The Pharmacokinetics of the CYP3A Substrate Midazolam After Steady-state Dosing of Delafloxacin

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ABSTRACT

Purpose: Delafloxacin is a novel anionic fluoroquinolone in Phase III development for the treatment of serious skin infections. The objective of this study was to evaluate the effects of delafloxacin on the pharmacokinetics of midazolam, a cytochrome P450 (CYP) 3A substrate.

Methods: CYP3A activity using midazolam as a probe was assessed before and after multiple doses of delafloxacin to reach steady state. In this nonrandomized, open-label, single-sequence, Phase I study, 22 healthy male and female subjects were administered a single 5-mg oral dose of midazolam on days 1 and 8, with oral delafloxacin 450 mg every 12 hours administered from days 3 to 8. Full pharmacokinetic profiles were obtained on days 1 and 8 (midazolam and 1-hydroxymidazolam) and days 3 and 7 (delafloxacin).

Findings: The geometric mean ratios (90% CIs) for $AUC_{0-\infty}$ and C_{max} of midazolam coadministered with delafloxacin versus midazolam alone were 89.4 (83.2–96.0) and 93.6 (83.7–104.6). Similarly, the geometric ratio for the $AUC_{0-\infty}$ of 1-hydroxymidazolam, the primary metabolite of midazolam, was 105.7 (97.7–114.3); the ratio of C_{max} was not equivalent at 116.1 (101.7–132.4), which was outside the CI of 80% to 125%. Multiple doses of oral delafloxacin for 6 days were generally well tolerated.

Implications: Steady-state dosing of delafloxacin produced no significant changes in midazolam pharmacokinetics, except for a small but not clinically relevant change in the C_{max} of 1-hydroxymidazolam. ClinicalTrials.gov identifier: NCT02505997. (*Clin Ther*. 2017;39:1182–1190) © 2017 The Authors. Published by Elsevier HS Journals, Inc.

Key words: CYP3A, delafloxacin, fluoroquinolones, midazolam, pharmacokinetics.

INTRODUCTION

Awareness of potential drug–drug interactions is important in drug development, notably with antibiotics because they are often concomitantly administered with other drugs such as pressors, other antibiotics for empiric therapy, and, in the case of fluoroquinolones, antacids and other multivalent cation-containing drugs.[1] These interactions may increase or decrease the action of either drug and change the rate and extent of absorption and plasma protein binding displacement; microbiologically, they may alter the ability of cell membranes or receptor sites to bind to either drug. Drug–drug interactions can be either pharmacokinetic or pharmacodynamic in nature, which could lead to a change in efficacy and/or toxicity.

Fluoroquinolones are widely used in both inpatient and outpatient settings; thus, clinicians ought to be aware of any drug–drug interactions. Apart from the aforementioned antacids, which reduce the oral absorption of many fluoroquinolones, other interactions have been described in the literature for fluoroquinolones with xanthines, including theophylline and caffeine, warfarin, probenecid, phenytoin, and digoxin.[2–4] Delafloxacin, a novel anionic fluoroquinolone for the treatment of gram-positive and gram-negative infections (including atypicals and anaerobes), is undergoing clinical development for acute bacterial skin and skin

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structure infections and community-acquired bacterial pneumonia.[5–7]

The US Food and Drug Administration's Draft Guidance on Drug Interaction Studies[8] recommends that pharmacokinetic interactions be defined during drug development as part of the drug's safety and effectiveness. Delafloxacin has been studied in in vitro metabolic studies and is not an inhibitor of cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5, nor is it an inducer of CYP1A2 or CYP2B6. However, delafloxacin is a mild in vitro inducer of CYP3A in cultures of human hepatocytes (data on file, Melinta Therapeutics, Lincolnshire, IL). Midazolam, a benzodiazepine sedative-hypnotic agent, is metabolized by CYP3A and has been adopted as a metabolic probe of CYP3A in humans.[9,10] We therefore studied the in vivo impact of delafloxacin on midazolam pharmacokinetics in healthy subjects to assess any potential for clinical drug–drug interactions. This study also study evaluated the pharmacokinetics of multiple doses of oral delafloxacin.

SUBJECTS AND METHODS

This Phase I, nonrandomized, open-label study was designed to evaluate the effect of multiple oral doses of delafloxacin on the pharmacokinetic profile of a single oral dose of midazolam. The protocol was approved by the investigator's institutional review board (IntegReview IRB, Austin, Texas) before study initiation, and the study was conducted by PPD Phase I Clinic (Austin, Texas) according to the International Conference on Harmonisation of Good Clinical Practice Guidelines. All subjects signed informed consent before admission into study.

Study Population

Twenty-two male and female subjects between 18 and 55 years of age with no history of significant medical problems were enrolled in the study. Subjects abstained from alcohol-, caffeine-, and methylxanthine-containing beverages or food for 96 hours before entry into the clinical study on day −1 until discharge on day 9. Subjects were either nonsmokers or abstained from any nicotine-containing products for a minimum of 180 days before admission. Subjects were excluded if they had received any investigational drug within 8 weeks before administration of the first dose of the study drug, within 6 months for biologic therapies, or within 5 half-lives of the investigational drug, whichever time period was longer; or previously received delafloxacin in a clinical study; had a positive urinary test result for amphetamines, barbiturates, benzodiazepines, cocaine metabolites, and other illegal substances at screening or on day −1; had a positive screening test result for hepatitis B, C, and/or HIV; and were taking prescription or over-the-counter medication (except for acetaminophen) within 2 weeks of the start of the study drug (4 weeks with drugs known to inhibit or induce CYP enzymes). Additional exclusion criteria included oral/intravenous antibiotics within 4 weeks of the first dose; routine use of >2 g of acetaminophen daily; any medical or surgical condition that might have interfered with the absorption, distribution, metabolism, or excretion of either drug; consumption of any food or drink that could influence CYP enzyme activity or transporters within 7 days; blood donation (400 mL) within 30 days; strenuous activity within 4 days; clinically significant gastrointestinal disease; and allergies or reactions to the study drugs.

Study Design

Subjects underwent screening evaluations to determine eligibility within 28 days before admission into the clinical unit on day −1 for baseline assessments. On day 1, subjects received a single oral 5-mg dose of midazolam after an overnight fasting period of 10 hours, which continued for 4 hours after drug administration. On day 3, subjects were administered oral delafloxacin 450 mg every 12 hours for 5 days, concluding with a single dose in the morning of day 8. A single oral dose of midazolam was coadministered on day 8 under the same fasting conditions as day 1. Subjects were confined to the clinical unit until discharge on day 9. As with other quinolones, concurrent administration of oral delafloxacin with cations (eg, calcium, magnesium, or aluminum antacids) was avoided or delafloxacin was administered at least 2 hours before or 6 hours after taking these products.

Safety and tolerability were assessed throughout the study period by monitoring and recording adverse events, clinical laboratory results (hematology [including coagulation parameters], serum chemistry, and urinalysis), vital sign measurements, 12-lead ECG results, and physical examination findings.