The counts obtained within these regions were corrected for background radioactivity, radioactive decay and tissue attenuation of gamma rays (Pitcairn and Newman, 1997). In regions where both anterior and posterior images were recorded, the geometric mean of counts in both images was calculated. Determination of the percentage of the dose deposited in the oropharynx included activity adhering to the mouth and pharynx together with any swallowed activity detected in the oesophagus, stomach and intestine. The counts for each area were expressed as a percentage of the metered dose, which was determined from the sum of the total body counts in addition to those retained in Monodose inhaler and capsule, deposited on the Turbuhaler DPI mouthpiece, and on the exhalation filter. Data were recalculated as mass of drug deposited in the lungs by multiplying the percentage of the metered dose in the lungs by the nominal metered dose (total 400 μg).

Regional lung deposition patterns were assessed by dividing the lungs into central, intermediate and peripheral regions of interest (Newman et al., 1998). The peripheral lung zone to central lung zone deposition ratio (P/C ratio) was calculated as an index of regional lung deposition (Newman et al., 1998).

2.8. Statistical analysis

The Wilcoxon matched-pairs signed-ranks test was used to compare the lung deposition data and pharmacokinetic data obtained with the two devices, and at different inhaled flow rates.

3. Results

3.1. Radiolabelling validation

Data for the Monodose inhaler are shown in Fig. 1. These data showed a good match between the mean (SD) FPFs of drug before labelling (33.1 (1.8)%), drug after labelling (31.3 (3.2)%) and radiolabel (32.3 (3.0)%). The FPMs of drug before labelling and drug after labelling were 114.1 (15.0) and 117.5 (23.0) μg, respectively. Data for the Turbuhaler DPI are shown in Fig. 2. The fractionation between impactor induction port and stage 1 proved to be highly variable, reflecting powder which was deposited on the induction port, but which could fall subsequently onto stage 1 under gravity. Hence the data for induction port and stage 1 have been pooled. There was a good match between the mean (SD) FPFs of drug before labelling (36.2 (1.0)%), drug after labelling (40.7 (1.1)%) and radiolabel (36.9 (4.1)%). The FPMs of drug before labelling and drug after labelling were 76.6 (6.4) and 81.2 (9.3) μg, respectively. It was concluded that the radiolabelling methods for the two DPI formulations were suitable for use in the clinical study.

3.2. Deposition data

The data were fractionated between percentages of the dose deposited in the whole lungs and

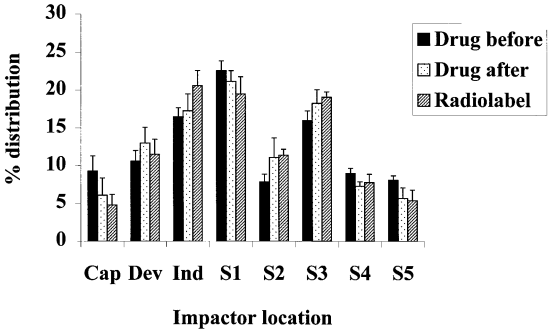

Fig. 1. Radiolabelling validation data for the Monodose inhaler, showing distributions in a HPMLI of drug before labelling ($n = 5$), drug after labelling ($n = 5$) and radiolabel ($n = 5$). Cap, capsule; Dev, device; Ind, induction port; S1 to S5: stages 1–5.

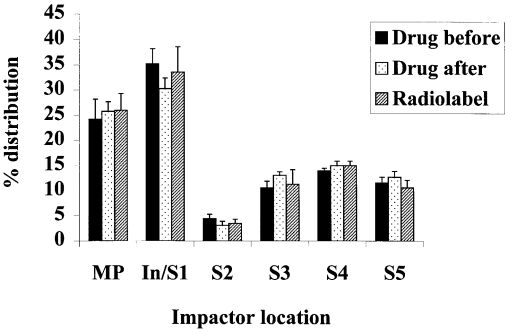

Fig. 2. Radiolabelling validation data for the Turbuhaler DPI, showing distributions in a HPMLI of drug before labelling ($n = 5$), drug after labelling ($n = 4$) and radiolabel ($n = 4$). MP, mouthpiece; In/S1, induction port plus stage 1; S2 to S5: stages 2–5.

oropharynx, retained in the device, and recovered from the exhaled air filter (Table 1). Mean (SD) whole lung deposition for the Monodose inhaler was 21.4 (4.3) and 21.4 (7.5)% of the dose at targeted flow rates of 90 (maximal inspiratory effort) and 45 l/min (sub-maximal inspiratory effort), respectively, indicating that whole lung deposition was independent of inspiratory effort over the range of flow rates tested. By contrast, while whole lung deposition averaged slightly higher for the Turbuhaler DPI at 60 l/min (25.1 (6.1)%) than for the Monodose inhaler, lung deposition fell significantly for the Turbuhaler DPI with reduced inspiratory effort (PIFR 30 l/min) to 18.5 (6.5)% ($P < 0.05$). These percentage depositions corresponded to the following mean masses of budesonide deposited in the lungs, assuming a total dose of 400 μg: Monodose inhaler 90 l/min: 85.6 μg; Monodose inhaler 45 l/min: 85.6 μg; Turbuhaler DPI 60 l/min; 100.4 μg; Turbuhaler DPI 30 l/min: 74.0 μg). Whole lung depositions for the Monodose inhaler at either flow rate did not differ significantly from those for Turbuhaler DPI at either flow rate.

