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Effect of changing the fine particle mass of inhaled beclomethasone dipropionate on intrapulmonary deposition and pharmacokinetics

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Reformulation of beclomethasone dipropionate (BDP) in the chlorofluorocarbon (CFC)-free propellant hydrofluoroalkane-134a (HFA) gave the opportunity to produce a solution formulation that provides a greater total mass of fine drug particles than the current CFC suspension metered dose inhaler (MDI). The HFA–BDP MDI was studied in three pharmacokinetic trials in asthmatic patients. Serum levels of BDP plus metabolites [total beclomethasone (total BOH) assay] were used to test whether the increased fine particle mass of HFA–BDP would result in improved intrapulmonary deposition and subsequent differences in serum profiles. Serum levels, maximum serum concentrations and area under the serum concentration–time curves of total BOH following both single and multiple doses of HFA–BDP were similar to those obtained with approximately twice the dose of CFC–BDP. The observed lower bioavailability of CFC–BDP compared with HFA–BDP could be explained if most of each inhaled dose from the CFC–BDP MDI was swallowed and absorbed from the gastrointestinal tract, while most of each inhaled dose from the HFA–BDP MDI was absorbed from the lungs. Deposition studies have confirmed this explanation. These results suggest that asthmatic patients can be treated with lower total daily doses of drug from HFA–BDP extrafine aerosol than from CFC–BDP.

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Introduction

Hydrofluoroalkane-134a (HFA) has been shown to be a safe replacement for chlorofluorocarbons (CFCs) as a pharmaceutical propellant, with the advantage that it has no ozone-depleting potential (1). This propellant was successfully used in the formulating of a salbutamol sulphate metered dose inhaler (MDI), marketed as Airomir™ or Epaq™ in Europe, New Zealand and Asia and as Proventil-HFA™ in the U.S.A. The reformulation of beclomethasone dipropionate (BDP) in HFA provided the opportunity to modify the physical characteristics of the aerosol formulation in view of current understanding of pulmonary deposition, making significant changes from the CFC–BDP formulation that was developed 20 years ago.

BDP formulated in HFA is a solution with no added surfactant; the commercial CFC–BDP formulation, in contrast, is a suspension consisting of a mixture of two CFC propellants and a surfactant (2). The HFA–BDP solution MDI delivers an aerosol with particles of mass mean aerodynamic diameter (mmad) of 1·1 μm when the MDI is activated and the propellant evaporates, while the CFC–BDP suspension MDI delivers particles with mmad of 3·5–4·0 μm (2). Furthermore, 52% of the particles delivered by the HFA–BDP extrafine aerosol are in the fine particle range (<4·7 μm), compared with only 34·5% of the particles from the CFC–BDP MDI (3). Because fine particle mass has been associated with the amount of drug deposited in the lungs, it was predicted that the HFA–BDP extrafine aerosol would be likely to deposit more drug in the airways than the CFC–BDP product.

The studies described in this review investigated

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TABLE 1. Study outlines

Study	Number of patients	Design	Dosage	Objective
A	23	Single-dose, randomized, three-period cross-over; total BOH and BOH measured	200 μg HFA–BDP, 400 μg HFA–BDP, 400 μg CFC–BDP	To compare the rate and extent of absorption of CFC–BDP and HFA–BDP
B	40	Multiple-dose, dose ranging, placebo-controlled, randomized, parallel-group study; blood collected on days 1 and 14 for total BOH assay	Twice daily for 14 days: 100 μg HFA–BDP, 200 μg HFA–BDP, 400 μg HFA–BDP, 400 μg CFC–BDP, HFA–placebo	To compare single-dose and multiple-dose pharmacokinetics of HFA–BDP and CFC–BDP
C	40	Single-dose, two-period cross-over; each patient received one inhalation dose and one oral dose; there were 10 different treatment sequences, and four patients were allocated to each sequence; BOH measured	HFA–BDP: 200 μg, 800 μg Oral BDP: 200 μg, 500 μg, 1000 μg, 2000 μg, 5000 μg	To determine the oral doses that give comparable C_{max} and AUC to inhaled doses

AUC, area under the serum concentration – time curve.

whether differences in fine particle mass observed in the laboratory studies of these two propellant formulations resulted in measurable differences in pharmacokinetics. Significant differences in serum profiles between HFA–BDP and CFC–BDP would support the hypothesis that increased fine particle mass results in increased airway deposition of drug and subsequent differences in absorption characteristics.

