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Beclomethasone Relative Availability of Oral versus Inhaled Beclomethasone Dipropionate from an HFA-134A Metered Dose Inhaler

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ABSTRACT: 3M has formulated a new chlorofluorocarbon-free (CFC-free) beclomethasone dipropionate (BDP) metered-dose inhaler (MDI) with the use of the propellant HFA-134a (HFA). Lung deposition studies demonstrated that the HFA BDP MDI delivers to the lungs approximately 56% of the BDP dose (ex-adaptor), a substantially higher percentage than the 5–30% delivered by conventional CFC BDP MDIs. As new sensitive bioanalytical methods are becoming available to quantitate systemic levels of inhaled corticosteroids, pharmacokinetic evaluations are emerging as sensitive and reproducible methods that can be used as a complement to the data obtained from lung deposition studies to assess and compare the performance of MDIs. The present study was designed to determine the beclomethasone (BOH) availability of oral BDP relative to inhaled HFA BDP as a first step to alloy MDI product comparisons in the future. Forty mild asthmatic patients completed this open-label, randomized, single-dose, two-period crossover study. Each patient received an oral dose of BDP (0.2, 0.5, 1, 2 or 5 mg) in one period and an inhaled dose of BDP (0.2 or 0.8 mg) in the other period, with four patients allocated to each of ten different treatment sequences. The BOH availability of orally administered BDP was approximately 40% relative to inhaled HFA BDP. In addition, the fraction of an oral dose that reaches the systemic circulation was estimated from the 40% relative availability and previous lung deposition data to be 0.26. These estimated pharmacokinetic parameters will be used in the future to further characterize the pharmacokinetics of inhaled BDP and to compare the performance of different MDI products. © 1998 John Wiley & Sons, Ltd.

Key words: beclomethasone; pharmacokinetics; bioavailability; inhalation; HFA-134a

Introduction

The performance of metered dose inhalers (MDI) can be determined by the relative amount of the dose delivered to the lungs to that swallowed. One way of assessing *in vivo* lung deposition after inhalation is with the use of gamma scintigraphy techniques. This technique provides a direct measurement of lung deposition by incorporating a radiolabelled marker into the formulation. A second way of assessing and comparing *in vivo* the performance of MDIs is by studying the pharmacokinetics of inhaled drugs [1]. Due to the lack of sensitive bioanalytical assays, the pharmacokinetics of inhaled drugs, specially of inhaled corticosteroids, has not been fully characterized. Recent development of sensitive assays for inhaled corticosteroids opens the possibility of using pharmacokinetics as a sensitive tool to assess and compare the performance of different MDIs. Pharmacokinetic studies provide an indirect and reproducible *in vivo* measurement of the amount of drug delivered to the lungs which can complement the data obtained from the use of scintigraphy techniques [1].

3M has formulated a new chlorofluorocarbon-free (CFC-free) beclomethasone dipropionate (BDP) metered-dose inhaler (MDI) with the use of the propellant 1,1,1,2-tetrafluoroethane or HFA-134a (HFA). Scintigraphy lung deposition studies have shown that this HFA BDP MDI formulation delivers to the lungs approximately 56% of the BDP dose (ex-adaptor) [2], a substantially higher percentage than the 5–30% delivered by conventional CFC BDF MDIs. The pharmacokinetics of inhaled drugs is determined by the amount of drugs deposited in the lungs, the amount of drug swallowed, and the absorptive rate, extent and first-pass effect through the pulmonary and gastrointestinal routes. Therefore, in order to compare the performance of the two BDP MDI formulations, extent of absorption and first-pass effect through the pulmonary and gastrointestinal routes must be known. The purpose of the present study was to determine the relative availability of these two routes as the first step to permit a product performance comparison.

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The amount of an oral BDP dose that reaches the systemic circulation (A_{po}) is the product of the BDP dose (X_{po}) and the fraction of the dose that is available systemically (F_{po}):

$$A_{po} = F_{po} \cdot X_{po}. \quad (1)$$

The total amount of an inhaled BDP dose from a MDI that reaches the systemic circulation (A_{in}) is dependent on the amounts swallowed and deposited in the lungs, according to:

$$A_{in} = F_{po} \cdot D_{po} \cdot X_{in} + F_l \cdot D_l \cdot X_{in}, \quad (2)$$

where X_{in} is the inhaled BDP dose; D_{po} and D_l are the fractions of the inhaled dose swallowed and deposited in the lungs, respectively; F_l is the fraction of the amount deposited in the lungs that reaches the systemic circulation; and F_{po} is the fraction of the amount swallowed that is available systemically.