Oropharyngeal deposition (Table 1) for the Monodose inhaler averaged slightly higher at 90 (63.4 (5.8)%) than at 45 l/min (57.3 (8.8)%), but device retention was somewhat lower (15.1 (2.8) vs 21.3 (4.3)%). Oropharyngeal deposition for the Turbuhaler DPI was lower than that for the Monodose inhaler, but mouthpiece retention was

Table 1
Mean (SD) fractionation of the dose between lungs, oropharynx, device and exhaled air filter, for the four study regimens in 12 patients with mild to moderate asthma

	Targeted flow rate			
	Monodose inhaler		Turbuhaler DPI	
	90 l/min	45 l/min	60 l/min	30 l/min
Lungs	21.4 (4.3)	21.4 (7.5)	25.1 (6.1)	18.5 (6.5)
Oropharynx	63.4 (5.8)	57.3 (8.8)	51.2 (10.1)	50.2 (10.7)
Device[a]	15.1 (2.8)	21.3 (4.3)	23.5 (14.2)	31.2 (8.8)
Exhaled air	0.2 (0.1)	0.1 (0.2)	0.3 (0.2)	0.2 (0.1)

[a] Device retention comprises capsule and empty inhaler for Monodose inhaler, and device mouthpiece for Turbuhaler DPI.

higher, and the fall in lung deposition at 30 l/min for Turbuhaler DPI was mostly accounted for by increased mouthpiece retention (60 l/min: 23.5 (14.2)%; 30 l/min: 31.2 (8.8)%). Less than 0.5% of the dose was exhaled for all four regimens.

Deposition in each of peripheral, intermediate and central lung zones is shown in Table 2, together with the peripheral zone/central zone ratio (P/C ratio). This parameter averaged 0.8 and 0.9 for maximal and sub-maximal effort through the Monodose inhaler, and 0.8 and 0.7 for the Turbuhaler DPI. The deposition patterns were relatively central, consistent with the presence of airway narrowing in the asthmatic patients.

3.3. Pharmacokinetic parameters

AUC and C_{max} showed the same trends as those for whole lung deposition (Table 3 and Fig. 3). Plasma concentrations and AUCs were highest for the Turbuhaler DPI with maximal inspiratory effort. They were slightly lower, but independent of inspiratory effort, for the Monodose inhaler. The Turbuhaler DPI with sub-maximal inspiratory effort showed markedly lower plasma levels, leading to significantly reduced AUC and C_{max} compared with the other study regimens ($P < 0.05$).

3.4. Inhalation details and lung function

Peak inhaled flow rates were close to targeted values (Table 4). Mean inhaled volumes averaged between 3.2 and 3.7 l, and mean breath-holding pauses between 8.9 and 9.5 s. One subject showed a fall in FEV_1 of more than 15% after inhaling 400 μg budesonide from the Monodose inhaler, but FEV_1 had recovered to the pre-dose value after 1 h. Otherwise, there was no evidence of any bronchoconstriction occurring as a result of inhaling the budesonide dry powder formulations.

Table 2
Regional lung deposition: Mean (SD) percentage deposition in peripheral, intermediate and central lung zones, and mean (SD) peripheral zone/central zone deposition ratio (P/C ratio)

	Targeted flow rate			
	Monodose inhaler		Turbuhaler DPI	
	90 l/min	45 l/min	60 l/min	30 l/min
Peripheral zone (%)	6.1 (2.0)	6.4 (2.8)	6.8 (2.6)	4.9 (2.3)
Intermediate zone (%)	7.3 (1.6)	7.4 (2.7)	8.8 (2.2)	6.4 (2.2)
Central zone (%)	8.0 (1.4)	7.5 (2.5)	9.5 (3.3)	7.1 (2.6)
P/C ratio	0.8 (0.2)	0.9 (0.3)	0.8 (0.4)	0.7 (0.3)

Table 3
Mean (SD) pharmacokinetic parameters

	Targeted flow rate			
	Monodose inhaler		Turbuhaler DPI	
	90 l/min	45 l/min	60 l/min	30 l/min
AUC (ng/ml h)	2.25 (1.18)	2.25 (1.62)	2.83 (2.62)	1.12 (1.28)
C_{max} (ng/ml)	1.29 (0.94)	1.18 (0.75)	1.55 (1.10)	0.76 (0.75)
T_{max} (h)	0.92 (0.44)	1.00 (0.86)	1.34 (0.94)	0.58 (0.42)

AUC, area under plasma concentration vs time curve; C_{max}, maximum plasma concentration; T_{max}, time after inhalation to maximum plasma concentration.

