Conjunctival Tissue Pharmacokinetic Properties of Topical Azithromycin 1% and Moxifloxacin 0.5% Ophthalmic Solutions: A Single-Dose, Randomized, Open-Label, Active-Controlled Trial in Healthy Adult Volunteers

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ABSTRACT

Background: Effective ocular tissue concentrations and prolonged residence times of antibacterial agents are important in treating both acute and chronic diseases. Conjunctival biopsy allows the determination of specific tissue concentration data for topical ophthalmic agents. Drug concentration analysis at various time points following instillation allows interpretation of the residence time and a rationale for dosing frequency.

Objective: This study compared the pharmacokinetic parameters of 2 currently available topical ocular antibiotics—azithromycin ophthalmic solution 1% and moxifloxacin ophthalmic solution 0.5%—in the conjunctiva of healthy volunteers after a single topical administration.

Methods: This single-dose, randomized, open-label, active-controlled clinical trial was conducted at ORA Clinical Research and Development, North Andover, Massachusetts. Subjects were randomly assigned to receive a single dose of azithromycin or moxifloxacin and to undergo biopsy sampling at 30 minutes or 2, 12, or 24 hours after administration. Concentrations of azithromycin and moxifloxacin were determined using liquid chromatography tandem mass spectrometry. Adverse events (AEs) were assessed at all visits using visual acuity measurements, slit-lamp biomicroscopy, and direct questioning.

Results: Forty-eight subjects (mean age, 40.0 years; 48% female; 96% white, 2% black, and 2% Asian) underwent conjunctival biopsy. Mean (SD) concentrations of azithromycin in conjunctival tissue (lower limit of quantitation [LLOQ], 1 μg/g for 1-mg biopsy specimen) were 131 (89), 59 (19), 48 (24), and 32 (20) μg/g at 30 minutes and 2, 12, and 24 hours, respectively (median values, 117, 69, 46, and 30 μg/g). Mean concentrations of moxifloxacin in conjunctival tissue (LLOQ, 0.05 μg/g for 1-mg biopsy sample) were 1.92 (2.03), 3.77 (8.98), 0.02 (0.04), and 0.01 (0.02) μg/g at 30 minutes and 2, 12, and 24 hours, respectively (median values, 1.12, 0.12, <0.05, and <0.05 μg/g). Thirteen subjects (6 in the azithromycin group and 7 in the moxifloxacin group) experienced 20 AEs, 11 of which were considered possibly related to study treatment, and 15 of which were ocular (most commonly conjunctival hemorrhage).

Conclusions: In this single-dose study of 2 currently available topical ocular antibiotics in healthy volunteers, therapeutic concentrations were achieved with both agents. Both treatments were well tolerated in the population studied. Clinical Trials Identification Number: NCT00564447. (*Clin Ther.* 2008;30:2005–2014) © 2008 Excerpta Medica Inc.

Key words: azithromycin, moxifloxacin, conjunctiva, pharmacokinetics.

INTRODUCTION

While acute bacterial conjunctivitis is generally self-limiting in healthy individuals, if left untreated it potentially presents risks for spreading to others in the community, reinfection, chronic colonization, development of resistant bacterial populations, and the possibility of threatening visual sequelae (eg, ulcerative keratitis).[1] The most common causative organisms of bacterial conjunctivitis are *Haemophilus influ-*

Accepted for publication September 22, 2008

Express Track online publication October 30, 2008.
doi:10.1016/j.clinthera.2008.10.020
0149-2918/$32.00

enzae, *Streptococcus pneumoniae*, and *Staphylococcus aureus*.[2] Effective treatment of the infection with topical ocular antibiotics necessitates efficient penetration into ocular tissue and prolonged residence time in the conjunctiva, the site of bacterial adherence during infection. One predictive measure of an antibacterial agent's potential efficacy against bacteria is the concentration achieved with the medication in the target tissue relative to its minimal inhibitory concentration (MIC). The MIC value measures the drug concentration required to inhibit the growth of a specific bacterial strain in vitro (MIC_{50} = the MIC required to inhibit the growth of 50% of a selection of bacterial strains); a lower MIC indicates that less antibiotic is required for efficacy against a given bacterial strain.[3]

