Original Article

Determination of the Bioavailability of 3 Intranasal Formulations of Azelastine Hydrochloride in Healthy Male Volunteers

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Abstract

The primary objective of the study was to determine the bioavailability of 2 new formulations of azelastine (AZE) hydrochloride (0.10% and 0.15% AZE) containing sorbitol and sucralose compared with the commercially available 0.10% AZE. This study was performed in healthy volunteers based on the pharmacokinetic parameters maximum plasma concentration and area under the plasma concentration–time curve from time zero to the last measurable concentration. This was a Phase 1, open-label, single-center, randomized, parallel-group study. Subjects were randomized to 1 of 3 treatment groups: (1) 0.10% AZE (treatment A), (2) 0.15% AZE (treatment B) (Groups 1 and 2 both containing sorbitol and sucralose), and (3) the commercially available 0.10% AZE (treatment C). A total of 54 subjects were randomized and received treatment A, B, or C. Maximum plasma concentration and area under the plasma concentration–time curve were similar when compared in treatments A and C (0.1%) for AZE and its metabolite, desmethylazelastine. The most frequently reported adverse events were rhinorrhea (5.6%) and sneezing (5.6%).

Keywords

allergic rhinitis, azelastine hydrochloride, desmethylazelastine, pharmacokinetics

Allergic rhinitis (AR) is a symptomatic disease that is linked to an inflammation of the nasal mucosa caused by the interaction of immunoglobulin E and allergen following allergen exposure.[1] According to the most recent atllergic rhinitis and its impact on Asthma guidelines, the choice of medication for patients with AR should take into consideration their age, preferences, degree of symptoms, effectiveness of treatment,

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speed at which effects manifest, and past responsiveness to treatment.[2] For the majority of patients, current monotherapies like intranasal corticosteroids, oral and intranasal decongestants, oral and intranasal anticholinergics, and oral and intranasal antihistamines are unable to control their AR. Patients are reluctant to use intranasal corticosteroids because they are worried about the possible systemic effects of steroids. Steroid phobia is not lessened by increasing the patient's understanding of corticosteroids.[3]

Azelastine (AZE) is an intranasal antihistamine used in the treatment of AR. One of the common side effects of AZE is a bitter taste, which many patients find aversive. To address this issue, AZE has been reformulated to include sucralose and sorbitol in 2 new formulations (0.10% and 0.15% AZE)[4]: 0.15% AZE (MP03-36) is a higher-dose formulation of AZE that exhibits greater efficacy for better symptom relief in patients with seasonal and perennial AR while having comparable safety and tolerability to 0.10% AZE (MP03-33).[5–8] The daily applied dose for 0.15% AZE is 822 μg when administered as 2 sprays per nostril once daily and 1644 μg when administered as 2 sprays per nostril twice daily.

AZE is rapidly absorbed following intranasal administration, reaching maximum plasma concentrations (C_{max}) in 2-3 hours.[9–13] AZE is metabolized primarily through oxidative pathways mediated by cytochrome P450 (CYP) enzymes (CYP3A4 and CYP2D6). The primary active metabolite of AZE is desmethylazelastine.[9,10] The elimination half-lives of AZE and desmethylazelastine are 22 and 54 hours, respectively.[9,11] About 88% of AZE binds to plasma proteins, while approximately 97% of desmethylazelastine binds to plasma proteins.[12,14] AZE is predominantly excreted via feces, with less than 10% excreted unchanged in urine.

