Improved airway targeting with the CFC-free HFA–beclomethasone metered-dose inhaler compared with CFC–beclomethasone

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Improved airway targeting with the CFC-free HFA–beclomethasone metered-dose inhaler compared with CFC–beclomethasone. C.L. Leach, P.J. Davidson, R.J. Boudreau. ©ERS Journals Ltd 1998.
ABSTRACT: Hydrofluoroalkane-134a (HFA) beclomethasone dipropionate (BDP) was formulated in a metered-dose inhaler (MDI) to deliver a particle size of 1.1 μm compared with 3.5 microns for currently marketed chlorofluorocarbon (CFC)–BDP products. Two phase I single-dose human deposition studies were conducted using technetium 99m-radiolabelled BDP in a press-and-breathe actuator without an add-on spacer.

A healthy volunteer study (n=6) showed that 55–60% of the HFA–BDP ex-actuator dose was deposited in the lungs, with 29–30% deposited in the oropharynx. CFC–BDP deposition was 4–7% in the lungs and 90–94% in the oropharynx. The pattern of deposition within the lung showed that HFA–BDP was spread diffusely throughout the lung airways, whereas CFC–BDP was confined to the central airways with little, if any, peripheral airway deposition. A second study with asthmatics (n=16) confirmed that 56% of the HFA–BDP dose was deposited in the airways, with 33% in the oropharynx.

In conclusion, hydrofluoroalkane-134a–beclomethasone dipropionate deposition was much greater in the airways than chlorofluorocarbon–beclomethasone dipropionate, with a concomitant reduction in oropharyngeal deposition. The increased lung deposition efficiency of the hydrofluoroalkane propellant has led to a reduction in the amount of beclomethasone dipropionate needed to achieve a similar efficacy. The penetration of the hydrofluoroalkane to the small airways may provide asthma treatment not afforded by conventional chlorofluorocarbons.
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The production of chlorofluorocarbons (CFCs) has been banned by more than 100 signatory countries of the Montreal Protocol [1]. Currently, there are only two temporary exemptions for the production of CFCs, the Space Shuttle programme and the essential use in metered-dose inhalers (MDI) for asthma treatment. The exemption of MDI expired in 1997 and must be renewed annually on a case-by-case basis. Proposals for phase-out encompass policies that call for CFC product elimination when a "technical and economically feasible alternative" exists. It has been proposed by the US Food and Drug Administration (FDA) [2] that when three suitable substitutions in a therapeutic category are available (*e.g.* the steroid class), authorities may phase out CFC category products from the market. Alternatively, substitutions may be forced on a molecule-by-molecule basis [2]. Hydrofluoroalkane (HFA)-134a is an alternative to the CFCs that does not contain chlorine and so has no potential to destroy ozone [3]. The safety of HFA-134a as a pharmaceutical propellant was established by the pharmaceutical consortium, International Pharmaceutical Aerosol Consortium for Toxicological Testing of HFA-134a (IPACT-I) and HFA-134a has now been globally accepted as a safe alternative for CFCs, in both pharmaceutical and industrial applications [4–6].

The use of corticosteroid aerosols to treat asthma and other diseases is increasing dramatically worldwide owing to the ability of steroids to treat more the underlying causes of asthma, as opposed to β-agonists which treat symptoms [7]. Currently marketed steroids (*e.g.* CFC–beclomethasone dipropionate (BDP)) are relatively safe and effective but there is substantial need and opportunity to improve on the delivery characteristics in order to reach central as well as peripheral airways and to reduce side-effects. For example, CFC and dry-powder formulations of steroids typically deposit 5–30% in the lungs and the remainder of the emitted aerosol in the oropharynx [8]. The oropharyngeal deposition can result in local side-effects such as candidiasis and thrush. Oral deposition also adds to systemic exposure and subsequently may effect the hypothalamic–pituitary–adrenal axis, bone metabolism and growth [9]. In addition, because of the large particle size of the CFC–BDP aerosol, deposition in the peripheral airways of the lungs is minimal [10]. Therefore, peripheral airway inflammation is not optimally treated with current therapy, although asthma has been shown to be a disease of the peripheral airways as well as of the large central airways [11]. In addition, steroid receptors are located throughout the lungs [12]. Considering this information, it was

desirable to develop a new formulation/delivery system that would deposit less drug in the oropharynx and more in the lungs, especially in the peripheral as well as the central airways. BDP can be formulated as a solution with the propellant HFA-134a. When the propellant evaporates during dosing, it has been found that much smaller aerosol particles are delivered to the patient than with the currently marketed CFC–BDP suspension products. Principles of aerosol physics suggest that the smaller particles from the new HFA–BDP MDI would be distributed throughout the airways.

Materials and methods

The MDIs tested included HFA–BDP 50 and 100 μg ex-valve strengths (QVAR®; 3M Pharmaceuticals, St Paul, MN, USA) and CFC–BDP 50 and 250 μg ex-valve strengths (Beclovent® and Becloforte®; Allen and Hanburys, Greenwood, UK). The ex-actuator delivery is approximately 40 μg for the HFA–BDP 50 μg, 80 μg for the HFA–BDP 100 μg, 42 μg for the CFC–BDP 50 μg and 210 μg for the CFC–BDP 250 μg products.