The pharmacokinetic studies measured serum levels of beclomethasone directly (BOH) or following hydrolysis (total BOH). The total BOH fraction consists of the contributions from BDP and its metabolites (17-monopropionate, 21-monopropionate and BOH) present in the serum following hydrolysis of all components in the sample to BOH. At the time of these studies, assays for the individual components of the total BOH fraction were not available. More than 75% of the material in the total BOH fraction at all sampling times is derived from beclomethasone 17-monopropionate (unpublished observation), the most pharmacologically active component (4), so the total BOH assay appears to be representative of active BDP metabolites.

Studies Reviewed

The patient population was standardized across the studies included in this review. Males and females, aged 18–60 years, with a history of mild to moderate asthma controlled by an inhaled β-agonist, were included in the studies. Patients had never smoked or had abstained from smoking for at least 1 year. All were within ±20% of ideal body weight and were steroid naive (had not received any steroids for the past 3 months). All were able to use a press-and-breathe MDI satisfactorily, had a forced expiratory volume in 1 s ≥ 60–70% of predicted normal after withholding all asthma therapy for 8 h, and had demonstrated reversibility of ≥ 15% within 30 min of administration of an inhaled bronchodilator (salbutamol or pirbuterol).

The objectives and designs of the three studies are given in Table 1. Similar procedures were used in all studies. Medications were self-administered by the patients. All dosing procedures were monitored and timed by a study coordinator. Inhalations began at the same time of day (±15 min) in each period and used a standardized inhalation technique. Patients held their breath for 10 s following each inhalation and waited a total of 30 s before taking the next inhalation. Time zero for each dose was defined as the time when the MDI was first actuated.

BOH serum concentrations were measured in studies A and C with the use of a liquid chromatograph equipped with a triple quadrapole mass spectrometer.

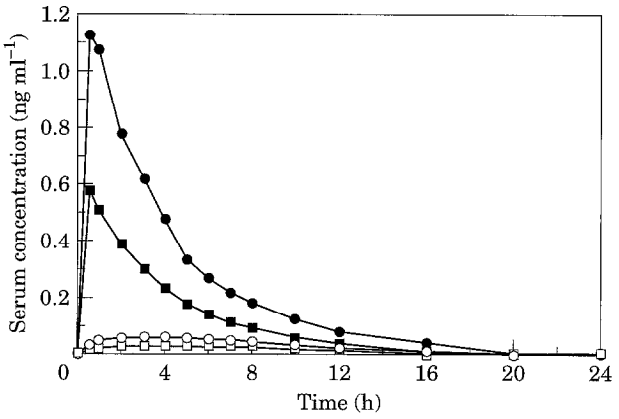

FIG. 1. Mean serum BOH (□, ○) and total BOH (■, ●) concentrations after single inhaled doses of HFA–BDP (□, ■, 200 μg; ○, ●, 400 μg).

The analytical range for this method was 0·010–0·300 ng ml^{-1}. Serum total BOH concentrations were measured in studies A and B by separating the analytes from the serum by liquid–liquid extraction and then hydrolysing the extracts to convert BDP and any monopropionates to BOH. The total BOH in the sample, which represented the sum of any BDP, 17-monopropionate, 21-monopropionate and BOH present, was measured with the BOH assay. The method used to determine total BOH was linear over the calibration range 0·036–0·709 ng ml^{-1}. Details of the accuracy and precision of the BOH assay have been published (5).

Non-compartmental pharmacokinetic analyses were performed on the serum level data. The maximum serum concentration (C_{max}) and the area under the serum concentration–time curve (AUC) were the primary pharmacokinetic parameters in all the studies carried out. Statistical analyses were done on the logarithmically transformed data using analysis of variance methods appropriate for the cross-over design in studies A and B or using Jonckheere's test for increasing trend in study C. Standard methods for equivalence testing were employed. T_{max}, defined as the time of C_{max}, was also calculated.

Additional details of the studies have been published elsewhere (6–8).

