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Bioequivalence of 400 mg moxifloxacin tablet in healthy Thai volunteers

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Abstract

Moxifloxacin-HCl, a fluoroquinolone, is a broad spectrum antibacterial agent against respiratory tract pathogens, including Gram-positive and Gram-negative bacteria, anaerobic bacteria and atypical respiratory tract pathogens. In order to ensure the efficacy and safety of generic moxifloxacin formulations, the bioequivalence study of these products need to be evaluated. Thus the aim of this study was to compare the rate and extent of absorption of a new generic moxifloxacin formulation (Rapiflox®, Atlantic Laboratories Corporation Ltd., Bangkok, Thailand) with that of a Reference formulation (Avelox®, Bayer HealthCare AG, Leverkusen, Germany) when given at a dose of 400 mg. A single dose randomized two treatments, crossover with 2 weeks washout period was performed in twenty health Thai volunteers. The subjects received either 400 mg of the Reference or Test formulation. Blood samples were collected at predose (0 hr) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 and 34 hr post dose. Moxifloxacin plasma level was measured by HPLC with fluorescence detector. Pharmacokinetic parameters were calculated using non-compartmental model. The mean C_{max} $\pm$ SD for the Test and Reference formulations were 4,279.1 $\pm$ 1,186.5 and 4,302.5 $\pm$ 976.9 ng/ml, respectively. Furthermore, the mean $\pm$ SD of AUC_{0-t} for the Test and Reference formulations were 50,686.4 $\pm$ 9,148.7 and 52,535.3 $\pm$ 8,548.9 ng.hr.ml^{-1} whereas $AUC_{0-\infty}$ were 52,777.5 $\pm$ 9,016.5 and 55,048.9 $\pm$ 8,615.7, ng.hr.ml^{-1}, respectively. The mean T_{max} for Test and Reference formulations were 2.01 $\pm$ 1.57 and 2.24 $\pm$ 1.87 hr, respectively. The mean ratios (90% confidence intervals) for pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were 0.9963 (0.8321-1.1219), 0.9962 (0.8707-1.0534) and 0.9957 (0.8652-1.0485), respectively. Therefore, it can be concluded that two moxifloxacin tablets (Test and Reference formulation) were bioequivalent in healthy Thai volunteers under fasting condition.

Keywords: bioequivalence, moxifloxacin, pharmacokinetic parameters

Introduction

Moxifloxacin hydrochloride is a synthetic broad spectrum antibacterial agent and is available as AVELOX Tablets for oral administration and as Avelox I.V. for intravenous administration. Moxifloxacin, a fluoroquinolone, is available as the monohydrochloride salt of 1-cyclopropyl-7-[(S, S)-2,8-diazabicyclo[4.3.0]non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinoline carboxylic acid.

The bactericidal action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV required for bacterial DNA replication, transcription, repair, and recombination. Moxifloxacin is an extended spectrum of antimicrobial activity. Its activity normally kills gram-negative pathogens, including β-lactamase-negative and β-lactamase-positive, *Haemophilus influenzae*, *Moraxella catarrhalis*, and Enterobacteriaceae. Furthermore, moxifloxacin has extended activity against gram positive cocci, including penicillin-resistant strains of *Streptococcus pneumoniae*, anaerobic and intracellular bacteria,

and atypical organisms such as *Legionella*, *Mycoplasma*, and *Chlamydia.* Moxifloxacin has a broad range of activity against clinically significant pathogens, it is a potentially useful therapeutic agent for the treatment of respiratory tract and other infections. Moxifloxacin is now commercially available in several formulations. However, the efficacy of these generic formulations is of great concerned. To ensure the efficacy of these generic formulations, the bioequivalence study of these products need to be evaluated. The aim of this study was to compare the rate and extent of absorption of a new generic moxifloxacin formulation (Rapiflox®, Atlantic Laboratories Corporation Ltd., Bangkok, Thailand) with that of a reference formulation (Avelox®, Bayer HealthCare AG, Leverkusen, Germany) when given at a dose of 400 mg.

Methods

Drug and Chemicals:

Reference formulation used in the present study was Avelox® (Bayer HealthCare AG, Leverkusen, Germany, Batch No. BXF5112) and the Test product was Rapiflox® (Atlantic Laboratories Corporation Ltd., Bangkok, Thailand, Batch No. PD090019). The Test and Reference formulations were pharmaceutical equivalent according to the regulatory criteria.

Subjects:

Twenty healthy Thai male and female volunteers were included in the study. All subjects participating in the study were healthy under medical criteria from medical histories, physical examinations and standard clinical laboratory tests. Subjects were excluded if they had liver, kidney or cardiovascular diseases, including allergic history related to moxifloxacin, or other drugs in the medical history. All volunteers had signed the informed consent to participate in the experiment. This project was approved by The Khon Kaen University Ethics Committee for Human Research (HE511062).

Study Design:

The study was conducted using a single-dose, randomized, two-way, crossover design with two weeks wash-out period. The subjects received either 400 mg of the Reference or Test formulation. Blood sample of about 10 ml were collected at predose (0 hr) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 and 34 hr after drug administration.

