Eur J Clin Pharmacol (2002) 58: 197–201
DOI 10.1007/s00228-002-0466-1

PHARMACOKINETICS AND DISPOSITION

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Pharmacokinetics of beclomethasone 17-monopropionate from a beclomethasone dipropionate extrafine aerosol in adults with asthma

Received: 23 October 2001 / Accepted in revised form: 18 March 2002 / Published online: 8 May 2002

Abstract *Objective*: The objectives of this study were to test the dose and strength proportionalities of beclomethasone dipropionate (BDP) delivered from two strengths of a pressurized extrafine solution formulation.
Methods: Thirty adults with mild, stable asthma, aged between 18 years and 70 years, completed the study; written informed consent was obtained from all patients. Each patient received, according to a randomized four-period crossover design, 100 μg BDP as two inhalations from 50-μg/actuation strength, 100 μg BDP as one inhalation from 100-μg/actuation strength, 400 μg BDP as eight inhalations from the 50-μg/actuation strength, and 400 μg BDP as four inhalations from the 100-μg/actuation strength. Patients self-administered all inhalations at the same time of day during the study. Blood samples were collected for 12 h during each period to assay for the presence of BDP and metabolites. The log-transformed pharmacokinetic data were compared for proportionality equivalence using a confidence-interval approach.
Results: Almost all the BDP-derived material in the plasma was the active metabolite beclomethasone 17-monopropionate (17-BMP). Due to low levels, neither elimination half-life ($t_{1/2}$) nor the area under the plasma concentration–time curve (AUC) for 17-BMP could be calculated for the 100-μg BDP doses. Dose proportionality of the 100-μg and 400-μg BDP doses, using 17-BMP maximum plasma concentration (C_{max}) was demonstrated for each strength. Strength proportionality of the 50-μg and 100-μg/actuation strengths was observed for C_{max} at both dose levels and for AUC at the higher dose level. The $t_{1/2}$ of 17-BMP was found to be approximately 2.8 h.
Conclusion: This study demonstrated both the strength and dose proportionalities of the BDP extrafine aerosol. This important information will allow physicians maximum flexibility in prescribing this aerosol product.

Keywords Beclomethasone dipropionate · Asthma · Adults

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Introduction

Several reports have been published on the combined pharmacokinetics of beclomethasone dipropionate (BDP) and metabolites from a BDP extrafine aerosol in adults with asthma [1, 2, 3, 4]. These studies used bioanalytical methods that could not differentiate between BDP and its three metabolites. Thus, these pharmacokinetic reports on the total fraction of BDP plus metabolites in the serum provided useful but not definitive information on the absorption of drug from the aerosol.

The present pharmacokinetic study was undertaken after the development and validation of assays which could simultaneously measure BDP, beclomethasone 17-monopropionate (17-BMP), beclomethasone 21-monopropionate (21-BMP), and beclomethasone (B) in human plasma. Interest focused primarily upon 17-BMP, which has greater receptor binding activity than that of BDP [5] and also is the main component present in the plasma [6, 7].

The pharmacokinetics of 17-BMP were used to answer several questions on the performance of the BDP extrafine aerosol. First, dose proportionality of the BDP extrafine aerosol within the therapeutic range needed to be confirmed. A previous report on dose proportionality only measured B [8], which is a minor metabolite in the plasma [6, 7]. Second, as the BDP extrafine aerosol is available in two strengths (50 μg/actuation and

100 μg/actuation), the ability of one strength to substitute for the other strength needed to be established. Third, useful pharmacokinetic parameters, such as peak concentration and elimination half-life, were desired for 17-BMP, the active moiety.

The most appropriate way to compare the dose and strength proportionalities of the BDP extrafine aerosol was with a four-way crossover design powered for a proportionality equivalence determination. Thus, 30 subjects were included in our study, and 90% confidence intervals, per U.S. Food and Drug Administration bioequivalence guidance, were used to assess the results.