Radiolabelling technique

The radiolabelling method [13] was modified from the methods of FEW *et al.* [14], KÖHLER *et al.* [15] and NEWMAN *et al.* [16]. Technetium-99m (^{99m}Tc) was obtained from a commercial vendor as sodium pertechnetate (Na^{99m}TcO$_4$) in saline. The solution was placed in a clean 20-mL glass vial with 0.030 mL 27% ammonia, 0.006 mL tetraphenylarsonium chloride hydrochloride hydrate (1% solution) and 8 mL chloroform. The glass vial was capped, shaken for several seconds and sonicated for 10 min. After sonication, the mixture was passed through a phase-separation filter (Whatman 1 PS; Whatman, Maidstone, Kent) into an empty vial. The glass vial was rinsed with 4 mL chloroform, which was then passed through the phase-separation filter. The chloroform was slowly evaporated from the vial under a flow of nitrogen gas. Dry ice was used to cool both the radioactive vial and the vial containing the original test formulation to be labelled. The valve was removed from the test formulation vial and the formulation was poured into the radioactive vial. A new valve, appropriate for the original test formulation, was crimped on to the radioactive vial and tested for leaks. After being shaken, the mass and activity per actuation were determined using a glass wool filter through which the radiolabelled drug was drawn. The activity of the delivered drug was counted in a well counter and the mass of the drug determined by high-performance liquid chromatography (HPLC).

Radiolabel validation

It was necessary to ensure that the mass of the drug and the radioactivity per actuation were within expected limits. It was also necessary to ensure that the particle size distribution (*i.e.* mass median aerodynamic diameter (MMAD)), medication delivery (*e.g.* total mass of drug delivered ex-actuator) and respirable fraction (*e.g.* particles <4.7 μm) did not change after radiolabelling. The mass of the drug was determined by HPLC specific for BDP. An Andersen 1 actual cubic feet per minute (ACFM) particle sizing sampler (Mark II; Grasby Anderson, Smyrna, GA, USA) and a quartz crystal microbalance (QCM) cascade impactor system (California Measurements, Sierra Modre, CA, USA) fitted with a United States Pharmacopeia (USP) glass throat were used to determine these distributions. The QCM provided nearly real-time distributions for the mass and radiolabel on the day of the study. The Andersen samplers provided drug and radiolabel distributions at a later date for verification. Before the labelling procedure began, the canister containing the formulation was actuated into the QCM and an Andersen sampler (*i.e.* "before"). After the mass of the drug and activity per actuation were determined, the labelled canister was actuated into the QCM and a second Andersen sampler (*i.e.* "after"). The QCM crystals were removed from the impactor and the radioactivity on each crystal was counted in a gamma well counter (APTEC Nuclear, North Tonawanda, NY, USA). The "before" and "after" QCM mass distributions for each MDI were compared with each other and with the radiolabel distribution. During validation, the radiolabel and mass of the drug were also compared 24 h after the preparation of the inhaler. The amount of radiolabelled drug in the actuator and USP throat were also measured. If the particle size distributions agreed, the formulation was considered properly labelled for the clinical study. When they became available, data from the Andersen samplers were analysed for other parameters that determined whether the clinical data were usable. After the radioactivity in the canister had decayed to background levels, medication delivery, as determined by HPLC, was also tested to ensure that the values were within the original specifications.

Radionuclide imaging techniques

After inhalation of the ^{99m}Tc-labelled drug by the subjects, the following 90-s image regions were obtained: posterior thorax, anterior thorax, anterior upper abdomen, posterior upper abdomen, left lateral oropharynx, actuator and exhalation filter trap.

The total number of counts and the percentage of the total activity in each region were calculated as follows:
1) Average thorax = (left lung (posterior thorax) + right lung (posterior thorax) + left lung (anterior thorax) + right lung (anterior thorax))/2
2) Average abdomen = (anterior abdomen + posterior abdomen)/2
3) Total counts = average thorax + average abdomen + Actuator + oropharynx + filter trap
4) Actuator (%) = (actuator/total counts)×100
5) Oropharynx (%) = ((oropharynx + average abdomen)/total counts)×100
6) Lungs (%) = (average thorax/total counts)×100
7) Exhaled (%) = (filtertrap/total counts)×100

The patients were instructed not to speak or swallow until the scans were completed, thus minimizing the amount of drug in the stomach. For simplicity reasons, the oropharyngeal numbers include the amount measured in the oropharynx plus the swallowed portion in the abdomen. Deposition in the mediastinum was minimal and not included in this report.

Each subject underwent a xenon (Xe)-133 lung ventilation imaging procedure using standard clinical imaging techniques. These images provided an outline of the lungs against which the labelled drug scintigraphs could be compared. The original counts were not multiplied by tissue attenuation factors since these are not possible to calculate exactly. Since each subject served as their own control in the study design, attenuation effects would be minimized in the comparison of one device with another.

