Pharmacokinetic Profile of Beclomethasone Dipropionate Hydrofluoroalkane After Intranasal Administration Versus Oral Inhalation in Healthy Subjects: Results of a Single-Dose, Randomized, Open-Label, 3-Period Crossover Study

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ABSTRACT

Background: Beclomethasone dipropionate (BDP) is an anti-inflammatory corticosteroid that is rapidly metabolized to the pharmacologically active monoester, beclomethasone-17-monopropionate (17-BMP). Recently, a hydrofluoroalkane (HFA)–propelled nasal aerosol formulation of BDP was developed to treat allergic rhinitis. However, the pharmacokinetic profile of BDP HFA nasal aerosol has not been previously investigated.

Objective: This study evaluated and compared the systemic levels of 17-BMP and BDP after a single dose of intranasally administered or orally inhaled BDP HFA in healthy subjects.

Methods: In this single-center, randomized, open-label, 3-period crossover study, healthy subjects received single doses of intranasal BDP HFA (80 and 320 μg) and orally inhaled BDP HFA (320 μg). The primary pharmacokinetic parameters assessed were area under the concentration-time curve until the last measurable value (AUC_{last}) and C_{max} for 17-BMP. For AUC_{last} and C_{max}, point estimates for treatment differences and CIs were calculated on the log scale and then exponentiated to provide estimates of the geometric mean ratios (GMRs) and associated CIs.

Results: Thirty subjects were randomized to receive study medication (aged 18–45 years, 66.7% male). Mean plasma concentrations of 17-BMP after intranasal administration of BDP HFA (for both 80- and 320-μg doses) were substantially lower than that of orally inhaled BDP HFA (320 μg) across all time points. Mean AUC_{last} values of 17-BMP for intranasal 80 μg, intranasal 320 μg, and orally inhaled 320 μg were 295.8, 1139.7, and 4140.3 pg·hr/mL, respectively. Mean C_{max} values were 92.1, 262.7, and 1343.7 pg/mL, respectively. The GMR of AUC_{last} for 17-BMP with intranasal BDP HFA 320 μg versus orally inhaled BDP HFA 320 μg was 0.275, indicating substantially lower systemic bioavailability with intranasal administration than with oral inhalation. Similarly, the GMR of AUC_{last} for 17-BMP with intranasal BDP HFA 80 μg versus 320 μg was 0.260, suggesting approximate dose proportionality (4-fold difference). Pharmacokinetic results for BDP were similar to those seen for 17-BMP. All doses of intranasal and orally inhaled BDP HFA were well tolerated, and no treatment-related adverse events were reported.

Conclusions: The results of this study suggest that 80 and 320 μg BDP HFA nasal aerosols have substantially lower systemic bioavailability than 320 μg orally inhaled BDP HFA in healthy subjects. All treatments were well tolerated. ClinicalTrials.gov identifier: NCT01537692. (*Clin Ther*. 2012;34:1422–1431)

Key words: 17-BMP, allergic rhinitis, BDP, beclomethasone dipropionate, intranasal, nasal aerosol, pharmacokinetics, systemic bioavailability.

INTRODUCTION

Allergic rhinitis (AR) is a chronic inflammatory disease characterized by sneezing, nasal itch, rhinorrhea, nasal obstruction, and frequent allergic conjunctivitis.[1] AR is estimated to affect ~60 million people in the United States, and its prevalence has increased during the past 3 decades, with recent estimates of 10% to 30% in

Accepted for publication April 24, 2012.
http://dx.doi.org/10.1016/j.clinthera.2012.04.023
0149-2918/$ - see front matter

adults and 40% in children.[2] An estimated 20% of AR cases are seasonal, 40% are perennial, and 40% are perennial with seasonal exacerbations.[3]

