Population Pharmacokinetic–Pharmacodynamic Analysis to Compare the Effect of Moxifloxacin on QT Interval Prolongation Between Healthy Korean and Japanese Subjects

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ABSTRACT

Purpose: The goal of this study was to evaluate the moxifloxacin-induced QT interval prolongation in healthy male and female Korean and Japanese volunteers to investigate interethnic differences.

Methods: This multicenter, randomized, double-blind, placebo-controlled, 2-way crossover study was conducted in healthy male and female Korean and Japanese volunteers. In each period, a single dose of moxifloxacin or placebo 400 mg was administered orally under fasting conditions. Triplicate 12-lead ECGs were recorded at defined time points before, up to 24 hours after dosing, and at corresponding time points during baseline. Serial blood sampling was conducted for pharmacokinetic analysis of moxifloxacin. The pharmacokinetic–pharmacodynamic data between the 2 ethnic groups were compared by using a typical analysis based on the intersection-union test and a nonlinear mixed effects method.

Findings: A total of 39 healthy subjects (Korean, male: 10, female: 10; Japanese, male: 10, female: 9) were included in the analysis. The concentration–effect analysis revealed that there was no change in slope (and confirmed that the difference was caused by a change in the pharmacokinetic model of moxifloxacin). A 2-compartment model with first-order absorption provided the best description of moxifloxacin's pharmacokinetic parameters. Weight and sex were selected as significant covariates for central volume of distribution and intercompartmental clearance, respectively. An E_{max} model ($E[C]=[E_{max} \cdot C]/[EC_{50}+C]$) described the QT interval data of this study well. However, ethnicity was not found to be a significant factor in a pharmacokinetic–pharmacodynamic link model.

Implications: The drug-induced QTc prolongations evaluated using moxifloxacin as the probe did not seem to be significantly different between these Korean and Japanese subjects. ClinicalTrials.gov identifier: NCT01876316. (*Clin Ther.* 2016;38:2610–2621)

Key words: ethnic difference, Japanese, Korean, moxifloxacin, QT interval prolongation.

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INTRODUCTION

Drug-induced QT interval prolongation is associated with the occurrence of polymorphic ventricular tachycardia known as torsades de pointe[1] and is a major reason for drug withdrawal from the market and for discontinuing development of some new chemical entities.[2] To determine drug-induced delay in cardiac repolarization as detected by QT interval prolongation, the International Conference on Harmonisation E14 guideline, adopted in 2005, calls for the evaluation of new drugs with a thorough QT/QTc (TQT) study. In this type of study, a substance known to prolong the QT interval to the threshold level (at least a 5-millisecond change in the QTc) is required as a positive control for the assay sensitivity.[3]

Moxifloxacin, a fluoroquinolone antibiotic, is a reversible blocker of the rapid component of the delayed rectifier potassium channel. Moxifloxacin increases the QTc interval by a mean of 10 to 14 milliseconds between 2 and 4 hours after a single oral dose of 400 mg without proarrhythmia.[4–7] Moxifloxacin prolongs the action potential duration in a concentration-dependent manner.[8] Therefore, moxifloxacin has been recommended and widely used as a positive control for assay sensitivity testing in both clinical and preclinical studies.[6]

Several subject-related factors such as genetics, sex, age, weight, and food intake affect the QT interval.[9] Among them, ethnicity has not been considered as a significant factor in drug-induced QT interval prolongation. However, interethnic differences in the QT interval prolongation were found in terms of different frequencies of variants in cardiac sodium (SCN5A) and potassium channels (KCNQ1, HERG, KCNE1, and KCNE2) implicated in congenital long QT syndrome across ethnic groups.[10] Although the functional significance of many single nucleotide polymorphisms of these genes has not been investigated, this interindividual and interethnic variability of gene may underlie the different susceptibilities of individuals to the occurrence of QT interval prolongation such as long QT syndrome.

According to collective consideration of pharmacogenetic and clinical information, white subjects were believed to be more sensitive to drug-induced QT prolongation than other ethnic populations.[11] Hence, interethnic differences in fluoroquinolone-induced QT interval prolongation between Japanese and white patients were recently explored.[4,12,13] However, to our knowledge, comparison of fluoroquinolone-induced QT prolongation between Asian subjects has not yet been reported. In addition, QT studies in Korean subjects are rare compared with those in Japanese subjects. Understanding the interethnic differences in moxifloxacin-induced QT interval prolongation between Korean and Japanese subjects may help to bridge the clinical QT data between the 2 populations.

The aim of the present study was to evaluate the interethnic differences in moxifloxacin-induced QT interval prolongation between healthy Korean and Japanese subjects by using a concentration–effect analysis. The study used an intersection-union test and a population pharmacokinetic–pharmacodynamic (PK-PD) approach.

SUBJECTS AND METHODS

This study was conducted at the Clinical Trial Centre of Inje University Busan Paik Hospital, Busan, Korea, and Kitasato University East Hospital, Tokyo, Japan. The study protocol and informed consent form were reviewed and approved by the institutional review board of each institution. The study was conducted in accordance with the principles of the Declaration of Helsinki (2013) as outlined in the Guidelines for Korea and Japan Good Clinical Practice.[14] Informed consent was obtained from all individual volunteers included in the study before any study-related procedures were conducted.

Subjects

Healthy volunteers aged between 20 and 35 years with a body mass index between 17.6 and 26.4 kg/m^2 were enrolled in this study. Korean and Japanese subjects were considered healthy, with no clinically significant findings in medical history, physical examination, ECGs, and clinical laboratory evaluations. The following exclusion criteria were used: administration of inducers or inhibitors of drug-metabolizing enzymes within 28 days; history of epilepsy or electrolyte imbalance such as hypokalemia; heart rate <45 beats/min or >100 beats/min; a 12-lead ECG result of QT ≥ 500 milliseconds; a corrected QT interval according to Fridericia's formula (QTcF) ≥ 450 milliseconds for men and ≥ 470 milliseconds for women; abnormal rhythms, such as incomplete right bundle branch block, marked sinus arrhythmia, wandering