Clinical study design

These studies were performed in accordance with Good Clinical Practices, Good Laboratory Practices and the ethical principles enunciated in the revised Declaration of Helsinki. The study was approved by the University of Minnesota Institutional Review Board and informed written consent was obtained from each subject.

Study 1: healthy subjects. This was an open-label pilot study in six healthy male volunteer subjects (data were combined from two identical pilot studies) to examine the lung deposition and distribution of radiolabelled HFA–BDP (n=6 for 50 μg; n=3 for 100 μg strength) and/or CFC–BDP (n=6 for 50 μg; n=3 for 250 μg strength) in MDIs without add-on spacers. Dose strengths of the HFA-134a and CFC–BDP products studied in this trial were chosen based on similar ex-valve drug delivery (HFA–BDP, 50 μg *versus* CFC–BDP, 50 μg) and on similar anticipated efficacy (HFA–BDP, 100 μg *versus* CFC–BDP, 250 μg). A critical aspect of this pilot study was to ensure standardization of the delivered dose, *i.e.* inhaled dose. To facilitate comparability of dosing, subjects of similar physique and pulmonary function were selected. Standardization of inhalation was achieved through the use of a custom-made breath pattern monitor. The respiratory device allowed subjects to observe a visual display of their real-time breath pattern on a computer screen (*i.e.* time of inhalation, time to actuation and breath-hold time). Subjects could be trained to reproduce the desired breath pattern, ensuring standardization of inhaled doses. Subjects underwent screening and prestudy procedures and, if qualified, entered the study period within 14 days.

Radiolabelled BDP canisters were prepared on the morning of each study day. On each study day, subjects received radiolabelled BDP from the respective HFA or CFC MDI. One inhalation consisting of ð11.1 MBq (300 μCi) was administered per subject on each study day. The breath pattern monitor was utilized during study drug inhalation to document the breath patterns for each subject. Following inhalation, deposition of the drug in the lungs, upper abdomen, oropharynx and inhaler mouthpiece and the amount that the subject expired into an exhalation filter trap were measured by gamma scintigraphy.

Study 2: asthmatic patients. This was an open-label study examining the lung deposition of radiolabelled HFA–BDP (50 μg strength) and utilizing 16 patients with mild asthma. Methods were similar to those described for Study 1.

Subject and patient selection

Study 1: Healthy subjects. Males of 18–55 yrs (inclusive) underwent screening procedures to confirm that they were healthy nonasthmatics as determined by medical history, physical examination, 12-lead electrocardiography (ECG), clinical laboratory tests and pulmonary function tests. Subjects were also required to demonstrate an acceptable MDI technique and reproducible inspiratory technique, using the breath pattern monitor, to be included in the study. Safety was assessed by the analysis of adverse events, blood pressure and pulse rate, physical examination, 12-lead ECG with interpretation and clinical laboratory tests.

Study 2: Asthmatic patients. Male or female mild asthmatics of 18–55 yrs (inclusive), who were otherwise healthy, were screened. All patients were required to be nonsmokers for Š1 yr and have a smoking history of <15 pack-yrs. Patients had a screening forced expiratory volume in one second (FEV1) >70.0% of the predicted normal and a documented history of FEV1 reversibility to β-agonists. All patients demonstrated an acceptable technique in the use of an MDI and reproducibility of their inspiratory flow pattern using the breath pattern monitor.

Safety was assessed by the analysis of adverse events, blood pressure and pulse rate, physical examination, 12-lead ECG with interpretation, pulmonary function tests and clinical laboratory tests.

Statistical analysis

Group mean data for the healthy subject study group receiving HFA–BDP, 50 μg·shot⁻¹ and CFC–BDP, 50 μg· shot⁻¹ were compared using Students t-test [17]. A value of pð0.05 was considered statistically significant.

Results

Demographic and baseline lung function values are presented for study 1 (healthy subjects) and study 2 (asthmatic patients) in tables 1 and 2, respectively.

Particle size data for the unaltered HFA–BDP and CFC–BDP products, as measured by the Andersen cascade impactor testing apparatus, are presented in figure 1. Examination of these *in vitro* data suggested several important differences between the two products. Firstly, much

Table 1. – Demographic and baseline lung function

Study 1: healthy subjects		
Subjects n	6	males
Age yrs	34	(25–50)
Height cm	179	(165–188)
Weight kg	79	(69–94)
FEV1 L	4.8	(4.2–5.4)
FEV1 % pred	109	(10l–120)
Study 2: asthmatic patients		
Subjects n	5 males,	11 females
Age yrs	32	(18–52)
Height cm	169	(156–186)
Weight kg	68	(45–99)
FEV1 L	3.0	(2.2–4.3)
FEV1 % pred	84	(69–97)

Data are shown as means. The values in parentheses are ranges. FEV1: forced expiratory volume in one second.

