Single and Multiple Ascending-dose Studies of Oral Delafloxacin: Effects of Food, Sex, and Age

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ABSTRACT

Purpose: The objective of this report is describe the results of 2 studies that examined the pharmacokinetic parameters, safety profile, and tolerability of single and multiple ascending doses of oral delafloxacin and the effects of food, sex, and age on oral delafloxacin pharmacokinetic parameters, safety profile, and tolerability.

Methods: The first study contained 3 parts and used unformulated delafloxacin in a capsule. Part 1 was a randomized, double-blind, placebo-controlled, single (50, 100, 200, 400, 800, 1200, and 1600 mg) ascending-dose study of oral delafloxacin in healthy men. Part 2 was a single-dose crossover study in which 20 men received 250 mg delafloxacin with or without food. Part 2 also included a parallel group, double-blind, placebo-controlled study in 16 women and 16 elderly men and women who were randomized (3:1) to receive 250 mg delafloxacin or placebo. Part 3 was a randomized, double-blind, placebo-controlled, multiple (100, 200, 400, 800, 1200 mg once daily for 5 days) ascending-dose study of oral delafloxacin in healthy men. The second study was a single-dose, randomized, 3-period crossover study in which participants received 900 mg delafloxacin (2 × 450-mg tablets) under fasted conditions, with a high-fat meal, or fasted with a high-fat meal 2 hours after dosing. Serial blood samples were collected, and plasma pharmacokinetic parameters of delafloxacin were determined.

Findings: Delafloxacin C_{max} and $AUC_{0-\infty}$ increased with increasing oral dose over the dose range of 50 to 1600 mg. The increases in delafloxacin $AUC_{0-\infty}$ were dose proportional at doses of ≥200 mg. Steady state was reached by day 3 of dosing with minimal accumulation of delafloxacin. The C_{max} of delafloxacin was decreased slightly in the presence of food. No sex difference in delafloxacin pharmacokinetic parameters was observed. In the elderly men and women, mean delafloxacin C_{max} and $AUC_{0-\infty}$ were 35% higher than observed for young adults, which could be partially explained by a decrease in the creatinine clearance in the elderly men and women. Delafloxacin was well tolerated at the tested doses, with gastrointestinal adverse effects observed more commonly at doses ≥1200 mg.

Implications: Delafloxacin exhibits linear pharmacokinetic parameters that reached steady state after 3 days of daily oral dosing with minimal accumulation. Delafloxacin was well tolerated throughout both studies, with gastrointestinal effects observed at the higher doses (≥1200 mg). (*Clin Ther*. 2016;38:39–52) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: delafloxacin, food, elderly, pharmacokinetics, sex, tolerability.

INTRODUCTION

Delafloxacin (RX-3341, ABT-492, WQ-3034) is an investigational fluoroquinolone antibiotic with a broad spectrum of activity against gram-positive pathogens (methicillin-susceptible *Staphylococcus aureus*, methicillin-resistant strains of *S aureus*, *Streptococcus pyogenes*, and *Streptococcus enterococci*), gram-negative pathogens (*Escherichia coli, Klebsiella* species, and *Pseudomonas aeruginosa*), and anaerobes.[1–3] The bactericidal action of delafloxacin results from dual inhibition of topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA

Accepted for publication October 18, 2015.
http://dx.doi.org/10.1016/j.clinthera.2015.10.016
0149-2918/$ - see front matter

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replication, transcription, repair, and recombination.[4,5] Delafloxacin has an anionic structure, which may be a potential advantage over other fluoroquinolones in that its antibactericidal potency is increased under acidic conditions.[6,7] This could be a benefit in the treatment of infections such as *S aureus,* which can survive in mildly acidic environments.[7] In a randomized Phase II trial comparing 2 doses of intravenous delafloxacin with tigecycline in patients with various complicated skin and skin-structure infections, IV delafloxacin given at 300 mg or 450 mg every 12 hours produced clinical cure rates comparable to tigecycline.[8] In a separate Phase II study, in patients with acute bacterial skin and skin structure infections (ABSSSIs), cure rates were similar between delafloxacin and linezolid but statistically greater with delafloxacin versus vancomycin.[9] In these 2 Phase II studies, delafloxacin was well tolerated, with the most frequent adverse events (AEs) reported being nausea, vomiting, and diarrhea. Currently, delafloxacin is in Phase III trials being developed both as an intravenous and oral treatment of ABSSSIs.[10]

The present report describes the results of 2 studies conducted to evaluate the safety profile, tolerability, and pharmacokinetic parameters of oral doses of delafloxacin. The first study was a single and multiple ascending-dose study that included evaluations of the effects of food, sex, and age. In this first study, delafloxacin was administered as an unformulated chemical in a gelatin capsule. The second study was a food-effect study. The second study used delafloxacin in a formulated tablet, which is the same tablet formulation currently being used in a Phase III study on the treatment of ABSSSI with intravenous and oral delafloxacin.

PATIENTS AND METHODS

Both studies were conducted according to good clinical practice and followed the ethical principles of the Declaration of Helsinki. An independent ethics committee (Integreview, Austin, TX, and Guy's Research Ethics Committee, London, United Kingdom) approved the study protocols and all amendments. Written informed consent was signed by all the participants.

Study Participants

Study participants were healthy based on medical history, physical examination, clinical laboratory evaluations, and 12-lead ECG. Participants were able to comply with the protocol and had a body mass index >18 through 28 kg/m^2 (18–30 kg/m^2 for the food-effect study). In the 3-part dose-escalation study, participants were men and women 18 through 40 years of age; elderly individuals were ≥ 65 years of age. In the food-effect study, men and women 18 through 55 years were included. Women were postmenopausal, surgically sterile, or used adequate contraception. Participants were nonsmokers and willing to abstain from alcohol, caffeine, grapefruit, or grapefruit juice (ascending-dose study) and methylxanthine-containing beverages or food (food-effect study).

The following individuals were excluded: those who had history of adverse reactions to quinolone antibiotics; those with evidence of clinically significant disease; those undergoing any surgical procedure that would interfere with gastric motility, pH, or absorption; those with gastric upset 1 week before the study start; those with a positive drug or alcohol screen result; users of prescription or over-the-counter medications; those with positive hepatitis A IgM, hepatitis B antigen, hepatitis C antibody, or HIV test results; or users of known inhibitors or inducers of drug metabolism 1 month before the start of the study. Individuals who used >2 g/d of acetaminophen were excluded from the food-effect study.

Single and Multiple Ascending-Dose Study (Unformulated Drug in Capsule)

This was a Phase 1, single-center study that consisted of 3 parts. Part 1 was a randomized, parallel-group, placebo-controlled study to evaluate the safety profile, tolerability, and pharmacokinetic parameters of single ascending oral doses of delafloxacin in healthy mean (aged 18–40 years). Fifty-six men were assigned 1 of 7 dose groups (50, 100, 200, 400, 800, 1200, and 1600 mg). In each dose group, 8 men were randomly assigned in a 3:1 ratio to receive a single oral dose of delafloxacin ($n = 6$) or placebo ($n = 2$). The dosing schedule was such that successively higher doses of delafloxacin were given after the safety profile of the preceding dose was determined. Delafloxacin was administered in the morning after an overnight fast of at least 8 hours.

Part 2 was designed to determine the effect of food on the bioavailability of delafloxacin and to assess the safety profile, tolerability, and pharmacokinetic parameters of delafloxacin in women and healthy elderly

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