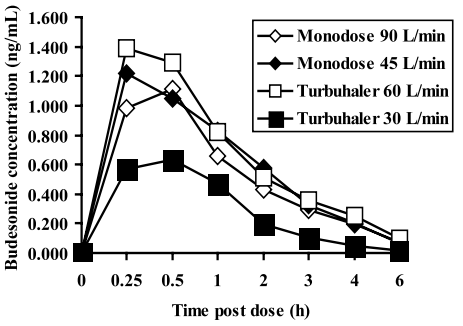

Fig. 3. Mean plasma concentrations of budesonide plotted vs time for the four study regimens.

4. Discussion

Deposition of drug from DPIs depends upon a complex interaction between the device, the formulation, and the patient, who controls the rate of flow of inhaled air through the system. Maximal inspiratory effort leads to a pressure drop across the inhaler in the region of 4 kPa, but the numerical value of inhaled air flow will depend upon the resistance of the device. Hence maximal inspiratory effort resulted in a flow rate of about 90 l/min for the Monodose inhaler, but only 60 l/min for the Turbuhaler DPI, which has higher resistance. Assuming maximal inspiratory effort, the amount of drug from a DPI deposited in the lungs using conventional micronised particle formulations varies from device to device, ranging from around 10% (Pitcairn et al., 1997; Cass et al., 1999) to $>30\%$ (Warren et al., 1998; Pitcairn et al., 2000; Newman et al., 2000a). Lung deposition from the Turbuhaler DPI has ranged between 14 (Newman et al., 1989) and 32% of the dose (Thorsson et al., 1994) in various studies. Changes to the formulation can markedly enhance both fine particle dose and lung deposition. In one recent study, lung deposition of salbutamol from the Clickhaler DPI was increased from a mean 26.8% of the dose for conventional lactose to 34.9% for a formulation which included a ternary component

Table 4
Mean (SD) inhalation details

	Targeted flow rate			
	Monodose inhaler		Turbuhaler DPI	
	90 l/min	45 l/min	60 l/min	30 l/min
PIFR (l/min)	96 (10)	47 (8)	66 (8)	33 (5)
IV (l)	3.2 (0.6)	3.7 (1.1)	3.5 (0.9)	3.5 (0.9)
BHP (s)	9.4(0.7)	8.9 (0.7)	9.4 (0.7)	9.5 (0.5)

PIFR, peak inhaled flow rate; IV, inhaled volume; BHP, breath-holding pause.

intended to occupy high energy binding sites on the lactose powder surface (Warren et al., 1999).

All currently marketed DPIs are breath-actuated, and do not require patients to 'press and breathe' simultaneously. While this is seen as an advantage, especially for patients with poor hand-lung coordination, it closely linked to a disadvantage, namely that the lung dose will depend upon the degree of inspiratory effort (Clark, 1995). In both drug/lactose blends (as used in the Monodose inhaler), and in pure drug formulations (e.g. the Pulmicort Turbuhaler DPI), maximal inhalation serves to separate drug and lactose complexes, or pure drug aggregates, more effectively in a turbulent inhaled airstream (Dolovich, 1999). A reduction in inspiratory effort results in poorer de-aggregation, and may lead to lower values of FPF, FPM, and lung deposition. The Turbuhaler DPI was already known to be highly inspiratory effort dependent: in a previous study, deposition of budesonide fell from 27% of the dose at a PIFR of 60 l/min to 14% at a PIFR of 30 l/min (Borgström et al., 1994). Although the fall in lung deposition for the Turbuhaler DPI was less marked in this study, the data essentially verify earlier findings.

By contrast, lung deposition from the Monodose inhaler was independent of inspiratory effort over a range of PIFRs between 45 and 90 l/min. This observation may be a result either of the mechanics of the device, or of the formulation. The data suggest that the drug powder and lactose carrier easily de-agglomerate within the Monodose inhaler, either because of the nature of the turbulent airflow within the device, or because the forces holding drug and lactose together are relatively weak, or as a result of both those factors. The Monodose inhaler formulation contained both fine- and coarse-particle lactose, and the presence of the former could help to optimize the FPF, even with sub-maximal inspiratory effort (Lucas et al., 1999). Relative flow rate or inspiratory effort independence has been shown previously, not only for an 'active' DPI (Spiros, Dura, San Diego) in which the powder is dispersed by an electric motor (Hill et al., 1996), but also for two breath-actuated devices, the Taifun DPI (Pitcairn et al., 2000) and Clickhaler DPI (Warren et al., 1998).