Table 2. – Breath parameters for the inhaled dose of beclomethasone dipropionate (BDP)

Product	Subjects n	Inspiratory time s	Time to actuate s	Breath hold s	Inspiratory volume L
Study 1: Healthy subjects					
HFA–BDP, 50 µg·shot⁻¹	6	3.1±0.2	0.5±0.1	10.4±0.4	5295±1080
HFA–BDP, 100 µg·shot⁻¹	3	3.4±0.2	0.4±0.2	10.0±0.4	4503±340
CFC–BDP, 50 µg·shot⁻¹	6	3.2±0.2	0.4±0.1	10.3±0.2	5388±1238
CFC–BDP, 250 µg·shot⁻¹	3	3.1±0.1	0.4±0.1	10.2±0.3	5190±482
Study 2: Asthmatic patients					
HFA–BDP, 50 µg·shot⁻¹	16	3.1±0.3	0.4±0.1	10.9±0.4	3460±820

Values represent mean±SD. HFA: hydrofluoroalkane; CFC: chlorofluorocarbon.

less HFA–BDP than CFC–BDP was held up in the throat of the apparatus, which simulates the oropharynx of humans. Secondly, the average particle size of the HFA–BDP was much smaller than that of the CFC–BDP (*i.e.* 1.1 µm MMAD for the HFA–BDP *versus* 3.5 µm for the CFC–BDP). The smaller particle size and range of distribution of sizes for the HFA–BDP suggested that in patient exposures, HFA–BDP would be deposited throughout the airways. The particle size data also predicted that much less CFC–BDP would be deposited in the lungs and that the deposition of CFC–BDP would be primarily confined to the large airways. The HFA–BDP particle size data also showed that approximately 10% of the particles were <0.4 µm, which suggested that approximately 10% of the BDP had the potential to be exhaled by the patients.

Graphs of typical radiolabelling validation schemes for HFA–BDP and CFC–BDP are presented in figure 2a and b, respectively. HFA–BDP is a stable solution in the MDI canister; therefore, the potential of achieving a homogeneous radiolabel with proper labelling technique was higher than that expected for a suspension aerosol product such as CFC–BDP. Results of the HFA–BDP radiolabelling showed that the radiolabelling process did not alter the particle size distribution of the original product, *i.e.* the chemical specific mass of the drug at each stage did not change after the radiolabelling process, and remained unchanged for Š24 h. (The patients used the radiolabelled product δ6 h after the radiolabelling.) The results also

showed that the radioactive count distribution matched precisely the mass distribution of the drug immediately after radiolabelling and remained unaltered for Š24 h. The radiolabelling process did not change the particle size distribution of the CFC–BDP products, but the association of radiolabel with the larger particles (*i.e.* particles >4.7 µm) was visibly, but not statistically, less than the association of radioactivity with the smaller particles. This was to be expected since CFC–BDP is a suspension of particles in the propellant and radiolabelling a suspension of particles places the radiolabel on the surface of the particle. Since large particles have fewer drug molecules on the surface of the particle in proportion to the number of molecules in the interior, it is expected that large molecules would label less efficiently than small particles. This difference in labelling efficiency with the CFC–BDP was considered acceptable for the purposes of this experiment. Because the BDP of HFA–BDP is in solution, with complete association of drug molecules and ^{99m}Tc, the labelling of HFA–BDP was not subject to this potential discrepancy.

The breath pattern data, collected in real time during the actual inhalation dose, showed that subjects and patients could be trained to use the MDI accurately and reproducibly. The subjects and patients were asked to target an inspiratory time of 3 s, a time to actuate the MDI at the beginning of inspiration (within the first 15% of the breath) and a breath-hold of 10 s. The inspiratory volume varied with the lung capacity of the individuals. Table 2 shows
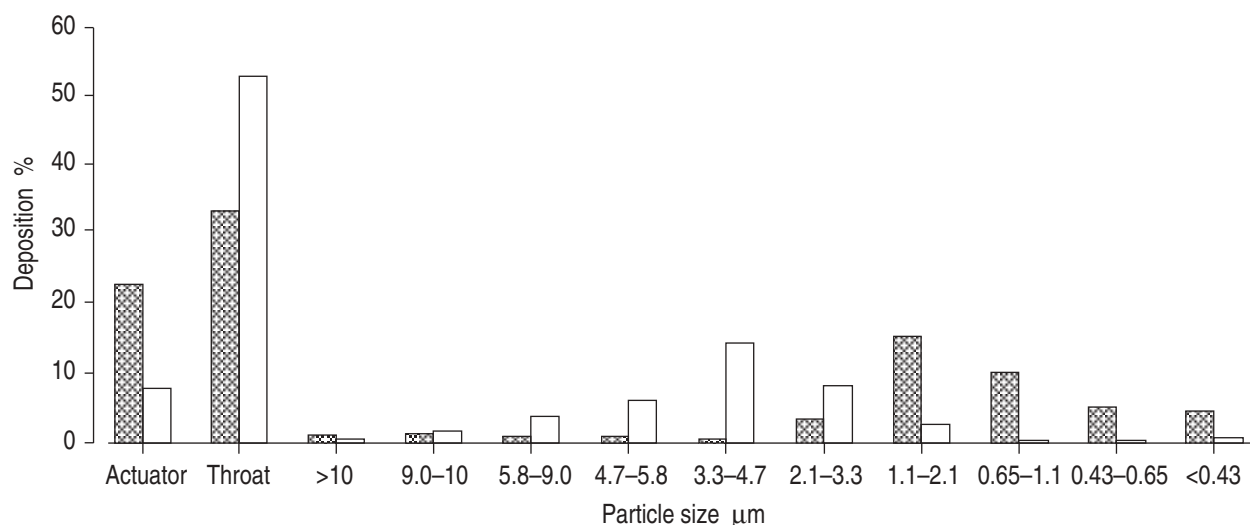

