Original Research

Effects of Celecoxib on the QTc Interval: A Thorough QT/QTc Study

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ABSTRACT

Purpose: Celecoxib is a selective cyclooxygenase-2 inhibitor widely used in patients with osteoarthritis and rheumatoid arthritis. Recently, nonclinical data on the inhibition of human ether-à-go-go–related gene potassium channels by celecoxib were reported, but there is no compelling evidence for this finding in humans. The aim of this study was to assess the potential effects of celecoxib on cardiac repolarization by conducting a thorough QT study, which was designed in compliance with the related guidelines.

Methods: This randomized, open-label, positive- and negative-controlled, crossover clinical study was conducted in healthy male and female subjects. Each subject received, in 1 of 4 randomly assigned sequences, all of the following 3 interventions: celecoxib 400 mg once daily for 6 days; a single dose of moxifloxacin 400 mg, which served as a positive control to assess the assay sensitivity; and water without any drug, which served as a negative control. Serial 12-lead ECG and blood samples for pharmacokinetic analysis were collected periodically over 24 h. Individually RR-corrected QT intervals (QTcI) and Fridericia method–corrected QT intervals (QTcF) were calculated and evaluated.

Findings: Twenty-eight subjects were allocated to 1 of the 4 intervention sequences. The largest time-matched mean effects of celecoxib on the QTcI and QTcF were <5 ms, and the upper bounds of the 1-sided 95% CIs of those values did not exceed 10 ms. Moreover, none of the subjects had an absolute QTcI value of >450 ms or a change from baseline in QTcI of >60 ms after multiple administrations of celecoxib. The QTcI did not show a positive correlation with celecoxib concentrations in the range up to ~2700 μg/L. The overall effects of moxifloxacin on the QTcI and QTcF were enough to establish assay sensitivity. No serious adverse events were reported, with a total of 11 AEs reported in 8 subjects.

Implications: Celecoxib caused no clinically relevant increase in the QT/QTc interval at the maximum dose level used in current practice settings. ClinicalTrials.gov identifier: NCT03822520. (*Clin Ther*. 2019;41:2204–2218)

Key words: celecoxib, proarrhythmic potential, QT prolongation, thorough QT/QTc study.

INTRODUCTION

Celecoxib is the first selective cyclooxygenase-2 inhibitor approved for use in treating inflammation and pain[1] and thus is known as a useful treatment option for osteoarthritis and rheumatoid arthritis. The risks for gastrointestinal and renal events with celecoxib use are significantly lower than with other NSAIDs,[2] while it has efficacy in pain relief and quality-of-life improvement similar to that of conventional NSAIDs.[3] However, celecoxib has been associated with fatal cardiovascular events, such as myocardial infarction and stroke, although the risk is not much different from that with other NSAIDs.[4,5]

An undesirable delayed cardiac repolarization by a drug creates an electrophysiologic environment that

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favors the development of cardiac arrhythmias, including QT prolongation and *torsade de pointes* (TdP).[6] The QT prolongation–related arrhythmia is one of the most common causes of withdrawal of drugs from the market.[7] If there is safer alternative to a drug with a risk for drug-induced QT prolongation, the drug would be unacceptable despite a low prevalence of drug-induced QT prolongation. Terfenadine, an antihistamine agent, is an example of a drug that was withdrawn, in 1998, for its arrhythmogenic effect with a prolonged QT interval.[6] For this reason, in the early stage of drug development it is important to assess the risk for QT prolongation using nonclinical assays. Among widely used nonclinical assays, the human ether-à-go-go related gene (hERG) method demonstrated good performance in predicting QT prolongation in humans.[8] Frolov et al[9] recently reported that celecoxib inhibited the hERG potassium channels and other TdP arrhythmia–related channels *in vitro*.

To date, a thorough QT/QTc (TQT) study result in humans has not been reported to confirm the QT-prolongation effect of celecoxib. Although there is no known clinical evidence suggesting an association between celecoxib and QT prolongation, it is worthy to characterize the effect of celecoxib on QT/QTc by conducting a well-controlled clinical study. The aim of this study was to assess the potential effects of celecoxib on cardiac repolarization with a TQT study, which was designed in compliance with the related guidelines.[10,11]

SUBJECTS AND METHODS

The study protocol was approved by the institutional review board at Samsung Medical Center (Seoul, Republic of Korea), and this study was conducted in accordance with the ethics-related principles of the Declaration of Helsinki and the Good Clinical Practice guideline. Prior to any study-related procedures, written informed consent was obtained from all subjects.

Study Design and Subjects

A randomized, open-label, positive- and negative-control, crossover clinical study was conducted in healthy male and female subjects. Each subject was randomly assigned to 1 of 4 sequences of the following 3 interventions: celecoxib* 400 mg once daily for 6 days; a single dose of moxifloxacin† 400 mg, which served as a positive control for the evaluation of assay sensitivity of the QT interval; and water without any drug, which served as a negative control. All celecoxib and moxifloxacin doses were administered with 150 mL of water, and 150 mL of water alone was administered as the negative control. While each positive and negative control intervention took only 1 day, the celecoxib intervention was of a relatively long duration. To efficiently conduct this clinical study, all subjects completed both the positive- and negative-control intervention periods, before or after the celecoxib intervention. Thus, only 4 intervention sequences were designed. There were flexible washout periods of 3–6 days between each intervention. Since the elimination half-life of celecoxib is reported to be between 11.2 and 15.6 h,[12] and that of moxifloxacin is ~12 h,[13,14] these washout periods were at least fivefold greater than the elimination half-lives of the study drugs.

