Urinary pharmacokinetic methodology to determine the relative lung bioavailability of inhaled beclometasone dipropionate

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Urinary pharmacokinetic methodology can be used to identify the relative bioavailability to the lungs and the systemic circulation after an inhalation but has not yet been extended to corticosteroids.
- Two (Qvar® and Clenil®) HFA (CFC-free) metered dose inhaler formulations of beclometasone dipropionate are now available. The recommended dose of Qvar is half that of Clenil but the two have yet to be compared.

WHAT THIS STUDY ADDS

- The urinary excretion of beclometasone dipropionate and its main metabolites (beclometasone-17- monopropionate and beclometasone) in the first 30 min post inhalation represents the relative bioavailability to the lungs after an inhalation.
- Similarly the 24 h urinary excretion of the main metabolites can be used to identify the relative bioavailability to the systemic circulation after an inhalation.
- The relative lung and systemic bioavailability between Qvar and Clenil confirms the two fold difference in their recommended doses.

AIM

Urinary pharmacokinetic methods have been identified to determine the relative lung and systemic bioavailability after an inhalation. We have extended this methodology to inhaled beclometasone dipropionate (BDP).

METHOD

Ethics Committee approval was obtained and all subjects gave consent. Twelve healthy volunteers received randomized doses, separated by >7 days, of 2000 µg BDP solution with (OralC) and without (Oral) 5 g oral charcoal, 10 100 µg inhalations from a Qvar® Easibreathe metered dose inhaler (pMDI) with (QvarC) and without (Qvar) oral charcoal and eight 250 µg inhalations from a Clenil® pMDI (Clenil). Subjects provided urine samples at 0, 0.5, 1, 2, 3, 5, 8, 12 and 24 h post study dose. Urinary concentrations of BDP and its metabolites, beclometasone-17-monopropionate (17-BMP) and beclometasone (BOH) were measured.

RESULTS

No BDP, 17-BMP or BOH were detected in any samples post OralC dosing. Post oral dosing no BDP was detected in all urine samples and no 17-BMP or BOH was excreted in the first 30 min. Significantly more ($P < 0.001$) BDP, 17-BMP and BOH were excreted in the first 30 min and the cumulative 24 h urinary excretions post Qvar and Clenil compared with Oral. The mean ratio (90% confidence interval) of the 30 min urinary excretions for Qvar compared with Clenil was 231.4 (209.6, 255.7) %.

CONCLUSION

The urinary pharmacokinetic methodology to determine the relative lung and systemic bioavailability post inhalation, using 30 min and cumulative 24 h post inhalation samples, applies to BDP. The ratio between Qvar and Clenil is consistent with related clinical and lung deposition studies.

Introduction

Inhaled corticosteroids (ICS) are the cornerstone of asthma management using either dry powder inhalers (DPIs) or pressurized metered dose inhalers (pMDIs). Although beclometasone dipropionate (BDP) is the oldest of the ICS, it is still widely used. It is a prodrug that is metabolized by esterases in the lung and liver (and elsewhere) to three main metabolites; beclometasone-17-monopropionate (17-BMP), beclometasone-21-monopropionate (21-BMP) and beclometasone (BOH). 17-BMP is the active metabolite whereas BOH and 21-BMP, as well as BDP, have a much lower binding affinity to the glucocorticoid receptor [1, 2]. The majority of products containing BDP for inhalation are pMDIs with only a few DPI products available.