Fig. 1. – Andersen cascade impactor comparison of the destinations of and the particle size distributions in an individual typical product of hydrofluoroalkane-134a (HFA)–beclomethasone dipropionate (BDP) (▨), 50 µg strength, and in chlorofluorocarbon (CFC)–BDP (▢), 50 µg strength.
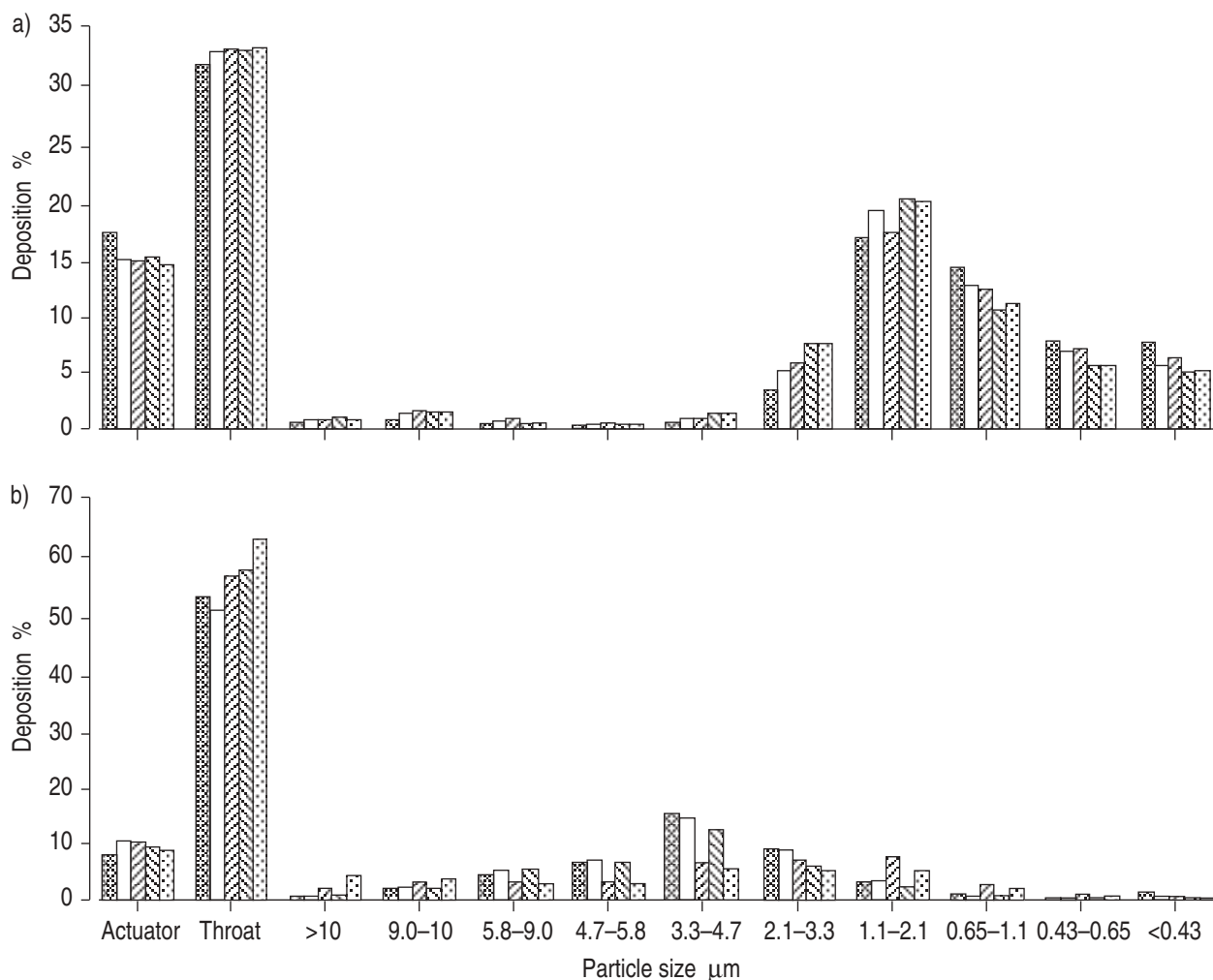
Fig. 2. – Andersen cascade impactor comparison of the destinations of and the particle size distributions in a) hydrofluoroalkane-134a (HFA)–beclomethasone dipropionate (BDP), 50 µg strength, (n=3) and b) chlorofluorocarbon (CFC)–BDP, 50 µg strength, (n=3) as determined by high-performance liquid chromatography for BDP and radioactive counts. ▨ : mass before labelling; ☐ : mass after labelling; ▨ :counts after labelling; ▨ : mass 24 h after labelling; ▦ : counts 24 h after labelling.

that the subjects and patients achieved these targets with remarkable accuracy. For example, mean inspiratory times varied by no more than 0.4 s, actuation times by no more than 0.1 s, and breath-holds by no more than 0.3 s. The subjects and patients received <10 min of training on the breath pattern monitor on each study day.