The relative availability of oral versus inhaled BDP can be defined as the ratio of the dose normalized A_{po} to A_{in}:

$$\text{Relative Availability} = \frac{A_{po}/X_{po}}{A_{in}/X_{in}} = \frac{F_{po}}{F_{po} \cdot D_{po} + F_l \cdot D_l}. \quad (3)$$

The present study was designed to determine the beclomethasone (BOH) availability of oral BDP relative to inhaled HFA BDP. In addition, this relative availability together with previous results from deposition studies [2] were used to solve Equation (3) for $F_{po.}$

Materials and Methods

Study Design and Patients

A total of 41 patients with mild asthma (33 males and 8 females) between 18 and 49 years of age were randomized into the study. All patients had a prestudy forced expiratory volume in 1 s (FEV_1) $\geq 70\%$ of predicted normal, were within 20% of ideal body weight, demonstrated proper technique in the use of a placebo press-and-breath metered dose inhaler (MDI) and were otherwise healthy as judged by medical history, physical examination, 12-lead ECG, and clinical laboratory tests. Most patients were non-smokers; of the seven patients who had smoked in the past, all had abstained from smoking for at least 1 year.

This study was an open-label, randomized, single-dose, two-period crossover trial. Patients received an oral dose of BDP (0.2, 0.5, 1, 2 or 5 mg) in one period and an inhaled dose of HFA BDP (0.2 or 0.8 mg) in the other period. There were ten different treatment sequences for the two periods and four patients were allocated to each of the ten treatment sequences. Five to 7 days separated the treatment periods.

Written informed consent was obtained prior to participating in the study. The study protocol and amendments were approved by the Western Institutional Review Board.

Drug Administration and Sample Collection

Five strengths of BDP capsules, containing 0.2, 0.5, 1.0, 2.0 and 5.0 mg BDP, were provided by 3M Pharmaceuticals (St. Paul, MN). Content uniformity, dissolution and stability tests were performed in randomly selected capsules for batch clearance. The HFA BDP MDIs used in this study delivered 100 mcg of BDP per actuation ex-valve and were manufactured on a production scale at the 3M Health Care facility (Loughborough, UK). Randomly selected inhalers were tested for content uniformity, ex-valve release and fine particle mass prior to lot clearance.

Patients fasted overnight prior to receiving the oral and inhaled BDP doses at approximately 08:00 h (± 15 min.) and for 4 h after dose administration. On the morning of each treatment day, patients swallowed a BDP capsule of the appropriate strength with 6 ounces of water or administered themselves two or eight inhalations of HFA-BDF MDI. Each inhalation was separated by a 30-s interval; time 0 was considered to be the time of actuation of the first inhalation. All inhalations were administered under supervision.

Venous blood samples, 15 mL, were drawn just before dosing and at 0. 5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, and 24 h postdose for the determination of BOH levels.

Bioanalytical Assay

After separation with a liquid–liquid extraction procedure, serum BOH concentrations were measured with the use of a validated LC/MS/MS method developed by 3M Pharmaceuticals. The linear range was 10–300 pg mL^{-1} for BOH in 1 mL of serum. The inter-day coefficient of variation was less than 10% for low (10 pg mL^{-1}), medium (100 pg mL^{-1}), and high (300 pg mL^{-1}) levels of BOH. The inter-day precision and accuracy was calculated from the analysis of three quality control (QC) samples at low (18 pg mL^{-1}), medium (95 pg mL^{-1}), and high (198 pg mL^{-1}) concentration levels. The coefficient of variation at all concentration levels for BOH was less than 10%. The relative error at all concentrations was within the range of -10 to $+10\%$.

Pharmacokinetic Analysis

Noncompartmental pharmacokinetic analysis was performed with the use of Pharm-NCA, Version 1.31b (SIMED S.A., Créteil, France). Peak serum concentration (C_{max}) was defined as the highest measured serum concentration throughout the 24 h sampling period following the time of BDP administration and time to peak concentration (T_{max}) was the time of C_{max}. Area under the serum concentration–time curve (AUC(0–t)) was calculated by the linear trapezoidal rule from time zero until the time of the last quantitatible serum concentration (t). Extrapolated AUC($t-\infty$) was calculated as the last measurable serum concentration divided by the terminal elimination rate constant K_e. K_e was calculated by the least squares method as the slope of the linear regression of the postabsorptive phase of natural logarithm (serum concentration)–time curve. K_e was considered valid if the coefficient of determination (R^2) was ≥ 0.850. AUC(0–∞) was calculated as the sum of AUC(0–t) plus the extrapolated AUC($t-\infty$) was included in mean data if the extrapolated AUC was less than 20% of the total AUC. The BOH availability after oral administration of BDP relative to inhaled BDP was calculated as the ratio of the dose-normalized AUC(0–∞) after oral BDP to the dose-normalized AUC(0–∞) after inhaled BDP.