Worldwide the pMDI is the most commonly used inhaler. The phase out of chlorofluorocarbon (CFCs) propellants, due to their detrimental effect on the ozone layer [3], has led to the reformulation and design of pMDIs with environmentally safer propellants such as hydrofluoroalkane134a (HFA). Unlike other corticosteroids (notably fluticasone propionate), the reformulation of BDP with the HFA propellants presented a challenge. These HFA BDP pMDI products, otherwise referred to as CFC-free, are now formulated as solution based aerosols instead of the traditional formulations of micronized drug particles suspended in the propellant. At present, there are two HFA pMDI BDP formulations available. These two products (Qvar and Clenil) are not equivalent and have different dosage recommendations. The innovator BDP product, Becotide® (GlaxoSmithKline), a CFC pMDI, has been discontinued. The first HFA BDP pMDI, Qvar® (Teva Pharmaceuticals, Israel), was formulated as a solution aerosol that emits much smaller particles (known as extrafine because the 'average' particle size was around 1 µm) than conventional pMDIs. Lung deposition, systemic delivery and clinical equivalence are all more than double that of the innovator Becotide product [4–8]. Hence the recommended dose of Qvar is half that of the innovator product. Despite the greater systemic delivery [7] it has a favourable safety profile compared with other inhaled corticosteroids [9, 10]. Clenil® (Chiesi, Italy) has been formulated as a solution aerosol with Modulite® technology to control the particle size of the emitted aerosol so that it is interchangeable with Becotide and other CFC-BDP containing pMDIs [11, 12]. Pharmacokinetic studies have shown similar systemic delivery and clinical equivalence with Becotide in children and adults with asthma [11, 13].

Pharmacokinetic methods using plasma [11, 14] or urine [15, 16] samples can be used to identify the relative lung deposition and total systemic delivery following an inhalation. Hindle & Chrystyn [16] first reported a urinary pharmacokinetic method to determine the relative bioavailability of salbutamol to the lung and to the body following an inhalation. The amount of salbutamol excreted in the urine over the first 30 min post inhalation represents

drug delivered to the body by the pulmonary route and excreted rapidly in the urine. This index represents the relative bioavailability to the lungs following an inhalation. The cumulative amount of salbutamol and its metabolites excreted in urine over the 24 h period post inhalation is an index of systemic delivery. This index is the relative bioavailability to the body following inhalation [16].

We have developed a sensitive and simple assay to measure BDP and its metabolites (17-BMP and BOH) in urine and have used the original methodology reported by Hindle & Chrystyn [16] to identify the feasibility of using this urinary pharmacokinetic method for inhaled BDP. The application of this approach has been determined by comparing urinary excretions post Qvar and Clenil inhalations. These two HFA pMDI products have not been compared and dosing comparisons have been made from separate studies that compared them with the innovator product [4–14].

Methods

Apparatus and chromatographic conditions

The analysis of BDP, 17-BMP and BOH in urine samples was performed using a liquid chromatographic mass spectrometric system (LC-MS). A 5 µm Spherclone ODS2, 2 × 250 mm column (Phenomenex, UK) was used with a mobile phase of acetonitrile : water (60 : 40% v/v) at a flow rate of 0.3 ml min⁻¹. Detection was carried out using a Bruker Esquire HCT ion trap mass spectrometer using electrospray ionization in positive mode (Bruker UK, Coventry, UK). The desolvation temperature was 280°C and the capillary and skimmer voltages were 4.0 kV and 40V respectively. A solid phase extraction method (SPE) using 3 ml Discovery DSC-CN (500 mg) solid phase extraction cartridges (Supelco, USA) was used to isolate BDP, 17-BMP and BOH from urine samples. The cartridges were first conditioned with 3 ml methanol followed by 3 ml water. Each 1 ml urine sample was pretreated by adding 2 ml of water containing the internal standard (IS), fluticasone propionate (FP) 90 ng ml⁻¹. This was then applied to the cartridge to retain the analytes. The cartridge was then washed with 3 ml of 20% v/v methanol in water and the analytes were eluted using 1 ml 100% methanol. This final eluate was evaporated to dryness, then reconstituted in 100 µl of the mobile phase and 10 µl was injected in to the LC-MS system. BDP was purchased (Sigma, UK) and the metabolites (17-BMP, 21-BMP and BOH) were gifts (GlaxoSmithKline, UK).

