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Full paper

Effects of moxifloxacin on the proarrhythmic surrogate markers in healthy Filipino subjects: Exposure-response modeling using ECG data of thorough QT/QTc study

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ABSTRACT

Effects of moxifloxacin on QTc as well as proarrhythmic surrogate markers including J-T_{peak}c, T_{peak}-T_{end} and short-term variability (STV) of repolarization were examined by using both standard E14 time-based evaluation and exposure-response modeling. The study was conducted with a single-blind, randomized, single-dose, placebo-controlled and two-period cross-over design in healthy Filipino subjects. QT interval was corrected by Fridericia's formula (QTcF). In the E14 time-based evaluation of ECG data, the largest ΔΔQTcF with 90% confidence interval was 14.1 ms (11.2−16.9) with C_{max} of 3.39 μg/mL at 3 h post-dose (n = 69; male: 35, female: 34), indicating a positive effect on the QTcF. Moxifloxacin significantly increased the ΔΔJ-T_{peak}c and ΔΔT_{peak}-T_{end}, whereas the ΔΔSTV was not altered. Meanwhile in the exposure-response modeling of the same ECG data, the slope of moxifloxacin plasma concentration-ΔΔQTcF relationship was 4.84 ms per μg/mL and the predicted ΔΔQTcF with 90% confidence interval was 13.8 ms (13.1−15.1) at C_{max}, also indicating a positive effect on the QTcF. Importantly, results in each proarrhythmic surrogate marker obtained by the exposure-response modeling also showed high similarity to those obtained by the E14 statistical evaluation. Thus, these results of moxifloxacin may become a guide to estimate proarrhythmic potential of new chemical entities.

1. Introduction

The ICH E14 has required the conduct of a well-designed, appropriately-powered and well-executed 'Thorough QT/QTc (TQT) Study'.[1] Since fluoroquinolone antibiotic moxifloxacin has a favorable cardiovascular safety profile[2] despite a well-documented and consistent QT-prolonging effect,[3] it has become a positive control of choice for TQT studies. TQT study demonstrates the mean difference between a drug and a placebo at each time point without considering the drug exposure. Recently, Innovation and Quality in Pharmaceutical Development and the Cardiac Safety Research Consortium (IQ-CSRC) performed exposure-response modeling (ERM) of QT interval in collaboration with the Food and Drug Administration (FDA) to evaluate whether this intensive QT evaluation in standard clinical pharmacology studies could replace the TQT study.[4] Based on regulators' accumulating experiences with ERM of QTc along with the results from the IQ-CSRC prospective study,[4] the revised ICH-E14 Q&A document (revision 3) approved the use of ERM of early clinical data as a potential replacement for the TQT study.[5]

Clinical as well as non-clinical studies have shown that J-T_{peak}c in the ECG can reflect the balance of inward and outward currents during an early repolarization phase.[6,7] Namely, selective *human*

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ether-à-go-go related gene (hERG) K^+ channel blockers with high torsadogenic risk prolong QTc, J-T_{peak}c and T_{peak}-T_{end}, whereas multichannel blockers having low torsadogenic risk prolong the QTc and T_{peak}-T_{end}, but may shorten or hardly affect the J-T_{peak}c. Accordingly, a combined assessment of QTc and J-T_{peak}c can differentiate whether drugs are selective/predominant hERG K^+ channel blockers; drugs have balanced blockade of hERG and late Na^+ and/or Ca^{2+} channels; or drugs have no ion-channel effects. In addition, the beat-to-beat variability of QT interval; namely, short-term variability (STV) of repolarization, has been demonstrated as a reliable marker for predicting the development of serious ventricular arrhythmias both in non-clinical and clinical studies.[7–9]

The purpose of this study was to test whether E14-based evaluation and ERM could provide the same information with enough specificity and reliability. For that purpose, we investigated the effects of multichannel blocker moxifloxacin on the QTc as well as the proarrhythmic surrogate markers including the J-T_{peak}c, T_{peak}-T_{end} and STV of repolarization by using both evaluation methods, together with the gender subgroup analysis.[8,10]

2. Materials and methods

The study protocol was approved by the National Ethics Committee of the Philippines and the Institutional Review Board of INA Research Philippines, Inc. (No. DRP06-001), and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All subjects provided written informed consent prior to participating in the study.

2.1. Study subjects

The study population consisted of 72 healthy Filipino male and non-pregnant, non-lactating female subjects of ages between 20 and 60 years. The range of eligibility criterion for body weights was $\geq$50 kg for males (n = 36) and $\geq$40 kg for females (n = 36). Furthermore, the results of clinical laboratory tests, physical examinations and ECG had to be within the normal range and within the inclusion criteria of the trial site. Namely, QT interval corrected by Fridericia's formula ($QTcF = QT/RR^{1/3}$) must be <450 ms for all volunteers at screening and on the day prior to the start of dosing in the first session in each treatment group. The exclusion criteria included a history of seizures; positive serology for hepatitis B, hepatitis C or human immune deficiency virus infections; risk factors of torsade de pointes including heart failure, genetic predisposition, hypokalemia, hypomagnesemia and bradycardia; drug/alcohol abuse; electrolytic imbalance; heavy smoking; and/or postmenopausal woman.