Single-dose Pharmacokinetics

Serum levels of total BOH and BOH were measured following two doses of HFA–BDP in study A. From the results, it is clear that most of the BDP measured in the serum was derived from BDP directly and/or the monopropionate esters, not BOH (Fig. 1). The mean total BOH levels peaked much sooner and at least one order of magnitude higher than those of BOH.

C_{max} and AUC values for total BOH and BOH after inhalation of 400 μg HFA–BDP were approximately twice as high as those obtained after inhalation of 200 μg HFA–BDP (Table 2). The statistical criteria for linear proportionality were met in three of the four comparisons, implying that reducing the dose in half would give an equivalent reduction of the pharmacokinetic parameters (Table 3).

Steady-state Pharmacokinetics

A second study, study B, examined the pharmacokinetics of total BOH following the first and 27th (steady-state) doses of three HFA–BDP dose levels (Fig. 2). All doses were administered twice daily for 14 days. The good proportionality of the pharmacokinetic parameters on day 1 among the three HFA–BDP doses was similar to that observed following a single dose in study A. Good proportionality was also observed following the 27th (steady-state) dose as well as following the first dose, as shown by C_{max} (Fig. 3).

Study B also evaluated whether or not BDP and metabolites would accumulate to any significant extent in the serum on multiple dosing. Only small differences in serum concentrations of total BOH were seen between day 1 and day 14, suggesting little accumulation on multiple dosing. Approximately 33% accumulation would have been predicted for a drug

TABLE 2. Comparative total BOH pharmacokinetic parameters from study A; values are mean (SD)

Parameter	HFA–BDP 200 μg	HFA–BDP 400 μg
C_{max} (ng ml^{-1})	0·590 (0·200)	1·191 (0·385)
AUC (ng h ml^{-1})	2·339 (0·634)	4·962 (1·309)
T_{max}(h)	0·6 (0·3)	0·8 (0·5)

TABLE 3. Proportionality testing of HFA–BDP MDIs in study A

	C_{max} (ng ml^{-1})		AUC (ng h ml^{-1})	
	Total BOH	BOH	Total BOH	BOH
Geometric mean 400 μg HFA–BDP*	0·5643	0·0333	2·4094	0·3297
Geometric mean 200 μg HFA–BDP	0·5580	0·0329	2·2469	0·2834
Ratio (400*:200)	1·01	1·01	1·07	1·16
90% confidence interval for ratio	0·90–1·14	0·91–1·13	0·95–1·21	1·01–1·34
Maximum P value†	0·003	<0·0001	0·016	0·20

*Values divided by 2.
†P value ≤ 0·05 indicates that treatments met the definition of equivalence.

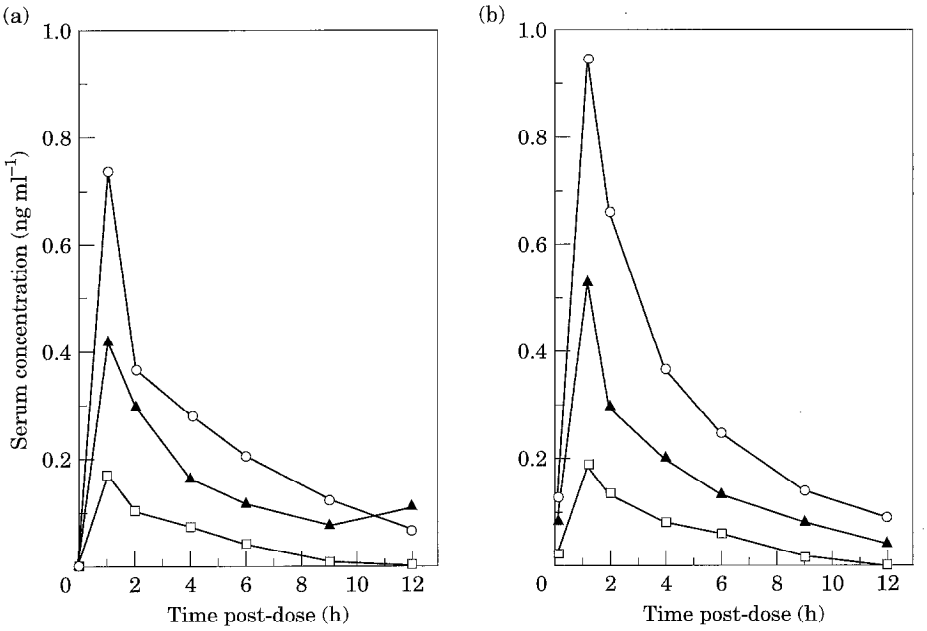

FIG. 2. Mean total BOH serum concentrations on (a) day 1 (single dose) and (b) day 14 (steady-state) of HFA–BDP multiple dosage regimens (□, 100 μg; ▲, 200 μg; ○, 400 μg): doses administered every 12 h.