Materials, methods, and patients studied

Materials

3M Pharmaceuticals (Northridge, Calif.) manufactured two strengths of an HFA–134a (chlorofluorocarbon-free) extrafine solution formulation of BDP (QVAR) in a conventional metered-dose inhaler. The two strengths delivered nominal doses of 50 μg BDP/actuation ex-valve or 100 μg BDP/actuation ex-valve. Inhalers were primed prior to use.

Study population

Thirty-two patients with stable mild asthma of at least 6-months duration, at least 18 years old, and otherwise healthy were enrolled in the study. Both sexes were allowed. Female patients were at least 2 years postmenopausal, surgically sterile, or, if of childbearing potential, using a barrier method or intrauterine device for birth control. Patients used only a short-acting inhaled beta-agonist to control asthma symptoms, had not used any steroid medication in the 6 months prior to screening, and had a forced expiratory volume in 1 s of at least 80% predicted normal after withholding beta-agonist treatment for a minimum of 6 h prior to each dose period. All patients demonstrated proper use of a placebo metered-dose inhaler. Most patients had never smoked; of the five patients who had a previous history of smoking, all had abstained from tobacco use for at least 6 months. All patients gave written informed consent in accordance with the Declaration of Helsinki. An independent medical ethics review committee approved the protocol.

Study design

This study was an open-label, randomized, single-dose, four-period crossover. Each patient received in separate periods 100 μg BDP as two inhalations from 50-μg/actuation strength, 100 μg BDP as one inhalation from 100-μg/actuation strength, 400 μg BDP as eight inhalations from 50-μg/actuation strength, and 400 μg BDP as four inhalations from 100-μg/actuation strength. Patients self-administered all inhalations at the same time of day under the supervision of a study coordinator. Patients used a 10-s breath hold and took each inhalation 30 s apart. Time zero for each dose was defined as the time when the inhaler was first actuated. Clinical status was monitored throughout the study.

Blood level monitoring

Blood samples (5 ml) were collected during each period to assay for the presence of BDP and metabolites at 0, 0.5, 1, 2, 4, 6, 9, and 12 h. The heparinized blood was centrifuged at 7°C, and the plasma was quickly frozen. Plasma samples were stored at –20°C until analysis.

BDP, 17-BMP, 21-BMP and B were extracted from the plasma using a liquid–liquid extraction procedure [1]. A sample was injected into a liquid chromatograph equipped with a triple-quadruple mass spectrometer. All four analytes were measured in a single analytical run. The linear ranges of the assay for a 1-ml plasma sample were 50–2000 pg/ml for BDP and 21-BMP, 75–2000 pg/ml for 17-BMP, and 10–2000 pg/ml for B. The precision and accuracy data for the validation inter- and intraday analyses (which included the respective lower and upper limits of quantification for each analyte) always showed less than a 12% coefficient of variation for all four analytes. Storage stability at –70°C and freeze/thaw stability were documented as part of the method validation.

Pharmacokinetic analysis

Standard pharmacokinetic calculation procedures and software were used as described previously [9]. Concentrations below the limit of quantification were treated as zero for the calculation of mean values. The primary analyte was 17-BMP, and the primary pharmacokinetic parameters were maximum plasma concentration (C_{max}) and area under the concentration–time curve (AUC). AUC_{0-t} was calculated from time zero until the last measurable plasma concentration and $AUC_{0-\infty}$ from time zero to infinity using the calculated elimination half-life ($t_{1/2}$) for each patient.

Analysis of variance methods, which included sequence, patient within sequence, period, and treatment as terms in the model, were used to compare the 17-BMP pharmacokinetic parameters. Ninety percent confidence intervals (CIs) were constructed for the log-transformed pharmacokinetic data. Proportionality equivalence for the dose-adjusted geometric means of a parameter was concluded if the 90% CI was completely contained within an interval of 0.80–1.25. The sample size estimate assumed an intra-patient coefficient of variation in the 17-BMP AUC of 20% and had at least 80% power to conclude equivalence with 28 patients.