2.2. Study drug

Moxifloxacin of 400 mg/tablet (Avelox®, Bayer HealthCare AG, Leverkusen, Germany) was used. Placebo tablets were encapsulated with edible lactose powder. Moxifloxacin tablets were repacked in the same capsules to match the appearance and weight of the placebo. The dosing materials were stored at 25 °C in a dry location inside the designated test material storage room.

2.3. Study design

A randomized, single-blind, placebo-controlled, two-period crossover study was designed to investigate the effect of moxifloxacin on ECG. Subjects were hospitalized at the INA Research Philippines, Inc., Clinical Pharmacology Center (Manila, Philippines) during the treatment periods. Moxifloxacin was administered as a single oral dose (400 mg/body) in accordance with the ICH guidelines for TQT study. Each subject was randomized to one of 2 groups; moxifloxacin was administered on Day 1 to one group, whereas it was done on Day 8 to the other group. The selected subjects were admitted to the trial site on Day −1. The placebo-1 was administered on Day 0. On Day 1, subjects were dosed with either placebo-2 or moxifloxacin. The subjects were discharged on Day 2. They were instructed to return to the trial site sixth day (Day 6) after their initial dosing to complete the study. The placebo-1 was administered on Day 7. On Day 8, subjects were dosed with either moxifloxacin or placebo-2. The subjects were discharged on Day 9. During and between the periods, meals, fluid intake and the surrounding environment were kept as controlled and consistent as possible.

2.4. Pharmacodynamic assessment

The subjects were kept in supine and resting position for $\geq$10 min before ECG recordings. Twelve-leads resting ECG was recorded on Day 0 and Day 7 at −25, −23.5, −23, −22, −21, −20, −18, −16 h before dosing of the placebo-2 or moxifloxacin with electrocardiograph (FX-7542, Fukuda Denshi Co., Ltd., Tokyo). On Day 1 and Day 8, ECG was recorded at −1, 0.5, 1, 2, 3, 4, 6 and 8 h after the dosing. On Day 2 and Day 9, ECG was recorded 23 h after the dosing. The ECG was recorded in triplicate at each time point with an interval of 1 min over the duration of 3 min to increase the assay sensitivity. The ECGs were reviewed by attending cardiologists at the Clinical Pharmacology Center. Ambulatory ECG (Holter) monitoring was also performed on all subjects for two consecutive days per scheduled admission to the trial site from Days 0−2, and 7 to 9 with a Digital Holter ECG Recorder (FX-180, Fukuda Denshi Co., Ltd.). The generated 24 h data were reviewed daily by the cardiologists for detection of extreme QT/QTc interval events, ST-level changes and arrhythmias that might asymptomatically occur during the admission days.

All data recorded on acquisition computer were transferred to DVD-RAM, and sent to the ECG laboratory (Yamanashi Research Center of Clinical Pharmacology, Yamanashi) for ECG analyses. The P wave-begin, QRS width-begin and -end, and T wave-peak and -end in three consecutive complexes of the ECG were automatically obtained with ECG analysis program (WReport™, Physio-Tech Co., Ltd., Tokyo), in which the begin and end were determined by baseline method.[1,5] Two technicians with extensive experience, who were blinded to time, date, treatment and other subject data, confirmed the measurements with the ECG analysis program on the computer screen and adjusted them when necessary. Then, one cardiologist approved by Japanese Circulation Society confirmed the measurements made by the technicians on the computer screen, and adjusted them when necessary before computer processing (VAR system™, Physio-Tech Co., Ltd.).

All evaluable ECGs were included in the analysis. The QTcF, J-T_{peak} and T_{peak}-T_{end} were expressed as the mean of the three averaged values at each time point. The J-T_{peak} was corrected for the heart rate with coefficient as previously described ($J\text{-}T_{peak}c = J\text{-}T_{peak}/RR^{0.58}$ with RR in second).[6,11] Correction was not made on the T_{peak}-T_{end}, since thorough QT studies have shown that the T_{peak}-T_{end} exhibited minimal heart rate dependency at resting heart rate.[6,11] In addition, the STV of repolarization was calculated with the following formula: $STV = \sum |QT_{n+1} - QT_n| / [(m-1) \times \sqrt{2}]$, where m represents the number of consecutive heart beats over 30 s.[8,9]

2.5. Pharmacokinetic assessment

Blood was sampled on Day 1 and Day 8 at −1 (C: Control), 0.5, 1, 2, 3, 4, 6, 8 and 23 h after the dosing for pharmacokinetic analysis.

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