with a 6 h half-life which is dosed every 12 h. A 6 h half-life appears to be a reasonable estimate for the elimination of beclomethasone 17-monopropionate which, being the main component in the serum, is the one most likely to show accumulation. The observation of similar curves in Fig. 2 for the data gathered on the first and 27th (steady-state) doses is important because it shows that all doses were affected as predicted; the magnitude of the effect was a 10–40% increase on average in serum levels and C_{max} at steady state (Fig. 3), which was as predicted from pharmacokinetic principles and was without clinical consequence.

Comparison with Chlorofluorocarbon–Beclomethasone Diproprionate

CFC–BDP (Beclovent™, Allen & Hanburys) was included as a treatment in studies A and B, thus allowing a pharmacokinetic comparison of both single-dose and steady-state doses with the two propellant formulations. In study A, C_{max} and the AUC of total BOH following a 400 μg CFC–BDP dose more closely resembled those following the 200 μg HFA–BDP dose than those following the 400 μg dose (Fig. 4). However, C_{max} was significantly lower and T_{max} was significantly later with CFC–BDP.

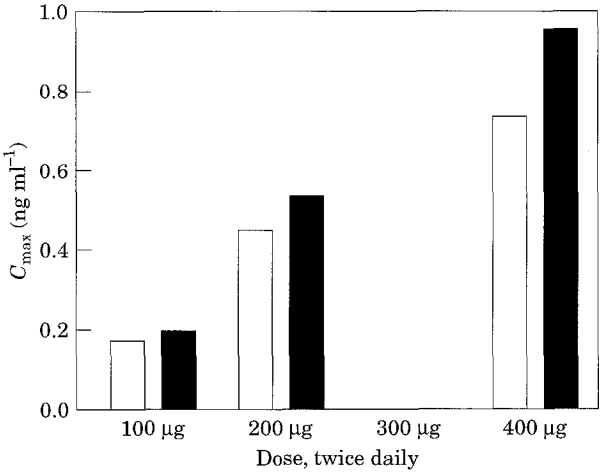

FIG. 3. Comparison of total BOH C_{max} values on day 1 (□; single dose) and day 14 (■; steady-state).

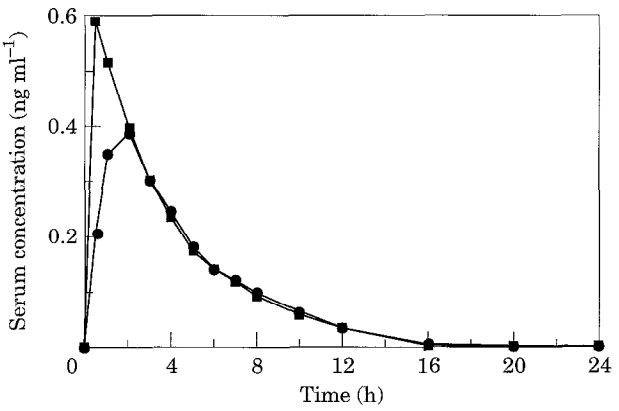

FIG. 4. Comparative mean serum total BOH concentrations following single inhaled doses of HFA–BDP (■; 200 μg) or CFC–BDP (●; 400 μg).