Deposition results from Study 1 with healthy subjects are presented in table 3. The results of the study were consistent with the results predicted by the *in vitro* cascade impactor results. The deposition of HFA–BDP in the lungs was 55–60% (ex-actuator), compared with 4–7% in the lungs for CFC–BDP. The deposition of HFA–BDP in the oropharynx was 29–30%, compared with 90–94% in the oropharynx for CFC–BDP. As expected, 11–14% of HFA–BDP was exhaled. Deposition results with asthmatic patients from Study 2 were consistent with Study 1 in healthy subjects. The deposition of HFA–BDP in the lungs was 56%, with 33% in the oropharynx and 9% exhaled.

Figures 3 and 4 represent typical gamma camera images collected during the studies. Figure 3 demonstrates the improved delivery of HFA–BDP to the lungs (*i.e.* 55–60% of the drug), not only in terms of the total mass of drug delivered to the lung, but also in the distribution of drug within the lung. The central, intermediate and peripheral airways exhibit deposition of drug from HFA–BDP. This is in contrast to CFC–BDP, where a much smaller amount of the drug reached the lungs (*i.e.* 4–7%) and what was deposited in the lungs appeared to be deposited in the central airways. Figure 4 shows that the amount of drug from HFA–BDP deposited in the oropharynx was approximately three times lower than that from CFC–BDP.

Discussion

The new HFA–BDP MDI with a particle size targeted for optimum lung deposition reversed the pattern of distribution from the current CFC–BDP MDI in that the majority of the drug from HFA–BDP MDI was deposited in the lungs. In contrast, only a small amount of drug from the CFC–BDP MDI was deposited in the lungs. Furthermore, the drug that reached the lungs from HFA–BDP reached the peripheral as well as the central airways, whereas drug from CFC–BDP was confined to the central airways. Asthma is now recognized as a peripheral as well as a central

Table 3. – Deposition of technetium-99m beclomethasone dipropionate (BDP)

Product	Subjects n	Lungs %	Oropharynx %	Exhaled %
Study 1: healthy subjects				
HFA–BDP, 50 µg·shot⁻¹	6	55±12*	29±13*	14±4*
HFA–BDP, 100 µg·shot⁻¹	3	60±14	29±18	11±4
CFC–BDP, 50 µg·shot⁻¹	6	4±3	94±4	0±0
CFC–BDP, 250 µg·shot⁻¹	3	7±3	90±14	2±1
Study 2: asthmatic patients				
HFA–BDP, 50 µg·shot⁻¹	16	56±9	33±9	9±4

Values represent mean±SD. HFA: hydrofluoroalkane; CFC: chlorofluorocarbon. *: p$\eth$0.05 compared with CFC–BDP at 50 µg·shot⁻¹.
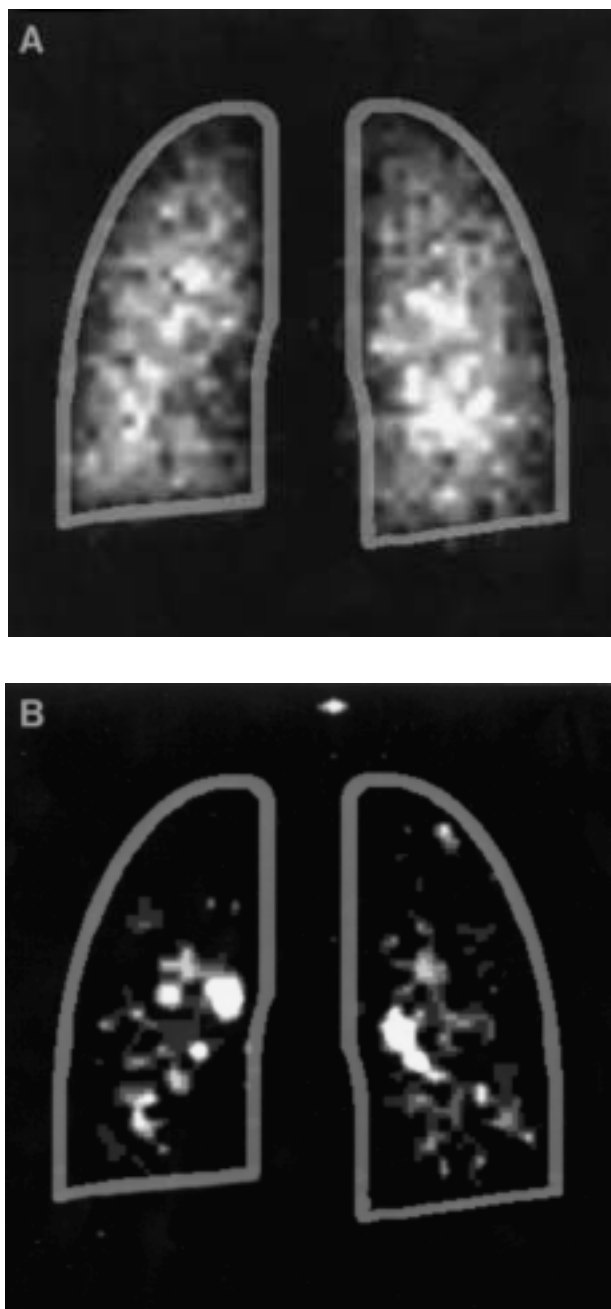