Allergen avoidance as well as pharmacologic treatment with antihistamines, decongestants, corticosteroids, combination therapy, and immunotherapy have been used to treat AR.[2,4] Multiple factors, including the type of rhinitis present (eg, allergic, nonallergic, mixed, or episodic), most prominent symptoms, severity, and patient age determine the most appropriate treatment option.[2,4] Among the available treatments, intranasal corticosteroids are considered the standard of care for the maintenance therapy of AR[4] because of their superior efficacy to oral antihistamines for relief of nasal blockage, nasal discharge, nasal itch, postnasal drip, and total nasal symptoms.[5]

Although intranasal corticosteroids, recommended as first-line therapy for AR,[4] provide greater nasal symptom relief than other available pharmacologic agents (eg, antihistamines or leukotriene inhibitors),[5] they are currently available only as aqueous formulations. However, undesirable side effects can be troublesome with aqueous nasal sprays.[6] Two national surveys of patients with AR, the Allergies in America and the Nasal Allergy Survey Assessing Limitations, highlight the bothersome side effects of currently available AR medications.[7,8] Therefore, a need is unmet for the development of a nonaqueous intranasal corticosteroid formulation for the treatment of AR.

Beclomethasone dipropionate (BDP) is an anti-inflammatory corticosteroid available for the treatment of asthma and AR. BDP was previously developed as aqueous nasal formulations (Beconase AQ,[9] Vancenase AQ) for the treatment of AR. BDP was also available in dry nasal aerosol formulations as chlorofluoro carbon (CFC) metered-dose inhaler nasal sprays (Beconase and Vancenase Pockethaler), but CFC-containing formulations have been withdrawn from the market and currently are not available.[10] BDP hydrofluoroalkane (HFA) inhalation aerosol (QVAR) currently is available for patient use and indicated for the maintenance treatment of asthma as prophylactic therapy in patients 5 years of age and older.[11] BDP HFA nasal aerosol (QNASL), an intranasal aerosol formulation, has been developed recently for the treatment of AR.[12]

Several studies have evaluated the pharmacokinetics of various formulations of BDP administered via oral, intranasal, or inhaled routes.[13,14] However, the pharmacokinetics of BDP HFA nasal aerosol have not been previously investigated. The purpose of the present study was to evaluate and compare the pharmacokinetic profiles of BDP HFA after single-dose intranasal administration with oral inhalation in healthy subjects.

PATIENTS AND METHODS

Study Design

This was a single-center, single-dose, randomized, open-label, 3-period crossover study in healthy subjects (**Figure 1**). The study consisted of a screening period (up to 14 days) followed by 3 single-dose treatment periods. Between each treatment period, there was a 7- to 14-day washout period. Subjects were randomly assigned to receive a single dose of BDP HFA nasal aerosol 80 μg (treatment A), BDP HFA nasal aerosol 320 μg (treatment B), or BDP HFA oral inhalation aerosol 320 μg (treatment C) in 1 of 6 treatment sequences (ABC, BCA, CAB, ACB, BAC, or CBA). The crossover design was composed of 2 Latin squares and was balanced for period and carryover effects. The study was conducted according to Good Clinical Practices and in accordance with the principles of the Declaration of Helsinki and was approved by the Sterling Institutional Review Board (Atlanta, Georgia). Written informed consent was obtained from each subject before study participation.

Subjects

Healthy male or female nonsmoking subjects, 18 to 45 years of age (inclusive) with a normal weight (body mass index [calculated as weight in kg divided by height in m^2] $\geq$18 to $\leq$30, and weight $\geq$50 kg) and assessed as healthy according to screening assessments, were eligible for enrollment. Subjects with a contraindication to corticosteroids, history of relevant nasal disorder, acute or chronic infections, history of respiratory infection within 28 days before screening, or other relevant allergic or medical condition were excluded. Subjects were also prohibited to receive treatment with any known inducer/inhibitor of cytochrome P450 3A4, with participation in any investigational drug study within 30 days, or with use of any other concomitant medication within 14 days before study medication administration (or $<$10 times the elimination half-life of the respective drug). Exposure to any systemic or orally inhaled corticosteroid for 60 days or