Despite the high sensitivity of the LC/MS/MS method, AUC(0–∞) could not be accurately estimated for either the 0.2 mg inhaled BDP dose or the 0.2 and 0.5 mg oral BDP doses. Therefore, in order to use the pharmacokinetic data obtained from the 40 patients and from all dose levels, an alternative method was used estimating relative availability as the inhaled dose divided by the comparable oral dose. The comparable oral BDP doses to 0.2 and 0.8 mg of inhaled BDP were estimated from the percentage change in BOH C_{max} after oral and inhaled BDP with the use of linear regression techniques (SAS Software, Version 6.08). The percentage change from inhaled dose in C_{max} was defined as the percentage of the difference between BOH C_{max} after oral and inhaled doses of BDP, normalized for the C_{max} after the inhaled dose. The slope and intercept of the regression lines were calculated and inverse regression was applied to determine the estimate of the oral dose that gave comparable mean C_{max} to the inhaled dose (i.e. the oral dose for which the percentage change from inhaled dose was zero). In addition, the comparable oral dose to the 800 mcg inhaled dose based upon AUC(0–∞)was also estimated to compare the relative availability obtained by the comparable dose ratio method and the AUC ratio method. The relative availability obtained from the comparable dose method was used together with results from previous deposition studies to estimate F_{po} from Equation (3).

Results

Of the 41 patients randomized into the study, 40 completed the two treatment period. One patient withdrew from the study after completing period 1 due to an upper respiratory tract infection not related to the study drug. Pharmacokinetic data analysis was performed for the 40 patients that completed the study.

Measurable BOH concentrations were obtained in all 40 patients after inhaled doses of HFA BDP. For the oral dose treatments all but two patients receiving the lowest dose level (0.2 mg) had quantitatible BOH levels at some time point throughout the 24 h period following BDP administration.

Mean BOH serum concentrations after the 2 mg oral dose of BDP were in a similar concentration range to those obtained after an inhaled dose of 0.8 mg, while those after a 0.5 mg oral dose were comparable to the levels obtained after the 0.2 mg dose of BDP (Figure 1). However, mean BOH concentration–time profiles after oral BDP lagged at least 1 h behind those obtained after inhaled BDP doses (Figure 1). Mean BOH T_{max} also reflected that BOH was systemically available approximately 1 h earlier after administration of inhaled HFA BDP than after oral BDP; mean BOH T_{max} ranged between 3–4 h after inhaled BDP and between 4–5 h after oral BDP (Table 1).

Mean BOH C_{max} was linearly proportional to the BDP dose for both routes of administration (Table 1 and Figure 2). BOH AUC was also reasonably proportional to the oral BDP dose within the 1–5 mg range (Table 1, Figure 2).

BOH serum levels declined monoexponetially after T_{max} with a mean $t_{1/2}$ ranging between 5.5–7.5 h after both oral and inhaled BDP (Table 1).

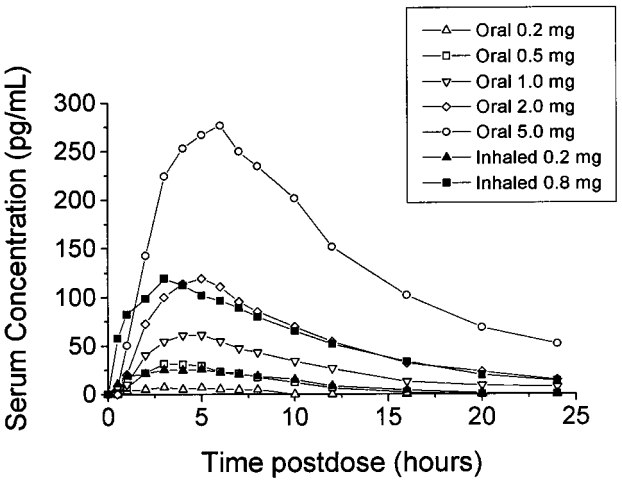

Figure 1. Mean serum beclomethasone concentrations following the administration of single oral and inhaled doses of beclomethasone dipropionate ($N = 20$ patients for each inhaled dose and $N = 8$ for each oral dose group)