Desmethylazelastine has a similar pharmacologic activity to its parent drug AZE such as anti-inflammatory properties, including the inhibition of leukotriene and cytokine release, which are crucial in managing AR and other allergic responses.[9,11,15] Both AZE and desmethylazelastine exhibit potent H1-receptor antagonist activity, contributing to their efficacy in treating allergic conditions. Desmethylazelastine has a longer elimination half-life compared to AZE (54 hours vs. 22 hours), which may contribute to its sustained antihistaminic effects.[9]

Desmethylazelastine uncompetitively inhibited CYP2B6 activity with an inhibition constant of 32.6 ± 4.8 μM.[16] AZE and desmethylazelastine competitively inhibited CYP2C9, CYP2C19, and CYP2D6 enzyme activities.[16] AZE and desmethylazelastine also competitively inhibited CYP3A4 activity. These compounds can potentially interact with other drugs metabolized via CYP2D6. However, the inhibition of CYP2C9, CYP2C19, and CYP3A4 by these compounds might not be clinically significant.[16] Drug–drug interaction studies have shown that AZE does not significantly interact with azole antifungals, macrolide antibiotics, H_2 receptor antagonists, or theophylline.[9,11]

The primary objective of the study was to determine the bioavailability of 2 new formulations of AZE hydrochloride (0.10% and 0.15% AZE) containing sorbitol and sucralose compared with the commercially available 0.10% AZE. The study was carried out in healthy volunteers based on the pharmacokinetic (PK) parameters C_{max} and area under the plasma concentration–time curve (AUC) from time zero to the last measurable concentration. The secondary end points were time to maximum drug concentration, half-life, AUC from time zero extrapolated to infinity, and safety.

Methodology

Study Design

This was a Phase 1, open-label, single-center (CEDRA Clinical Research, LLC, Austin, TX), randomized, parallel-group study (study period: August 2006 to September 2006). Subjects were randomized to 1 of 3 treatment groups: (1) 0.10% AZE (MP03-33, treatment A), (2) 0.15% AZE (MP03-36, treatment B) (Groups 1 and 2 both containing sorbitol and sucralose), and (3) the commercially available 0.10% AZE (treatment C) (Figure S1). All treatments were administered with 2 sprays per nostril as a single treatment. Subjects in each group received a single dose of treatment A, B, or C. Subjects had multiple PK samples drawn in-house, up to 48 hours after dosing, and then every 24 hours as outpatients at 72, 96, and 120 hours after dosing. Subjects were admitted to the clinical testing unit on the day before dosing until 48 hours after study drug administration. Subjects refrained from food intake, starting 4 hours before dosing and ending 4 hours after dosing. Thereafter, standard meals were consumed. All meals were standardized at the clinical testing facility. After dosing, the subject was required to consume 400 mL of water over 3 hours, beginning 1 hour after dosing.

Study Population

Healthy male nonsmokers were included in the study with the following criteria: (1) aged 18-50 years; (2) normal weight as defined by the Metropolitan Life Height/Weight table (±15% of the desirable body weight); and (3) negative for the presence of antibodies to hepatitis B, hepatitis C, and HIV. Exclusion criteria were (1) history of clinically relevant metabolic disorder; (2) history or suspicion of alcohol, barbiturate, amphetamine, or narcotic abuse; (3) history of cardiac arrhythmias, bronchospastic or cardiovascular disease,

diabetes mellitus, thyrotoxicosis, and drug allergy; (4) presenting with active AR at baseline; (5) history of allergic or idiosyncratic responses to AZE or related substances or excipients; and (6) inability to communicate, give written informed consent properly, or comply with study requirements.

Ethics

The study, study protocol, proposed informed consent form, and other information given to the subjects were approved by a properly constituted Institutional Review Board (IRB). The IRB for the study was IntegReview (Austin, TX). This study was conducted in compliance with the study protocol and in accordance with Good Clinical Practice, as described in (1) the International Committee on Harmonization Harmonized Tripartite Guidelines for Good Clinical Practice 1996; (2) the US Code of Federal Regulations dealing with clinical studies (21 US Code of Federal Regulations including parts 50 and 56 concerning informed consent and IRB regulations), and (3) the Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki, 1964; amended Tokyo 1975; Venice, 1983; Hong Kong, 1989; South Africa, 1996; Edinburgh, 2000; and Washington, DC, 2002).