Results

Patient population

Thirty patients completed the study. The mean (SD) age was 31.1 ± 12.6 years (range: 18.0–70.0 years) and the mean duration of asthma was 11.8 ± 9.8 years (range: 0.5–39 years). Twenty-two of the patients were female. All reported adverse events were mild to moderate, and no adverse event was deemed to be possibly or probably related to a study treatment. Two patients voluntarily withdrew from the study for reasons unrelated to the study treatments.

Pharmacokinetics

Almost all of the BDP-derived material in all the plasma samples was 17-BMP. BDP levels were low and transient following all doses in all patients. 21-BMP levels were low and transient in two or fewer patients in each treatment period; 21-BMP could not be quantified in any postdose sample in the remaining patients. Postdose B levels were always less than 70 pg/ml. Figure 1 presents the plasma profiles following both 400-μg doses; because of the many individual BDP, 21–BMP, and B concentrations below the level of quantification, median rather than mean values are presented. The median time

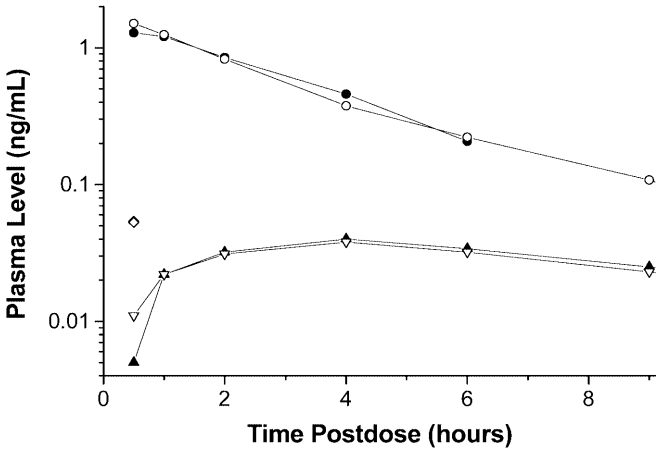

Fig. 1. Median beclomethasone dipropionate (BDP, *diamond*), beclomethasone 17-monopropionate (17-BMP, *circle*), and beclomethasone (B, *triangle*) plasma concentrations following administration of 400 μg extrafine BDP from the 50-μg/actuation strength (*closed symbol*) and 100-μg/actuation strength (*open symbol*) aerosols

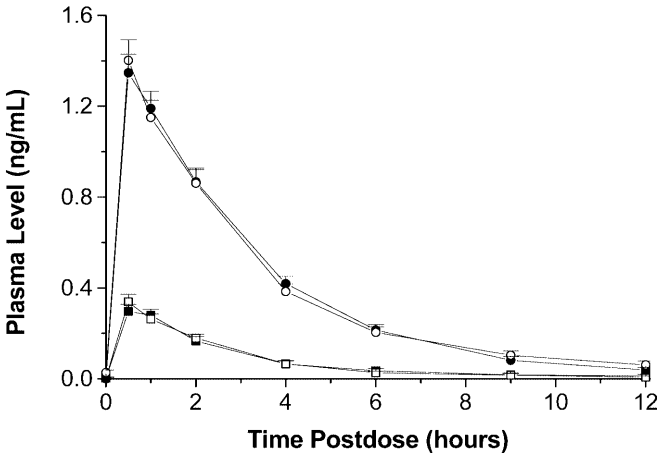

Fig. 2. Mean (SEM) beclomethasone 17-monopropionate (17-BMP) plasma levels following administration of 100 μg extrafine beclomethasone dipropionate (BDP, *square*) and 400 μg BDP (circle) from the 50-μg/actuation strength (*closed symbol*) and 100-μg/actuation strength (*open symbol*)

to C_{max} (t_{max}) of BDP and of 17-BMP was 0.5 h for all treatments; the median t_{max} of B was 6 h. The summary mean pharmacokinetic data for BDP and B are presented in Table 1.