Table 1. Mean ± S.D. beclomethasone pharmacokinetic parameters

BDP dose (mg)	C_{max} (pg mL^{-1})	T_{max} (h)	AUC(0−∞) (pg·h mL^{-1})	$t_{1/2}$ (h)
Inhaled[a]				
0.2	28 ± 6.8	4 ± 1.1	[d]	7.5 ± 2.1 (12)[c]
0.8	124 ± 25.3	3 ± 0.6	1535 ± 502.4	6.5 ± 1.1
Oral[b]				
0.2	12 ± 7.4	4 ± 1.0 (6)[c]	[d]	6.2 (2)[c]
0.5	33 ± 19.6	4 ± 0.9	[d]	5.2 ± 1.6 (6)[c]
1	63 ± 23.0	5 ± 0.7	788 ± 439.6 (5)[c]	6.3 ± 2.2
2	126 ± 31.4	5 ± 0.9	1378 ± 407.7 (7)[c]	6.4 ± 1.6
5	308 ± 72.8	5 ± 1.2	4016 ± 617.5	7.2 ± 1.4

[a] $N = 20$ unless indicated otherwise.
[b] $N = 8$ unless indicated otherwise.
[c] Number in parethesis indicates number of patients when parameter could not be calculated for all patients in treatment group.
[d] Could not be calculated.

The graphical representation of the inverse regression procedure used for the calculation of the comparable oral BDP dose to an inhaled HFA BDP dose of 0.8 mg is presented in Figure 3. Based upon BOH C_{max}, the comparable oral doses to 0.2 and 0.8 mg of inhaled HFA BDP were estimated to be 0.55 and 2.00 mg, respectively. Based upon BOH AUC, the estimated BDP oral dose comparable to the 0.8 mg inhaled BDP dose was 1.85 mg, in agreement with that estimated based upon BOH C_{max}. Thus, the BOH availability after oral BDP doses relative to inhaled HFA BDP doses was approximately 0.4 (Table 2). With the use of the AUC ratio method, the BOH oral availability to the inhaled dose of 0.8 mg was 0.44, similar to that obtained from the comparable oral dose method of 0.43 (Table 2).

Assuming an oral versus inhaled relative availability of 0.40 estimated as the average value from the comparable dose method (Table 2); a fraction of the inhaled HFA BDP dose deposited in the lungs of 0.56 (D_l) and swallowed of 0.34 (D_{po}) [2]; and that the drug deposited in the lungs reaches in its entirety the systemic circulation ($F_l = 1$); the fraction of the swallowed dose that reaches the systemic circulation (F_{po}) was estimated to be 0.26 from Equation (3).

Discussion

As new sensitive bioanalytical methods are becoming available to quantitate systemic levels of inhaled corticosteroids, PK evaluations are emerging as sensitive and reproducible methods to assess MDI performance. Ideally, IV dosing would be needed to determine F_{po} and F_l. Our approach was to make the comparison relative to pulmonary absorption by defining $F_l = 1$, which allowed the solution of Equation (4) for F_{po} with the current data. The fraction of an inhaled BDP dose that reaches the systemic circulation is given by rearranging Equation (2):

$$A_{in}/X_{in} = 0.26 \cdot D_{po} + D_l. \quad (4)$$

The percentage of the inhaled dose available systemically which arises from swallowed drug (%PO) can be estimated from Equation (4) as:

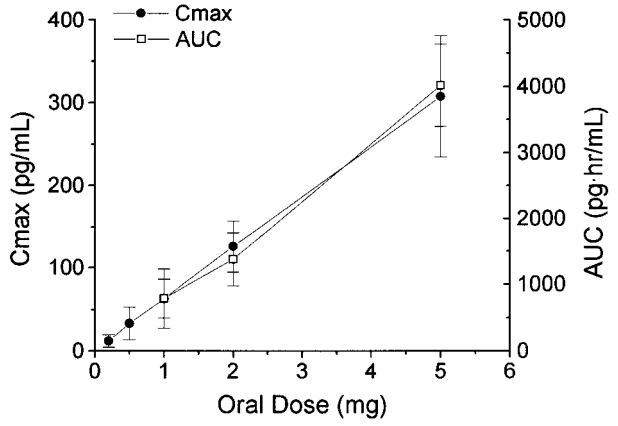

Figure 2. Mean ± S.D. beclomethasone maximum serum concentration and area under the curve versus beclomethasone dipropionate oral dose