The pharmacokinetic data showed the same trends as the whole lung deposition data, and this is not surprising. Plasma levels of budesonide derive mainly from pulmonary absorption, augmented by the small fraction of the oropharyngeally deposited budesonide dose which is bioavailable (Lipworth, 1996; Thorsson et al., 1994). AUC and C_{max} values were similar for the Monodose inhaler with maximal inspiratory or sub-maximal effort, and for the Turbuhaler DPI with maximal inspiratory effort. However, they were more than halved for sub-maximal effort with the Turbuhaler DPI, and the reduction in plasma levels was greater than the observed reduction in whole lung deposition, expressed as percentage of the dose. This may have resulted from a reduction not only in fine particle dose, but also in emitted dose, when the flow rate of inspired air through the Turbuhaler DPI was reduced (Meakin et al., 1995).

In gamma scintigraphic studies, it is necessary to carry out validation procedures which show that the radiolabel is an accurate marker for the drug, and that the drug formulation is unchanged by the radiolabelling process. This was demonstrated for both products using an HPMLI, operated at the calibration flow rate for this device (60 l/min). However, the in vivo studies were conducted at peak inhaled flow rates of 90 and 45 l/min for the Monodose inhaler, and 60 and 30 l/min for the Turbuhaler DPI. It has been suggested that validation data should be obtained for all inhalation flow rates to be used in an in vivo study (Snell and Ganderton, 1999). In practice however, differences in the quality of radiolabelling validation data at different flow rates are seldom seen; for instance, in a study to assess the deposition of nedrocromil sodium from a novel dry powder inhaler (Pitcairn et al., 1997), the radiolabelling validation data were equally good at flow rates of 60 and 40 l/min.

Recent data involving an experimental lactose formulation (Bondesson et al., 2002) have shown that it is possible for the size distributions of drug and radiolabel to show an acceptable match at one flow rate, but to demonstrate a mismatch at

another flow rate. In our study, the relationships between radiolabel and drug distributions, and between drug distributions of 'labelled' and 'unlabelled' products were not known at all inhaled flow rates that applied in the in vivo study. However, we consider it unlikely that the in vivo were affected adversely, for three reasons: first, the validation data obtained at 60 l/min showed very good drug/label associations with only minimal differences between 'labelled' and 'unlabelled' products, second, the data of Bondesson et al. are unusual, and are not typical of radiolabelling validation data, and third, the scintigraphic data and pharmacokinetic data lead to similar conclusions, in terms of showing little flow rate dependence for the Monodose inhaler, but marked flow rate dependence for the Turbuhaler DPI.

Despite some differences in lung deposition between devices and between flow rates, it is likely that when used in clinical practice, budesonide delivered from the two devices would have similar clinical effects. The dose–response curve to an inhaled corticosteroid is generally quite flat, so that it is difficult to detect differences between the effects of different doses of inhaled cortisosteroids (Zanen and Lammers, 1995). In a major recent study (Busse et al., 1999) CFC and non-CFC formulations of beclomethasone dipropionate (BDP) were given by pMDI to groups of over 50 asthmatic patients, as daily doses of 100, 400 and 800 μg. For the CFC formulation, which was delivered very inefficiently to the lungs, the mean increase in FEV_1 after 6 weeks treatment was 14.9, 17.7 and 21.4% for the 100, 400 and 800 μg doses. For the non-CFC formulation, which was delivered much more efficiently to the lungs, the increases in FEV_1 after 6 weeks averaged 18.1, 19.4 and 23.8%. The range of FEV_1 increases from 14.9 to 23.8% represented at least a 20-fold difference in lung dose of BDP. These considerations suggest that the differences in clinical response resulting from equivalent nominal doses of budesonide delivered by the Monodose inhaler and the Turbuhaler DPI are likely to be very similar. The data from this study therefore provide a firm platform with which to undertake a multicentre phase III study comparing the clinical responses to budesonide delivered from the two devices over treatment periods of several weeks. The gamma scintigraphic data act as a 'bridge' between in vitro data obtained on the two devices and the phase III study, enabling the dose required for the clinical study to be defined with confidence (Newman et al., 2000b).

In conclusion, the Monodose inhaler showed inspiratory effort independent drug delivery characteristics, and could prove be a valuable low-cost alternative to more complex devices such as the Turbuhaler DPI. The Monodose inhaler may be especially useful in groups of patients unable to inhale maximally through DPIs, including young children and adult patients with severe respiratory impairment.

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