Analytical Methods

Samples were analyzed for AZE hydrochloride and its metabolite, desmethylazelastine, at 0, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours after treatment. Ethylenediaminetetraacetic acid human plasma was analyzed for AZE and desmethylazelastine according to the CEDRA procedure ATM-998 (CEDRA Clinical Research, LLC; validation, effective January 31, 2006).[17] The method was validated for a range of 2.00-1000 pg/mL for both analytes based on the analysis of 0.500 mL of plasma. Human plasma containing AZE, desmethylazelastine, and the internal standards AZE-D3 and chlorodesmethylazelastine was extracted with an organic solvent mixture after the addition of sodium carbonate solution (liquid–liquid extraction). After extraction, the supernatant was evaporated, reconstituted in the mobile phase, and injected into a SCIEX API 5000 liquid chromatography–tandem mass spectrometry equipped with a high-performance liquid chromatography column (PVA-Sil, 5 micron, 4.0 × 50 mm cartridge; Waters Inc). The mobile phase for the high-performance liquid chromatography was acetonitrile, ethyl acetate, water, methanol, formic acid, and morpholine in the ratio 500:200:100:60:0.200:0.025. The peak area of the m/z 382→112 AZE product ion was measured against the peak area of the m/z 385→115 AZE-D3 internal standard product ion. The peak area of the m/z 368→98 desmethylazelastine product ion was measured against the peak area of the m/z 402→98 chlorodesmethylazelastine internal standard product ion.

Analysis Population. Fifty-four healthy male subjects were randomly allocated to 3 treatment groups of 18 subjects each participating in the study. The sample size was determined by assessing the size needed to provide at least 80% power at the 5% significance level for a comparison of AUC between the approved commercial formulation and 0.10% investigational formulation.

Analysis of PK Parameters. Summary statistics of all PK parameters were reported using appropriate statistical measures of central tendency (e.g., mean and median), and dispersion (e.g., variance, standard deviation, standard error, and minimum and maximum). Statistical analyses of the PK parameters were performed with SAS (SAS Institute). Statistical analysis of the PK parameters, both primary and secondary, were presented between treatments on selected PK variables. For those requiring log transformation, a mixed-effects linear model based on a power function was used. For PK variables not requiring log transformation, the mixed-effects linear model was based on a one-way analysis of variance model.

Results

Patient Disposition

A total of 54 subjects were randomized and received treatment A, B, or C. Eighteen subjects were assigned to each treatment group. Most subjects were white individuals (n = 36) followed by African American individuals (n = 11). The detailed demographics are presented in Table S1.

Pharmacokinetic Parameters

The mean AZE plasma concentration in the subjects after dosing is shown in Figure 1. The PK parameters for the 3 treatments are listed in Table 1. Mean PK profiles for all 3 formulations of AZE and its metabolite are presented in Figures 1 and 2. C_{max} and AUC are similar when compared in treatments A and C (0.10%) for AZE and its metabolite, desmethylazelastine.

Safety

A total of 18 adverse events (AEs) were reported from 54 subjects treated with the study drug. Seven of the AEs were judged to be study-drug related. The most frequently reported AEs were rhinorrhea (5.6%) and sneezing (5.6%). None of the subjects discontinued due to AEs. There were no serious AEs and no deaths. Only 1 subject reported dysgeusia. There were no

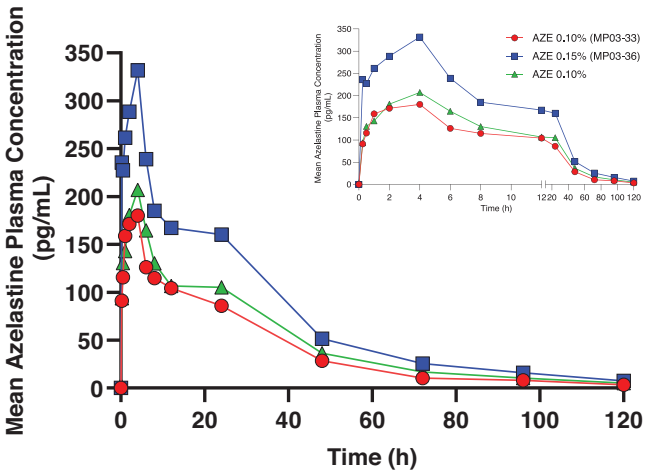

Figure 1. Mean azelastine plasma concentration with time. AZE, azelastine.