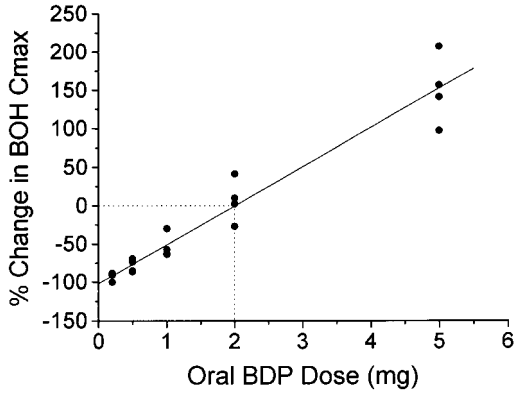

Figure 3. Estimation of BDP oral dose comparable to 0.8 mg inhaled dose of HFA-BDP based upon beclomethasone C_{max} ($N = 20$ patients). Solid line is the linear regression line and dotted lines represent the comparable dose estimation

Table 2. BOH availability after oral BDP relative to inhaled HFA BDP estimated by the comparable dose ratio and the AUC ratio methods

Inhaled BDP dose	Comparable oral dose method based upon		AUC ratio method
	BOH C_{max}	BOH AUC	
0.2	0.36[a]		
0.8	0.40[a]	0.43[b]	0.44 ± 0.15[b] (range: 0.22–0.59)

[a] Based on $N = 20$ patients.
[b] Mean $\pm$ S.D., based on $N = 11$ patients.

$$\%PO = \frac{0.26 \cdot D_{po}}{0.26 \cdot D_{po} + D_l} \times 100. \quad (5)$$

Previous lung deposition studies [2] estimated D_{po} and D_l to be 0.34 and 0.56, respectively, for HFA BDP, and 0.94 and 0.04, respectively, for CFC BDP. Thus, the percentage of the inhaled dose available systemically which arises from swallowed drug (%PO) for HFA BDP and CFC BDP was estimated to be 14 and 86%, respectively. These calculations of %PO indicate that the pharmacokinetic profile after inhalation of CFC BDP arises primarily from swallowed drug and should reflect the profile following oral BDP administration. Proof of these predictions comes from recently published data of an independent study of the pharmacokinetics following an inhaled dose of 2 mg of CFC BDP [3]. This study reported a BOH C_{max} of 121 pg mL^{-1} and T_{max} of 5 h [3], respectively, which are similar to the BOH C_{max} of 126 pg mL^{-1} and T_{max} of 5 h obtained in the present study after a 2 mg BDP oral dose (Table 1). The agreement between BOH levels after 2 mg of oral BDP and 2 mg of inhaled CFC BDP indicated that most of the BDP dose from the CFC BDP product was actually swallowed and supports the lung deposition data and our pharmacokinetic predictions for inhaled CFC BDP.

Product comparisons based on pharmacokinetic evaluations will be attempted in future studies, when the desired products can be administered according to the same protocol. Due to the complexity of the study design, a CFC treatment was not included in the present study.

Inhaled BDP is widely used for the treatment of asthma. BDP is activated *in vivo* by hydrolysis to beclomethasone 17-monopropionate (17-BMP) [4]. Assessed by their relative affinities to the glucocorticoid receptor, 17-BMP has approximately 20 times the pharmacological activity of either BDP or BOH, while beclomethasone 21-monopropionate (21-BMP) is inactive [4]. BDP is rapidly and almost completely hydrolyzed to 17-BMP in human serum and in human lung, liver and feces homogenates [5,6]. After inhalation of BDP, BDP is only detected in the first few blood samples [3,7]and rapidly declines with a half-life of 6 min [3]. Therefore, since 17-BMP is the active and major component of the systemic exposure of BDP [3], it is the molecule of choice to study the pharmacokinetics with the purpose of assessing and comparing the performance of MDIs. 3M Pharmaceuticals developed a sensitive LC/MS/MS method to quantitate BOH serum levels with a lowest level of quantitation of 10 pg mL^{-1}. At the time of sample analysis of the present study, this bioanalytical assay was not fully developed to quantitate 17-BMP and therefore BOH is used in this study as a surrogate molecule for the active metabolite of BDP. Recently, an assay has become available to measure primarily 17-BMP in serum [8]. In order to support the use of BOH as a surrogate for the estimation of the relative availability, the serum samples from four patients who received 800 mcg of inhaled HFA BDP and 2 or 5 mg of oral BDP were reanalysed with this assay. The relative oral availability calculated by the AUC ratio method for these four patients of 0.33 ± 0.09 was within the range of that estimated based upon BOH levels (Table 2). This relative availability of 0.33 was used to estimate a F_{po} value of 0.21 which is comparable to the 0.26 estimated from BOH levels and supports the use of BOH as surrogate for 17-BMP in the present study.

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