The profiles of plasma concentrations of the primary analyte, 17-BMP, were essentially the same from the two strengths for each dose (Fig. 2). Mean 17-BMP levels peaked at about 30 min and declined readily thereafter following each dose. AUC values and $t_{1/2}$ could not be calculated for the 100-μg doses, since the majority of the patients did not have measurable concentrations of 17-BMP after 2 h. Pharmacokinetic data for 17-BMP are summarized in Table 2.

Dose proportionality using 17-BMP could only be tested with C_{max} since AUC values could not be calculated for the lower strength. Dose proportionality of C_{max} was obtained for each strength of BDP extrafine aerosol for the two doses studied (Table 3). The calculated 90% CIs were contained within the target range for both strengths.

Strength proportionality could be compared using C_{max} at both doses and using AUC_{0-t} and $AUC_{0-\infty}$ values following the 400-μg BDP dose. The criteria for strength proportionality were met for all comparisons (Table 4).

Discussion and conclusions

The objectives of this study were to demonstrate both the strength and dose proportionalities of the extrafine BDP aerosol. In fulfilling these objectives, important information on the pharmacokinetics of 17-BMP from the aerosol was generated. The assumption of linear pharmacokinetics with BDP has been widely assumed with little evidence to support this assumption. The present study implies dose proportionality of 17-BMP C_{max} for the extrafine aerosol within the therapeutic range. The findings that 17-BMP is the main component in the plasma at 30 min and thereafter and that 17-BMP is eliminated from the plasma with a $t_{1/2}$ of under 3 h is consistent with previous findings [6, 7].

It is interesting to note that the disappearance of 17-BMP from the plasma was not associated with a corresponding increase in B levels. It is known that BDP is rapidly metabolized in human lung, liver, and plasma in vitro to 17-BMP and that once formed, 17-BMP is further metabolized to B [10, 11]. The human in vivo situation is similar to that of the in vitro in that both a rapid conversion of BDP to 17-BMP and an elimination $t_{1/2}$ of 17-BMP of under 3 h are seen. The fact that only low levels of B are observed in the plasma raises the

Table 1. Summary of mean (SD) pharmacokinetic parameters for beclomethasone dipropionate (BDP) and beclomethasone (B). C_{max} maximum plasma concentration, t_{max} time to C_{max}, *AUC* area under the plasma concentration–time curve

Dose (μg)	Strength (μg/puff)	C_{max} BDP (ng/ml)	C_{max} B (ng/ml)	t_{max} BDP (h)	t_{max} B (h)	AUC_{0-t} B[a] (ng·h/ml)
100	50	[b]	0.020 ± 0.027	[b]	4 ± 1.5	0.077 ± 0.112
100	100	[b]	0.014 ± 0.003	[b]	5 ± 1.3	0.056 ± 0.050
400	50	0.076 ± 0.023	0.040 ± 0.010	0.6 ± 0.4	5 ± 1.7	0.311 ± 0.106
400	100	0.088 ± 0.032	0.042 ± 0.011	0.5 ± 0.02	4 ± 1.9	0.322 ± 0.098

[a] AUC_{0-t} BDP could not be calculated
[b] Could not be calculated

Table 2. Summary of beclomethasone 17-monopropionate (17-BMP) mean (SD) pharmacokinetic parameters. C_{max} maximum plasma concentration, t_{max} time to C_{max}, AUC area under the plasma concentration–time curve, $t_{1/2}$ elimination half-life