Table 1. Mean PK Parameters of AZE for Treatments A, B, and C

Parameter	0.10% AZE (MP03-33) (treatment A), mean (SD)	0.15% AZE (MP03-36) (treatment B), mean (SD)	0.10% AZE (treatment C), mean (SD)
$t_{\frac{1}{2}}$ (hour)	22 (7.5)	25 (8.7)	24 (6.0)
t_{max} (hour)	2.7 (1.4)	3.1 (2.0)	3.2 (1.8)
C_{max} (pg/mL)	200 (67)	409 (160)	235 (88)
$AUC_{0\text{-}t}$ (pg•h/mL)	4917 (1394)	8941 (3749)	5903 (2264)
$AUC_{0\text{-}\infty}$ (pg•h/mL)	5122 (1546)	9312 (3950)	6122 (2373)
CL/F (mL/min/kg)	26 (9.5)	26 (15)	25 (18)
C_{max}/D (pg/mL/µg/kg)	27 (7.9)	35 (14)	32 (12)
$AUC_{0\text{-}\infty}$/D (pg•h/mL/µg/kg)	704 (207)	804 (375)	839 (329)

$AUC_{0\text{-}t}$, area under the plasma concentration–time curve from time zero to the last measurable concentration; $AUC_{0\text{-}\infty}$, area under the plasma concentration–time curve from time zero extrapolated to infinity; AZE, azelastine; CL/F, apparent clearance; C_{max}, maximum plasma concentration; C_{max}/D, dose-normalized maximum plasma concentration; PK, pharmacokinetic; $t_{1/2}$, half-life; SD, standard deviation; t_{max}, time to maximum drug concentration.

concomitant medications taken due to AEs. There were no clinically significant laboratory findings for hematology, chemistry, and urinary test variables. In most cases, the changes in mean values for the majority of the laboratory variables were within the reference range. Vital sign findings did not show any clinically significant changes.

Discussion

Comparison of the PK parameters (Figures 1 and 2) indicated that for both AZE and its metabolite, desmethylazelastine, the 548-µg (0.10% AZE) investigational formulation performed comparably to the 548-µg (0.10%) commercially approved formulation. This signifies that the new formulation with sucralose and sorbitol does not impact PK. Differences in the systemic exposure of both analytes with the 822-µg (0.15% AZE) formulation when compared to 0.10% AZE and the 0.10% commercial formulation can be explained by the higher dose. This is clearly demonstrated by the dose-normalized exposure parameters (C_{max}/D and dose-normalized AUC from time zero extrapolated to infinity) presented in Tables 1 and 2. In addition, the calculated terminal half-lives are consistent among the 3 formulations (Table 1).

A single oral dose of AZE (4 mg) has a half-life of 25 hours.[18] After a single oral dose of 4 mg, C_{max} of 3 µg/L occurs within 4-5 hours. With multiple doses of 4 mg twice daily, a mean C_{max} of 10 µg/L is achieved in 2.3 hours.[18] The C_{max} of 0.15% AZE was 38 pg/mL, which was well below the plasma concentration levels for oral AZE. Changes in plasma drug concentration reflect changes in drug concentrations at the receptor site, where the drug exerts its therapeutic effect.[19] As the plasma concentration increases, so does the concentration at the target site, leading to an increased effect. The mean plasma concentration of 0.15% AZE is higher than the 0.10% AZE, which may explain its improved efficacy. The half-lives for the present intranasal formulation of 0.10% AZE and 0.15% AZE was 22 and