Pharmacokinetic study

Local research ethics committee approval for the study was obtained from the University of Huddersfield (reference number: 5.90/SREP/24Jun09). All subjects were healthy, non-smoking volunteers and all gave written informed consent to take part in the study.

The quantity of oral activated charcoal to block completely BDP gastrointestinal absorption was first determined. This was based on measuring the urinary excretion in four healthy, non-smoking volunteers following the oral administration of a 20 ml 20% ethanol solution containing 2 mg BDP with different oral doses of activated charcoal. Each volunteer voided their urine before each study dose and then provided samples at 0.5, 1, 2, 3, 5, 8, 12 and 24 h post study dose. The charcoal was given as a slurry in water and was swirled around the mouth before swallowing. No BDP or its metabolites were detected in all the urine samples following oral BDP dosing with the concomitant oral administration of 5 g activated charcoal (5 g in 50 ml water before and after the inhaled dose)

On separate study days, each separated by a minimum of 7 days, subjects ($n = 12$) received the following study doses in a randomized order. Each subject completed all the study doses.

- Oral administration of a 20 ml solution (20% ethanol) containing 2 mg BDP (Oral).
- Oral administration of a 20 ml solution (20% ethanol) containing 2 mg BDP with 5 g activated charcoal in 50 ml water before and after the inhaled dose (OralC).
- Ten 100 μg (1 mg in total) inhalations of BDP from a Qvar® Easibreathe® (Teva Pharmaceuticals, UK) pMDI (Qvar).
- Ten 100 μg (1 mg in total) inhalations of BDP from a Qvar® Easibreathe® metered dose inhaler with concurrent oral administration of activated charcoal; 5 g in 50 ml water before and after the inhalation dose (QvarC).
- Eight 250 μg (2 mg in total) inhalations of BDP from a Clenil® Modulite® (Chiesi, Italy) pMDI (Clenil).

The difference between the inhaled doses was due to the different equivalence between Qvar and Clenil (the equivalent dose of Qvar is half the dose of Clenil).

All subjects were trained on how to use the Qvar Easibreathe pMDI according to the patient information leaflet. Subjects were trained to shake the MDI, open the cap, exhale slowly as far as comfortable, put the MDI into their mouth and seal their lips round the mouthpiece. They were then instructed to start a slow inhalation through their mouth. A check was made that the breath actuation process occurred (sound, taste and visual check of an external lever on the device that moves when a dose is released). This slow inhalation continued until their lungs were full of air (total lung capacity). To ensure that a slow inhaled flow was used each subject was trained to make a 5 s inhalation. After each inhalation, they held their breath for 10 s and the next dose was repeated 30 s later. The same inhalation technique was used for the Clenil pMDI except that the volunteers were trained so they actuated a dose by depressing the pMDI canister at the start of their slow inhalation. A visual check was made to ensure that this co-ordination step was performed with precision every time they inhaled a dose. Subjects voided their urine

pre-dosing and provided urine samples at 0.5, 1, 2, 3, 5, 8, 12 and 24 h post study dose. The volume of urine excreted was recorded and aliquots of each sample were frozen at -20°C prior to analysis.

In a further study the reproducibility of the urinary excretion was determined. Eight volunteers repeated the Qvar study doses on five separate occasions. Each voided their urine before the study doses and then provided a urine sample 30 min post inhalation and then pooled all their urine over the next 24 h.

In vitro characterization of the emitted dose

The aerodynamic characteristics of the dose emitted from Qvar and Clenil were determined using the Andersen Cascade Impactor (Copley Scientific, UK) according to standard compendial methodology [17]. The flow rate used was 28.3 l min^{-1} with an inhalation volume of 4 l. Each determination was performed 10 times. Using standard data analysis [17], the mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and the fine particle dose (FPD) were obtained. The total emitted dose (TED) was the amount of BDP emitted from the mouthpiece of the pMDI. The fine particle fraction (FPF) was the FPD divided by TED and also the FPF expressed as a % of the nominal dose.