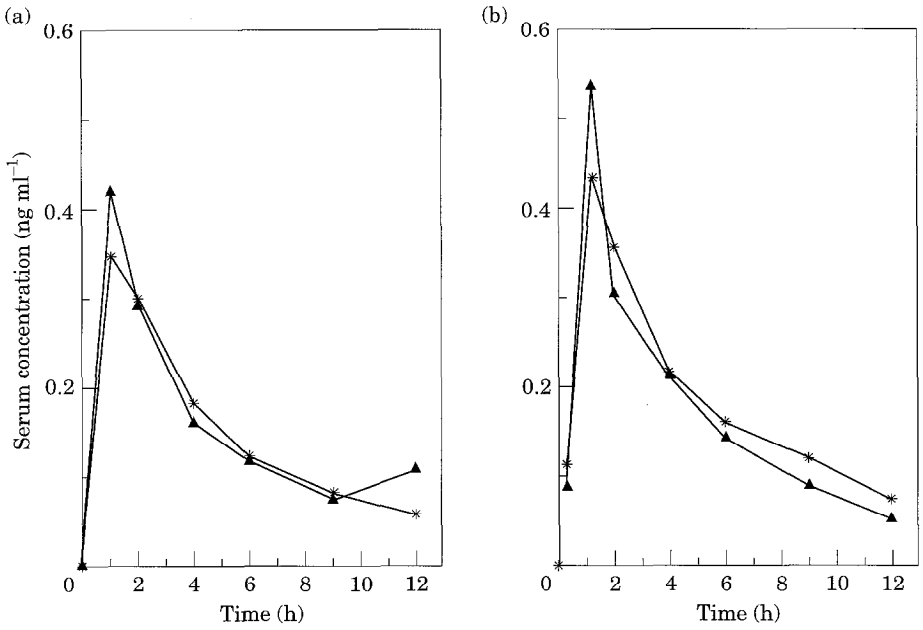

FIG. 5. Comparative mean serum concentrations of total BOH on (a) day 1 (single dose) and (b) day 14 (steady-state) following multiple dosage regimens with HFA–BDP (▲; 200 μg) or CFC–BDP (*; 400 μg): doses administered every 12 h.

A comparable pattern was obtained in study B, a multiple dosing study, in which similar serum levels and pharmacokinetic parameters of total BOH were observed between 400 μg CFC–BDP and half that dose administered as HFA–BDP (Fig. 5).

Relative Oral Absorption

To clarify the differences in drug bioavailability between the CFC–BDP and HFA–BDP products, study C was designed to determine the relative absorption of orally administered BDP compared with inhaled HFA–BDP. Oral BDP capsules were prepared and administered as five doses. As with the inhaled HFA–BDP doses, good proportionality of the pharmacokinetic parameters for BOH was observed between the oral doses (Fig. 6).

The oral doses that matched the BOH C_{max} and AUC of the two inhaled HFA–BDP reference doses were calculated. Oral doses of 500 μg and 2000 μg

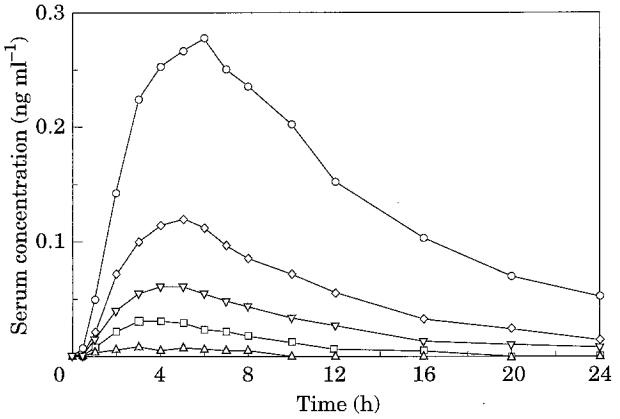

FIG. 6. Mean BOH serum concentrations following oral BDP; △, 200 μg; □, 500 μg; ▽, 1000 μg; ◇, 2000 μg; ○, 5000 μg.

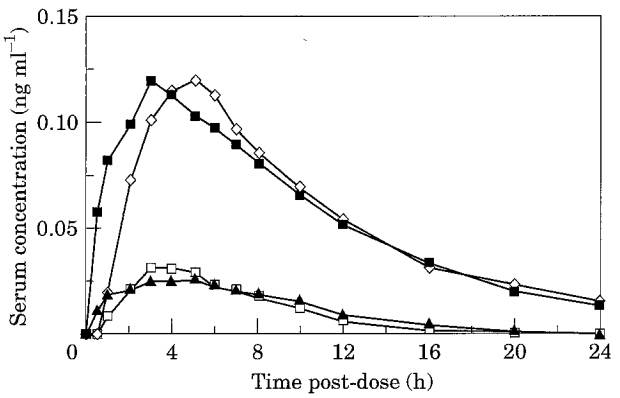

FIG. 7. Oral doses which gave similar serum BOH concentrations to inhaled HFA–BDP; □, 500 μg oral; ◇, 2000 μg oral; ▲, 200 μg MDI; ■, 800 μg MDI.

were determined as those required to give comparable pharmacokinetic parameters for BOH to the reference inhaled 200 μg and 800 μg HFA–BDP doses, which, by chance, were the oral doses used in the study (Fig. 7). Thus, the oral route required 2·5 times more drug to give the same BOH serum levels and AUC than did inhaled HFA–BDP. This study also showed that T_{max} for oral doses was later than for inhaled HFA–BDP, indicating a slower absorption with the oral route.