Fig. 3. – Gamma scintographic lung images produced using a) hydrofluoroalkane-134a (HFA)–beclomethasone dipropionate (BDP) metered-dose inhaler (MDI) and b) the chlorofluorocarbon–BDP MDI.

airway disease [11]. In addition, the unwanted drug deposited in the oropharynx from CFC–BDP was reduced three-fold with HFA–BDP. The reduced oropharyngeal deposition may lead to a clinical reduction in unwanted oral and systemic side-effects [9]. The use of add-on spacers with steroids is prominent, primarily because of the presumed reduction in oropharyngeal deposition as well as to improve lung deposition by overcoming disco-ordination issues [18–20]. With a three-fold reduction in oropharyngeal deposition and the high lung deposition with the HFA–BDP, the need for add-on spacers for this reason may be reduced or eliminated.

The particle size data presented in figure 1 clearly demonstrate a difference in average particle size and distribution between HFA–BDP and CFC–BDP. When using an Andersen cascade impactor for *in vitro* measurement of particle size, the respirable fraction is generally considered the fraction of drug <4.7 µm. The amount of HFA–BDP <4.7 µm is approximately 60%. Thus, the 60% respirable fraction measured by the cascade impactor is predictive of the 55–60% lung deposition measured in the human studies with HFA–BDP. The amount of CFC–BDP <4.7 µm is approximately 30%, a value consistent with that reported previously [21]. However, the fraction of CFC–BDP measured in the human studies was 4–7%. Thus, the use of 4.7 µm as a cut-off for the respirable fraction was not predictive of the human measurements in the case of CFC–BDP. This finding can be explained by applying lung-deposition probabilities reported in the literature [22–24]. Given a particle size of 1.1 µm MMAD and a geometric standard deviation (GSD) of 2.0, the HFA–BDP aerosol has a high probability of being deposited in the lungs. The CFC–BDP is much larger, with a particle size of 3.5–3.9 µm (MMAD) and a GSD of 2.1. This larger particle size has a much higher probability of being deposited in the oropharynx and a much lower probability of being deposited in the lungs. The literature models [22–24] also predicted that CFC–BDP particles would not reach the lower airways to any significant extent. This prediction is consistent with the human deposition findings reported here.

The increased lung deposition of HFA–BDP over CFC–BDP, by approximately 10-fold, raised the following questions: 1) is HFA–BDP 10 times more efficacious than CFC–BDP? and 2) is the side-effect profile 10 times greater than CFC–BDP? The answer to both questions is "no", for reasons relating to the shape of the dose–response curve. Rarely, if ever, does 10 times the dose of any drug result in 10 times the efficacy. However, such improved deposition should result in some degree of greater efficacy of HFA–BDP compared to CFC–BDP. The deposition data,
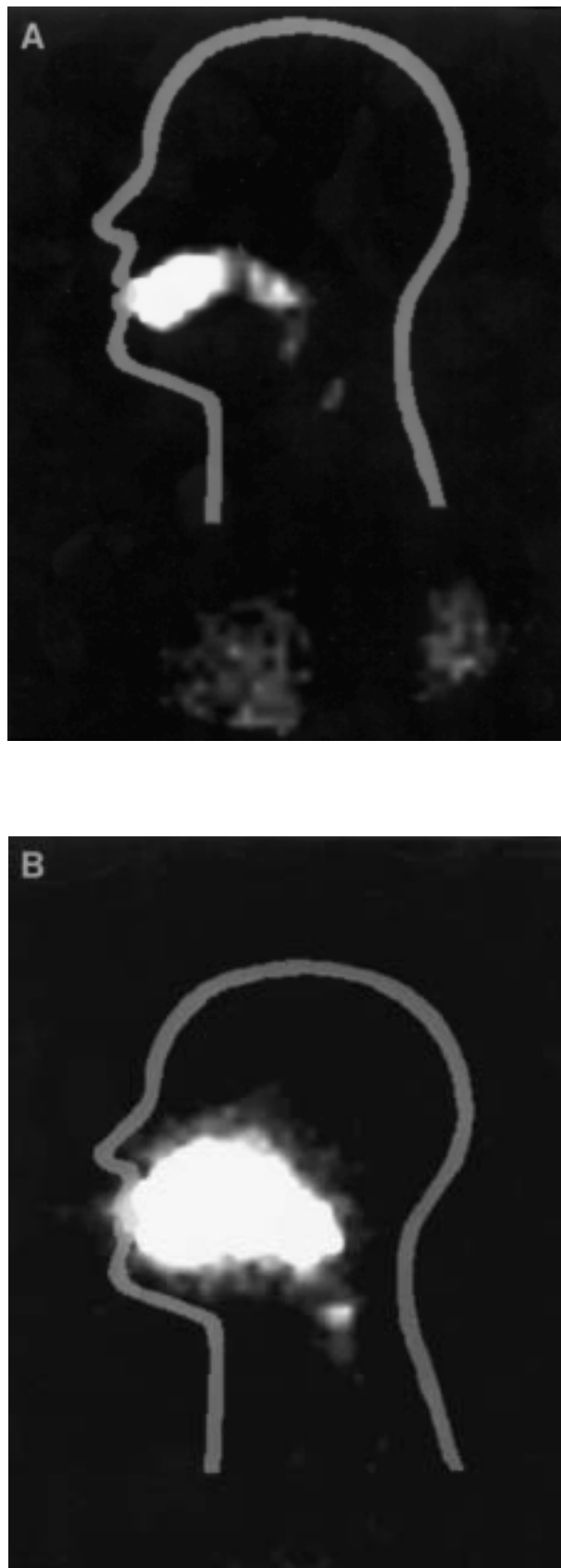
Fig. 4. – Gamma scintographic oropharyngeal images produced using a) hydrofluoroalkane-134a (HFA)–beclomethasone dipropionate (BDP) metered-dose inhaler (MDI) and b) the chlorofluorocarbon–BDP MDI.