Statistical analysis

Urinary excretions were compared using a one way analysis of variance with the application of the Bonferroni correction. These comparisons were made for the actual amounts and when normalized for the nominal dose. To identify equivalence between the two inhalers the 30 min and cumulative 24 h amounts were normalized for the nominal dose and then log transformed. From the mean square error of the ANOVA, using patients and inhalation method as the main factors, the mean ratio (90% confidence interval (CI)) was calculated.

Results

LC-MS assay

The retention times of BOH, 17-BMP, FP (IS) and BDP were 2.5, 4.0, 6.0 and 8.3 min, respectively. The assay had acceptable inter- and intra-day limits for both accuracy and precision ($\pm 15\%$) within the range of the urine concentrations of the study samples and all three analytes were stable in urine at -20°C for up to 2 months. The overall mean (SD) intra-day assay variability, determined for three concentrations (35, 80 and 150 ng ml^{-1}) of BDP, 17-BMP and BOH ($n = 5$ for each) was 6.2 ± 2.45 , 8.75 ± 3.35 and $9.43 \pm 2.31\%$, respectively. The inter-day assay variability, determined at the same three concentrations using five replicate runs on different days was 8.17 ± 2.79 , 10.13 ± 2.81 and $12.23 \pm 1.55\%$, respectively.

Figure 1

Individual urinary excretions of (A) BDP, (B) 17-BMP and (C) BOH over the first 30 min post inhaled study doses

Figure 2

Individual urinary excretions of (A) BDP, (B) 17-BMP and (C) BOH over the 24 h period post inhaled and oral study doses

The SPE method was found to be reproducible, as the mean (SD) recovery were 93.95 (1.76), 90.89 (4), and 92.71 (2.28) % for BDP, 17-BMP and BOH, respectively. The limit of detection was 4.39, 3.6 and 6.6 ng ml⁻¹ and the limit of quantification was 13.3, 11.11 and 19.7 ng ml⁻¹, respectively. A separate study revealed that when left for 24 h at ambient temperature there was no change in the urinary concentrations of BDP, 17-BMP and BOH.

Pharmacokinetic study

Twelve healthy volunteers (four females), whose mean (SD) age, weight and height were 33.8 (11.6) years, 68.5 (10.7) kg and 168 (8) cm, respectively, completed all the study doses. No BDP, 17-BMP or BOH was detected in any of the urine samples following the oral dose with concurrent charcoal administration (OralC). Individual 30 min and cumulative 24 h urinary excretions are shown in Figures 1 and 2 with mean (SD) amounts summarized in Table 1. These show that after the oral study dose no BDP, 17-BMP or BOH was detected in the first 30 min urine samples. In contrast significantly more ($P < 0.001$) BDP, 17-BMP and BOH were excreted in the urine 30 min after the inhalation of Qvar, Qvar with oral charcoal (QvarC) and Clenil. Furthermore,

Table 1 reveals that no BDP was detected in any of the urine samples post oral dosing. There was no difference in the amounts of BDP, 17-BMP and BOH excreted in the urine over the first 30 min post Qvar, Qvar with charcoal and Clenil study doses. A summary of the cumulative urinary excretion of BDP, 17-BMP and BOH at each sample time is presented in Figure 3. Comparison of the amounts excreted (for BDP and its metabolites) between Qvar and Clenil at each sample point revealed no difference.

A summary of the mean ratio (90% CI) between Qvar and Clenil with respect to the nominal dose and between each product and the oral dose is presented in Table 2. For this comparison all amounts were normalized for the nominal dose. These values are presented separately for BDP, 17-BMP and BOH as well as for all three combined. The latter, which represents an overall ratio, shows a mean ratio (90% CI) of 231.4 (209.6, 255.7) % for Qvar compared with Clenil which confirms the >two fold difference in equivalence between these two products.