Explanation of Observations: a Unifying Hypothesis

Considering that orally administered BDP has been shown to result in a slower and decreased absorption and reduced bioavailability compared with inhaled HFA–BDP, the observed lower bioavailability of the CFC–BDP MDI compared with the HFA–BDP MDI

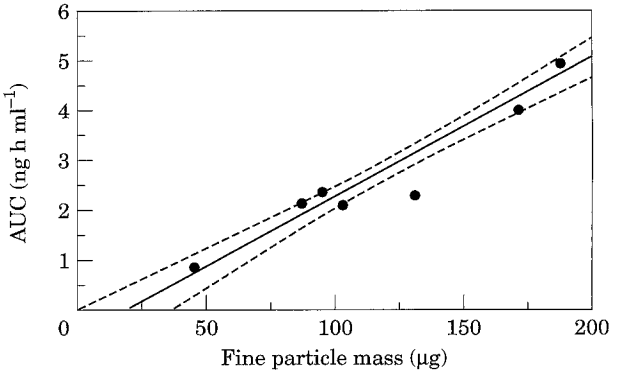

FIG. 8. Correlation between total BOH AUC and fine particle mass following HFA–BDP and CFC–BDP regression line and 95% confidence limits shown.

can be explained if most of each inhalation from the CFC–BDP MDI is swallowed and absorbed from the gastrointestinal tract, whereas most of the HFA–BDP MDI is absorbed from the lungs. This supposition has been confirmed in deposition studies with these two propellant formulations, as described by Leach (9). Such studies have shown that approximately 90% of the ex-actuator dose from the CFC–BDP MDI is swallowed whereas about 60% of the ex-actuator dose from the HFA–BDP MDI is deposited in the airways. The extensive oral deposition of the CFC product explains not only the lower extent of absorption but also the lower rate of absorption with this formulation.

The observed pharmacokinetic differences between the CFC–BDP and HFA–BDP MDIs were expected, based on the physical differences found between these products in fine particle mass. Our hypothesis that increased fine particle mass results in increased airways availability detected by increased drug absorption was confirmed. Indeed, if the administered dose was calculated in terms of the fine particle mass expected to reach the airways rather than the absolute dose given to the patient, all the observed data for both propellant systems could be correlated with the amount of total BOH in the serum (Fig. 8). This observation shows that fine particle mass is a direct correlate of *in vivo* pulmonary deposition and increased drug absorption.

Discussion

In vitro evidence of a higher mass of fine particles of BDP delivered by an HFA solution aerosol suggested an *in vivo* benefit of improved deposition in the intrapulmonary airways. A series of pharmacokinetic studies in asthmatic patients was undertaken to investigate

the implications on the serum profile of BDP and metabolites.

These studies demonstrated a serum level profile of BDP and active metabolites consistent with greater airways availability detected by an increased rate and extent of lung absorption from BDP extrafine aerosol compared with a CFC–BDP MDI. Fine particle mass showed a good correlation with the amount of BDP and active metabolites in the blood for both the HFA and the CFC formulations, providing strong evidence that delivery to the airways and serum profiles are largely related to the fine particle mass of BDP delivered to the patient. Consistent with the pharmacokinetic results, twice as much CFC–BDP was required to achieve a similar fine particle mass as HFA–BDP.

Considering that the airways are the target for the topical activity of BDP and metabolites, and that blood levels are a means to access the efficiency of delivering drug to the airways, the present results suggest that lower total daily doses of HFA–BDP extrafine aerosol will be required than withCFC–BDP. The potential beneficial implications of improved airways availability of HFA–BDP on its efficacy and safety in asthma are discussed elsewhere in this volume.

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