Determination of drug levels in plasma:

Plasma concentrations of moxifloxacin were measured by a pre-validated analytical method. Moxifloxacin plasma level was measured by HPLC with fluorescence detector.

Results

1) The mean plasma concentrations versus time profiles of moxifloxacin in healthy subjects (N = 20) after oral administration of the Test formulation and the Reference formulation are shown as linear plot in Figure 1.

2) The mean C_{max} of both formulations were similar, with mean moxifloxacin concentration of 4,302.5 ± 976.9 ng/ml and 4,279.1 ± 1,186.5 ng/ml for the Reference and Test formulations, respectively. The mean AUC_{0-t} for the Test formulation (50,686.4 ± 9,148.7 ng.hr.ml^{-1}) was also similar to that of the Reference (52,535.3 ± 8,548.9 ng.hr.ml^{-1}). Also, the mean $AUC_{0-\alpha}$ for the Test formulation (52,777.5 ± 9,016.5 ng.hr.ml^{-1}) was similar to that of the Reference (55,048.9 ± 8,615.7 ng.hr.ml^{-1}) .

3) The C_{max}, AUC_{0-t} and $AUC_{0-\alpha}$ were transformed to logarithmic values (Ln), the relative bioavailability was calculated as the ratio of Ln C_{max}, Ln AUC_{0-t} and Ln $AUC_{0-\alpha}$

between the Test and Reference (Test/Reference) (Table 1). The mean ratios (90% confidence interval) for Test/Reference of the Ln C_{max}, Ln AUC_{0-t} and Ln $AUC_{0-\alpha}$ were 0.9963 (0.8321-1.1219), 0.9962 (0.8707-1.0534) and 0.9957 (0.8652-1.0485), respectively.

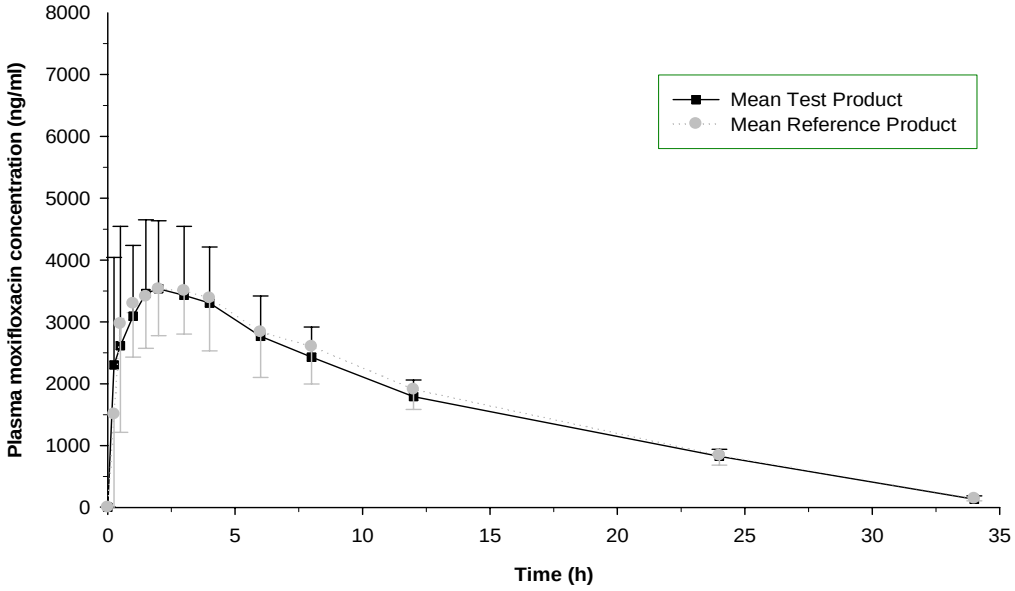

Figure 1 Linear plot of mean plasma Moxifloxacin concentrations versus time in healthy subjects (N = 20)

Conclusion

All volunteers participated in this study were well tolerated to both the Test formulation and the Reference formulation. The pharmacokinetic parameters of both the Test formulation and the Reference formulation were determined, with mean C_{max} of the Test formulation and the Reference formulation were 4,279.1 and 4,302.5 ng/ml, respectively. Mean AUC_{0-t} for the Test and Reference formulations were 50,686.4 and 52,535.3 $ng.hr.ml^{-1}$ whereas mean $AUC_{0-\infty}$ were 52,777.5 and 55,048.9 $ng.hr.ml^{-1}$, respectively. The 90% confidence interval of Ln ratios of either C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ between the Test formulation and the Reference formulation were in FDA acceptance range of 0.80-1.25. Therefore, the Test formulation, Rapiflox® 400 mg tablet of Atlantic Laboratories Corporation Ltd., Bangkok, Thailand is bioequivalent to the Reference formulation, Avelox® 400 mg tablet of Bayer HealthCare AG, Leverkusen, Germany in healthy Thai volunteers under fasting condition.

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