Eight (four females) volunteers completed the reproducibility study. Their mean (SD) age, weight and height were 27.4(5.9) years, 62.6 (7.8) kg and 167.8 (9.0) cm, respectively. The mean (SD) intra-subject coefficient of

Table 1

Mean (SD) urinary excretion following oral and inhaled study doses

Mean (SD) cumulative amount(μg)	BOH 0–0.5 h	0–24 h	17-BMP 0–0.5 h	0–24 h	BDP 0–0.5 h	0–24 h
(A) amounts excreted in the urine (μg)						
Qvar	5.99 (1.62)*	86.15 (21.58)*	3.87 (1.38)*	34.27 (10.63)*	4.16 (0.88)*	20.91(5.11)*
Qvar C	5.12 (1.79)*	57.75 (19.1)*	3.24 (1.16)*	22.64 (7.91)*	3.71 (0.98)*	22.29 (5.44)*
Oral	0 (0)	33.61 (9.77)	0 (0)	16.08(5.14)	0 (0)	0 (0)
Clenil	5.09 (1.49)*	78.46 (27.48)*	3.13 (0.77)*	30.87 (8.49)*	3.88 (1.37)*	24.07 (3.34)*
(B) amounts normalized for the nominal dose (%)						
Qvar	0.60 (0.16)*	8.61 (2.16)*	0.39 (0.14)*	3.43 (1.1)*	0.42 (0.09)*	2.09 (0.51)*
Qvar C	0.51 (0.18)*	5.78 (1.91)*	0.32 (0.12)*	2.26 (0.79)*	0.37 (0.1)*	2.22 (0.54)*
Oral	0 (0)	1.68 (0.49)	0 (0)	0.8 (0.26)	0 (0)	0 (0)
Clenil	0.25 (0.07)*	3.92 (1.37)*	0.16 (0.04)*	1.54 (0.42)*	0.19 (0.07)*	0.44 (0.11)*

*P < 0.001 with respect to the oral dose.

variation for BDP, 17-BMP and BOH was 9.5 (2.9), 10.6 (4.2) and 10.7 (5.2) % for the 0.5 h urinary excretion and was 8.9 (4.6), 8.2 (2.6) and 8.4 (1.5) % for the 24 h urinary excretion, respectively. The mean (SD) inter-subject coefficient of variation was 33.4 (3.3), 18.1 (3.2) and 25.4 (3.1) % for the 0.5 h urinary excretion and was 27.7 (4.7), 30.6 (3.8) and 24.4 (1.4) % for the 24 h urinary excretion, respectively.

In vitro determination of the emitted dose

A summary of the aerodynamic characteristics of the emitted dose from Qvar and Clenil is presented in Table 3. These results confirm the extrafine particles and high fine particle dose emitted from Qvar.

Discussion

The lack of BDP, BOH and 17-BMP in the urine samples at 30 min post the oral dose and the significant amounts of these post inhalation highlights that the urinary pharmacokinetic method first pioneered for salbutamol [16] can be applied to BDP post inhalation. The 30 min urinary excretion after an inhalation of BDP can be used to compare different inhaled products like we have done with the comparison of Qvar and Clenil in this study. This is the first time that these two HFA pMDI formulations of BDP have been compared. Previously all dose equivalence has been related to separate studies comparing each product with Becotide [4–14]. The ratio between the two products confirms that the dose of Qvar should be halved and the MHRA recommendation that HFA BDP pMDIs should be prescribed by brand name. The urinary pharmacokinetic method is simple and non-invasive. The method could be used in patient studies without altering their ICS therapy by switching them to a different corticosteroid because the assay discriminates between these drugs.