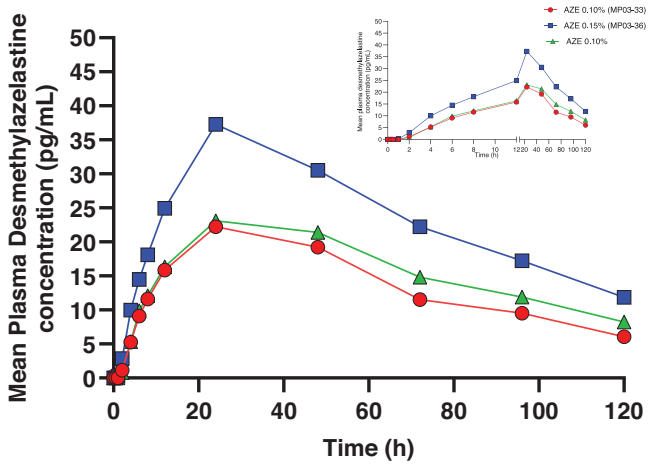

Figure 2. Mean desmethylazelastine plasma concentration with time. AZE, azelastine.

Table 2. Mean PK Parameters of Desmethylazelastine for Treatments A, B, and C

Parameter	0.10% AZE (MP03-33) (treatment A), mean (SD)	0.15% AZE (MP03-36) (treatment B), mean (SD)	0.10% AZE (treatment C), mean (SD)
$t_{\frac{1}{2}}$ (hour)	52 (21)	57 (23)	60 (22)
t_{max} (hour)	34 (19)	29 (10)	35 (15)
C_{max} (pg/mL)	23 (11)	38 (15)	24 (7.8)
$AUC_{0\text{-}t}$ (pg•h/mL)	1634 (603)	2780 (857)	1873 (553)
$AUC_{0\text{-}\infty}$/D (pg•h/mL)	2131 (609)	3824 (1184)	2615 (779)
CL/F (mL/min/kg)	61 (16)	57 (23)	53 (24)
C_{max}/D (pg/mL/µg/kg)	3.1 (1.3)	3.3 (1.3)	3.3 (1.1)
$AUC_{0\text{-}\infty}$/D (pg•h/mL/µg/kg)	292 (72)	328 (108)	357 (108)

$AUC_{0\text{-}t}$, area under the plasma concentration–time curve from time zero to the last measurable concentration; $AUC_{0\text{-}\infty}$, area under the plasma concentration–time curve from time zero extrapolated to infinity; AZE, azelastine; CL/F, apparent clearance; C_{max}, maximum plasma concentration; C_{max}/D, dose-normalized maximum plasma concentration; PK, pharmacokinetic; $t_{1/2}$, half-life; SD, standard deviation; t_{max}, time to maximum drug concentration.

25 hours, respectively. Despite the higher concentration of 0.15% AZE, the half-life of the metabolite desmethylazelastine was similar (57 hours) compared to the commercially available 0.10% AZE (60 hours).

The safety information did not show any unexpected AEs or abnormal laboratory findings in this group of subjects. There were no deaths, no serious AEs, and no events leading to discontinuation. Only 1 subject reported dysgeusia. A 1-year safety study in 862 subjects comparing the safety profile of 0.10% AZE (with taste masking) and original 0.10% AZE (without taste masking) reported that approximately 7% of patients receiving either the new or original formulation of AZE nasal spray experienced a bitter taste.[17] Lower reports of dysgeusia in the present study may be attributed to the small sample size and shorter duration.

Conclusion

The PK parameters were similar when compared between 0.10% AZE (MP03-33) and the commercially available 0.10% AZE for AZE and its metabolite, desmethylazelastine. In comparison to 0.15% AZE (MP03-36) and the commercially available 0.10% AZE, the data indicated that C_{max} and AUC were dose proportional for 0.10% AZE (MP03-33). Both formulations (0.15% AZE and 0.10% AZE) were safe and well tolerated by the subjects.

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Conflicts of Interest

M.L., D.T.N., and R.K.R. are employees of Viatris. All other authors have no declaration for this manuscript.

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Data Availability Statement

Raw data were generated at Viatris. Derived data supporting the findings of this study are available from the corresponding author (J.B.) on request.

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