coupled with pharmacokinetic data showing that approximately 21% of orally absorbed BDP is bioavailable to the serum, can be used to predict serum levels of BDP and its metabolites. Table 4 represents a theoretical determination of the serum levels projected to be present from 100 µg BDP delivered from HFA–BDP *versus* CFC–BDP. Calculations showed that 100 µg BDP from HFA–BDP would result in 66 µg available to the serum, whereas 100 µg BDP from CFC–BDP would result in 25 µg available to the serum. Thus, it would be expected that a given dose of drug from HFA–BDP would result in approximately 2.6-fold more drug in the serum than a similar dose of CFC–BDP. This approximate 2.6 factor has been confirmed in clinical pharmacokinetic studies [25], where all analytes of BDP were hydrolysed to free beclomethasone and subsequently analysed. In addition, clinical efficacy studies have confirmed that HFA–BDP has similar efficacy to approximately twice the dose of CFC–BDP [26, 27]. However, side-effect profiles measuring thrush, dysphonia and urine and plasma cortisol levels have shown that HFA–BDP has no more side-effects than equivalent doses of CFC–BDP [28]. A possible explanation for this is that these side-effects exhibit a much more shallow dose–response curve than the efficacy dose–response curve.

A survey of the radiolabelled drug deposition literature revealed that CFC MDI and dry-powder inhalers produce much less deposition in the lung than does HFA–BDP. The values from the literature cited below were normalized for ex-actuator delivery so that consistent comparisons could be drawn. In addition, the cited literature, at times, used unspecified multiplication factors to attempt to compensate for tissue attenuation of the gamma rays. The multiplication factors were typically 2× for lung counts and 1.2× for oropharyngeal counts. The data described in this report did not use multiplication factors because of the lack of standardization and validation of techniques for such factors. In addition, using the cross-over design employed here, the individual patient served as their own control, making tissue attenuation multiplication unnecessary. However, if typical multiplication factors were applied to the raw deposition numbers of HFA–BDP in this report, HFA–BDP lung deposition would increase from 56 to 70% and oropharyngeal deposition would decrease from 33 to 25% in the study with asthmatics. Examples of the deposition results are as follows: CFC-flunisolide deposited 27% of the ex-actuator dose in the lungs and 73% in the oropharynx [29]; terbutaline from the Turbuhaler™ deposited 17% in the lungs and 83% in the oropharynx [30]; budesonide from the Turbohaler™ deposited 18% in the lungs and 82% in the oropharynx [31]; and salbutamol from a dry-powder inhaler deposited 16% in the lungs and 84% in the oropharynx [32]. No data is available for the CFC–BDP MDI. Thus, deposition literature from a variety of CFC MDI and powder inhalers shows that 17–27% of the respective drug reached the lungs, compared with 55–60% of HFA–BDP reaching the lungs.

These radiolabelled drug deposition studies demonstrate that the delivery characteristics of the hydrofluoroalkane-134a–beclomethasone dipropionate metered-dose inhaler reverse the pattern of distribution typically seen with other corticosteroid inhalers. The majority of drug delivered to the patient from this inhaler is deposited in the central and peripheral airways, and a significantly reduced amount is deposited in the oropharynx.

Table 4. – Projected serum levels based on deposition results

	Bioavailability %	HFA–BDP 100 µg*		CFC–BDP 100 µg*	
		Dose µg	Amount in serum µg	Dose µg	Amount in serum µg
Oral deposition	21	30	6	95	20
Lung deposition	100	60	60	5	5
Serum Total			66		25
Ratio HFA–BDP: CFC–BDP			2.6		1

*: It was assumed that 100 µg beclomethasone dipropionate (BDP) was delivered to the patient. The amount of deposited beclomethasone dipropionate reaching the serum was calculated on the basis of bioavailability. HFA: hydrofluoroalkane; CFC: chlorofluorocarbon.

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