Consistent with previously reports no BDP was detected in any of the urine samples after the oral dose [18]. The rapid appearance of 17-BMP and BOH within the first 30 min post

inhalation was faster than when plasma concentrations were measured following inhalation of the discontinued innovator product, Becotide, CFC BDP pMDI [18]. This could be due to the inefficient lung deposition of the innovator product with a tendency for greater central lung deposition compared with a more even distribution [5, 6].

When using the 30 min urinary excretion then either BDP, 17-BMP or BOH can be used. Table 3 shows that there is little difference when these are used to compare the bioequivalence of Qvar and Clenil. When combining all the data the overall mean ratio was 231.4% with a 90% CI of 209.6, 255.7. This is consistent with the 2.6 potency ratio reported in a clinical study comparing these two products [8]. The 30 min excretions are also consistent with another pharmacokinetic study that compared the early pharmacokinetic profile of CFC and HFA BDP formulations of Beclazone® (Teva Pharmaceuticals, UK) [14]. Like Becotide these two Beclazone products have been discontinued.

The 30 min urinary excretion highlights the usefulness of this index as a measure of the relative bioavailability of beclometasone dipropionate to the lungs following an inhalation. The inter- and the intra-individual variation is consistent with that previously reported for salbutamol [16], as well as gentamicin [19], formoterol [20], sodium cromoglicate [21] and terbutaline [22].

To formulate the oral solution the BDP was dissolved in ethanol and then water was added. This formulation would, therefore, have increased the likelihood of faster and more complete oral absorption as well as an increased potential for buccal absorption. The lack of any BDP, 17-BMP or BOH post oral administration with oral charcoal confirms the effectiveness to block any gastrointestinal absorption. The lack of a difference between the 30 min excretions with and without charcoal for the Qvar inhalations is consistent with that of the salbutamol urinary pharmacokinetic method [16] and confirms that charcoal blocking is not necessary when using this urinary pharmacokinetic method to compare different inhaled BDP products or inhalation techniques.

Figure 3

The cumulative mean (SD) urinary excretions of (A) BDP, (B) 17-BMP and (C) BOH post study doses. (A) Qvar (—◆—); Clenil (—■—); QvarC (—▲—). (B) Clenil (—◆—); Qvar (—■—); QvarC (—▲—); Oral (—■—). (C) Clenil (—◆—); Qvar (—■—); QvarC (—▲—); Oral (—■—)

The greater 30 min urinary excretions are consistent with the particle size distributions of the emitted dose. The mass median aerodynamic diameter (MMAD) of $1.2\ \mu\text{m}$ and a high fine particle dose is consistent with previous reports [5, 23]. It has been shown that extrafine particles

(usually defined as a MMAD around $1\ \mu\text{m}$) of salbutamol provide greater lung deposition [24] although a pharmacokinetic BDP study has contradicted this [25]. However the process of generating the small BDP particles, the robustness of the particle size measurements together

Table 2

Mean ratio (90% CI) % for Qvar compared with Clenil and between each product and the oral dose

Urinary excretions	30 min urinary excretion	Cumulative 24 h urinary excretion		
	Qvar vs. Clenil	Qvar vs. Clenil	Qvar vs. oral	Clenil vs. oral
BDP	221.4(189.1, 259.6)	170.7 (148.3, 196.6)	–	–
17-BMP	236.6 (192.1, 291.2)	223.9 (202.2, 247.7)	430.6 (385.7, 480.2)	192.3 (172.3, 214.5)
BOH	236.8 (198.0, 283.5)	223.9 (206.7, 242.8)	517.6 (460.4, 581.8)	231.2 (205.6, 259.9)
All combined	231.4 (209.6, 255.7)	204.6 (189.6, 220.6)	451.3 (412.9, 492.8)	220.6 (202.0, 241.1)

Table 3Mean (SD) aerodynamic characteristics of the emitted dose ($n = 10$ determinations)