Dose (μg)	Strength (μg/puff)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)	AUC_{0-t} (ng·h/ml)	$AUC_{0-\infty fty}$ (ng·h/ml)
100	50	0.370 ± 0.138	0.9 ± 0.7	[a]	[a]	[a]
100	100	0.364 ± 0.167	0.9 ± 0.7	[a]	[a]	[a]
400	50	1.432 ± 0.401	0.7 ± 0.4	2.7 ± 0.79	4.336 ± 1.518	5.183 ± 1.299
400	100	1.419 ± 0.476	0.7 ± 0.3	2.8 ± 0.59	4.348 ± 1.596	4.985 ± 1.334

[a]Could not be calculated

Table 3. Dose proportionality of 100 μg and 400 μg extrafine beclomethasone dipropionate (BDP) as measured by beclomethasone 17-monopropionate (17-BMP) maximum plasma concentration (C_{max}). *CI* confidence interval

Calculation	C_{max} comparison	
	50 μg/puff	100 μg/puff
Geometric mean of 400 μg BDP divided by 4 (ng/ml)	0.341	0.323
Geometric mean of 100 μg BDP (ng/ml)	0.348	0.330
Ratio of geometric means	0.98	0.98
Standard error of $\log_{10}$ (ratio)	0.0400	0.0400
90% CI for ratio	0.84, 1.14	0.84, 1.14

Table 4. Summary of beclomethasone 17-monopropionate (17-BMP) strength proportionality equivalence analysis. *CI* confidence interval, *BDP* beclomethasone dipropionate. C_{max} maximum plasma concentration, *AUC* area under the plasma concentration–time curve

Comparison 100 μg/puff vs 50 μg/puff	90% CI for ratio	
	100 μg BDP	400 μg BDP
C_{max}	0.82, 1.11	0.81, 1.11
AUC_{0-t}	–	0.81, 1.22
$AUC_{0-\infty}$	–	0.82, 1.13

possibility that in vivo either 17-BMP is not eliminated primarily via metabolism to B or that B is very rapidly cleared from the plasma.

This study helps to resolve some uncertainties generated by previous BDP pharmacokinetic studies that utilized an assay that could not differentiate BDP from metabolites. In those studies, BDP and metabolites were hydrolyzed to B and then measured as a total B fraction. It has been alleged that this methodology is unreliable [6]. However, examination of Table 1 and Table 2 shows that if blood sampling began at 30 min or later following aerosol administration, greater than 90% of the material in the plasma through 12 h was 17-BMP. The lowest AUC_{0-t} ratio of 17-BMP to total components in plasma in this study was 0.91 ± 0.06, observed for the 400-μg BDP dose (100 μg/actuation). This same finding, that most of the material in the plasma is 17-BMP, has been reported following oral administration [6]. Thus the total B assay is essentially measuring a single component and is a good surrogate assay for 17-BMP. It follows that the total B assay was a good surrogate measure for 17-BMP in the published inhalation studies in question [1, 2, 3, 4], since blood sampling in these studies began at 30 min or later, and all involved comparisons with only aerosol and oral products. It is understood that a comparison of an aerosol with an intravenous reference would not be possible with a total B assay.

We recognize that there are still some limitations with the current 17-BMP assay. This assay was not sufficiently sensitive to measure 17-BMP plasma concentrations in most individuals after 2 h following the 100-μg dose. As a result AUC values for this dose could not be calculated, and dose proportionality comparisons had to be based upon only C_{max}. We also recognize that the blood sampling schedule was not optimized for C_{max}; however, in most individuals C_{max} occurred within a relatively narrow window of 30 min (either at 0.5 h or 1 h).

In conclusion, this study demonstrated both the strength and dose proportionalities of the extrafine BDP aerosol. This important information will allow physicians maximum flexibility in prescribing this aerosol product.

Acknowledgements This study was funded by 3M Pharmaceuticals, St. Paul, MN, USA. The authors thank members of the research staff of 3M Pharmaceuticals and Clinical Research Institute, Minneapolis, MN, USA, for additional technical assistance. The study described in this article complies fully with the current laws regarding experiments involving humans in the USA.

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