Conjunctival biopsy, as performed in this study, allows the collection of tissue to determine specific target tissue concentration data for topical ophthalmic antibacterial agents. This study utilized a biopsy technique that was employed in a prior study[4] and represents a standardized approach to evaluating the concentration of antibiotics in the human conjunctiva. Drug concentration analysis of the biopsies at different time points throughout a 24-hour period following instillation allows important interpretation of the residence time of topical ocular antibiotics in ocular tissue, as well as a rationale for dosing frequency.

Azithromycin is a broad-spectrum macrolide antibiotic of the azalide subclass that acts by reversibly binding to the 50S subunit of the bacterial ribosome to inhibit RNA-dependent protein synthesis.[5] Azithromycin ophthalmic solution 1%* has been approved by the US Food and Drug Administration (FDA) for the treatment of bacterial conjunctivitis, with a unique dosing regimen of 1 drop BID on days 1 and 2, and 1 drop QD on days 3 to 7.[6] Azithromycin is formulated in a proprietary polymeric mucoadhesive delivery system† designed to stay in contact with the conjunctiva and provide an increased delivery time of the active drug to the ocular surface, resulting in an 18-fold increase in the AUC of azithromycin formulated in the polymeric vehicle compared with azithromycin solution 1% administered without it.[7,8] A published Phase III, randomized, vehicle-controlled study of azithromycin ophthalmic solution 1% in 279 patients with acute bacterial conjunctivitis found MIC_{50} values of 1 µg/mL against *H influenzae*, 0.12 µg/mL against *S pneumoniae*, and 2 µg/mL against *S aureus*.[9] In a randomized, active-controlled clinical study,[10] azithromycin 1% administered using the polymeric vehicle was associated with eradication of 88.1% of bacteria in 159 patients with culture-proven acute bacterial conjunctivitis, including bacterial strains deemed to be azithromycin resistant in vitro, suggesting a possible disconnect between Clinical and Laboratory Standards Institute systemic break points and antibiotic efficacy in vivo with topical ophthalmic dosing.

Moxifloxacin is an 8-methoxy fluoroquinolone, and therefore works via a mechanism of action different from that of the macrolide class. Moxifloxacin has broad-spectrum antibiotic activity, with efficacy against various gram-positive and gram-negative microorganisms through inhibition of DNA gyrase and topoisomerase IV.[11] Also indicated for treating bacterial conjunctivitis, the FDA-approved dosing regimen for moxifloxacin ophthalmic solution 0.5%‡ for the treatment of acute bacterial conjunctivitis is 1 drop TID for 7 days. In a Phase III, randomized, vehicle-controlled study of azithromycin in 279 patients with acute bacterial conjunctivitis,[9,12] the in vitro MIC_{50} values for moxifloxacin were found to be 0.03 µg/mL against *Haemophilus* spp, 0.12 µg/mL against *S pneumoniae*, and 0.06 µg/mL against *S aureus*. On the other hand, previously published research suggests that standardized break points determined in vitro do not always correlate with susceptibility determinations against ocular conjunctival pathogens with topical ophthalmic dosing.[13,14]

The primary objective of the present study was to compare the relative pharmacokinetic (PK) parameters of topical azithromycin ophthalmic solution 1% versus moxifloxacin ophthalmic solution 0.5% at 30 minutes and 2, 12, and 24 hours after administration of a single dose in conjunctiva. Moxifloxacin ophthalmic solution 0.5% was chosen as the comparator based on its widespread use as treatment for bacterial conjunctivitis.[15]

SUBJECTS AND METHODS

This single-dose, randomized, open-label, active-controlled clinical trial was conducted at ORA Clinical Research and Development, North Andover, Massachusetts. An open-label design was used because the primary objective of the study was to assess the PK

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