	Qvar (100 µg)	Clenil (250 µg)
TED (µg)	372.6 (27.12)	381.8 (6.3)
TED (% nominal dose)	93.16 (6.78)	76.4 (1.66)
FPD (µg)	218 (29.1)	97.6 (20.6)
MMAD (µm)	1.2 (0.17)	2.8 (0.44)
GSD	3.6 (0.28)	2.2 (0.15)
FPF of nominal dose	54.5 (7.27)	19.5 (4.16)
FPF% of emitted dose	58.4 (5.22)	25.6 (5.4)

TED, total emitted dose; FPD, fine particle dose; MMAD, mass median aerodynamic diameter; GSD, geometric standard deviation; FPF, fine particle fraction.

with its non-specific methodology and the pattern of deposition in the lungs in the pharmacokinetic BDP study may have contributed to the unexpected results. The aerodynamic characteristics of the emitted dose from Clenil providing a MMAD of 2.9 µm and a fine particle dose that is approximately 20% of the nominal dose are consistent with those of the innovator, Becotide, product [11, 12].

The 24 h cumulative amounts post inhalation reflect the total systemic delivery from the gastrointestinal and pulmonary routes [16]. No BDP was excreted in the urine samples post oral dosing and so instead of using the 30 min urinary excretions there is a potential to use 24 h excretions of BDP for the relative lung bioavailability. However, the mean ratio shown in Table 3 for the Qvar comparison with Clenil is not consistent with the 30 min excretions. Whether this difference is affected by the difference in the metabolic balance between systemic delivery by the pulmonary and gastrointestinal routes or deposition in different zones of the lungs is not known.

The greater 24 h excretions post inhaled dosing compared with oral confirms the poor bioavailability of the oral dose. These differences also confirm that the lag time for BDP oral absorption is prolonged, hence the application of the 30 min urinary excretion to determine the relative lung bioavailability of inhaled BDP. When the 24 h 17-BMP and BOH data are combined these provide a mean ratio of 223.9 and 90% CI of 207.7, 241.3. This is consistent with the

pharmacokinetic profiles previously reported after inhalation of Qvar and the CFC innovator (Becotide) product [7]. However, the greater systemic delivery from Qvar is not consistent with the lower cortisol suppression compared with the Becotide pMDI [26]. This may be attributed to the shorter t_{max} for Qvar compared with Becotide which may provide less stimulus for the hypothalamic pituitary adrenal (HPA) axis to change its output of corticotrophin-releasing hormones and adrenocorticotrophic hormone [27].

Although all volunteers were intensively trained on how to use the recommended pMDI inhalation technique, the Easi-breathe version of Qvar was used because it is a breath actuated inhaler. This ensures there would have been no inconsistencies due to problems with the co-ordination between dose actuation and the start of an inhalation. However Clenil is only available as the conventional pMDI but the volunteers received intensive inhalation technique training and were closely observed during the inhalation manoeuvres so any differences due to inhalation technique should have been negligible [28].

In conclusion, the simple, non-invasive urinary pharmacokinetic method originally pioneered for salbutamol can also be applied to inhaled BDP. Urinary excretion of BDP or its main metabolites, 17-BMP and BOH, over the first 30 min post inhalation represents the relative bioavailability to the lungs following an inhalation of BDP. All three are assayed by the same method and so it is convenient to combine their data to provide an average when comparing inhaled products or inhalation techniques. The urinary excretion of the main metabolites, 17-BMP and BOH over the 24 h period post inhalation represents the relative bioavailability to the body following an inhalation of BDP. For this index, it is convenient to combine the excretion of both these metabolites when comparing inhaled products or inhalation techniques.

Competing Interests

AS and LH have no conflicts of interest. HC has no shares in any pharmaceutical companies. He has received sponsorship to carry out studies, together with some consultant agreements and honoraria for presentations, from several

pharmaceutical companies that market inhaled products. These include Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Innovata Biomed, Meda, Mundipharma, Orion, Teva, Trudell and UCB. Research sponsorship has also been received from grant awarding bodies (EPSRC and MRC).

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