Eligible subjects were healthy male and female volunteers aged between 19 and 40 years, with a body mass index from 20 to 30 kg/m^2 in men and from 18 to 26 kg/m^2 in women at screening. Subjects were determined to be of sound physical and mental health by physical examinations, vital sign measurements, 12-lead ECGs, and clinical laboratory tests prior to enrollment. Subjects were excluded if they had a significant ECG result at screening, including a baseline Fridericia method–corrected QT interval (QTcF) of >430 ms in men and >450 ms in women; if they had been exposed to any prescribed medicine within 2 weeks or any over-the-counter medicine within 1 week prior to the randomization; if they had a known hypersensitivity to medicine; if they had an allergic disease requiring treatment; or if they had a positive result on serology for hepatitis B virus, hepatitis C virus, HIV, or syphilis. Female subjects were to demonstrate a negative β-human chorionic gonadotropin urine test, and to agree to remain abstinent from coitus or to use 2 adequate methods of contraception to prevent pregnancy during this study.

* Trademark: Celebrex® capsules 200 mg (Pfizer Korea, Seoul, Republic of Korea).

† Avelox® tablets 400 mg (Bayer Korea, Seoul, Republic of Korea).

Subjects were at rest for at least 5 min before each standard 12-lead ECG recording and awake in the supine position during ECG recording. All ECGs were recorded using a digital electrocardiograph (Philips PageWriter TC70 Cardiograph, Philips Medical Systems, Andover, Massachusetts) with a sampling rate of 1000 Hz, speed of 25 mm/s, and amplitude of 10 mm/mV. Following an overnight fast of at least 10 h, baseline ECGs in each intervention were recorded at 1 h, 40 min, and 20 min before the first celecoxib dosing and the administration of moxifloxacin and water only. Thereafter, serial ECGs were obtained at 1, 2, 3, 4, 6, 8, 12, 16, and 24 h after the sixth celecoxib dosing and the administration of the positive and negative controls on the basis of the T_{max} values of the study drugs reported previously in healthy subjects.[13,15] At each time point, 3 consecutive ECGs were recorded at ~1-min intervals. Subjects received standardized meals at 4 and 9 h after the administration of the study drugs and water only, and water was allowed as desired except for 2 h before and after the study drugs administration.

Through a 22-gauge indwelling catheter in a vein at the forearm, serial venous blood samples (8 mL) for pharmacokinetic (PK) analysis were obtained before and at 1, 2, 3, 4, 6, 8, 12, 16, and 24 h after both the sixth celecoxib and moxifloxacin administrations. Within 30 min after blood collection, samples were centrifuged at 1800*g* for 10 min at 4 °C to separate the plasma, and the separated plasma was collected into tubes and stored at −70 °C until assay.

The sample-size calculation was based on the assumption of a true difference of 3 ms in time-matched differences in baseline-adjusted QT interval corrected for heart rate between celecoxib and the negative control, with an SD of 11 ms, and a number of ECG replicates of 3.[16] A sample size of 22 subjects was calculated as needed to provide >90% power to show that the upper bound of the 1-sided 95% CI of the effect of celecoxib would be < 10 ms, as specified in the guideline.[10] The enrollment target of 28 subjects was planned to account for a 20% dropout rate.

ECG Analysis

The digital ECGs from the recorder were recorded on compact flash memory cards and directly transferred electronically to the computer system as a US Food and Drug Administration–compliant XML format file using proprietary software provided by the electrocardiograph manufacturer.[17] ECG intervals were measured with a semiautomated method using CalECG version 3.8.1 (AMPS LLC, New York, New York), and a trained physician reviewed the fiducial points placed by the algorithm of on-screening caliper and adjusted points when it was necessary. The QT intervals were measured with the superimposed median beat derived from all 12 leads.[18] The QRS complex was measured from the earliest ventricular depolarization to the offset of ventricular depolarization. The QT interval was measured from the onset of the QRS complex to the T offset, the intersection of the terminal part of the T wave and the isoelectric line following the T wave. If the U wave interrupted the T wave before it returned to baseline, the end of the QT interval was measured at the nadir between the T and U waves.

The QT intervals were corrected for the heart rate using the RR intervals calculated as the arithmetic mean of heartbeats. The individually RR-corrected QT interval (QTcI) value was calculated as QT/RR^a, where *RR* was the RR interval and *a* was the subject's RR coefficient derived from all QT-RR pairs recorded in the negative control of each subject in the linear regression model; $\log(QT) = \text{Intercept} + a \times \log(RR)$. Also, QTcF value was obtained using the formula $QT/RR^{1/3}$. The QTc interval was determined as the median of 3 consecutive values at each time point.

Quantification of Celecoxib and Moxifloxacin

The plasma concentrations of celecoxib and moxifloxacin were determined with HPLC (Prominence UFLC XR; Shimadzu Corporation, Kyoto, Japan) with MS (TQ5500; AB Sciex, Framingham, Massachusetts).

The standards for celecoxib and the internal standard (IS), celecoxib_d_4, were manufactured by Sigma–Aldrich Chemical Company (St. Louis, Missouri) and Toronto Research Chemicals Inc (Toronto, Ontario, Canada), respectively. An aliquot of 100 μL of plasma was added to a polypropylene tube and mixed with 20 μL of IS solution and 500 μL of acetonitrile. The sample was vortexed for 1 min and then centrifuged for 5 min at 11000*g*. The 100 μL of supernatant was transferred and mixed

with 300 μL of 50% acetonitrile. A 2-μL aliquot thereof was then injected into a LC-MS/MS system. Chromatography was performed with a Unison UK-C_{18} column (75 × 2.0 mm, 3 μm internal diameter; Imtakt, Portland, Oregon). A mixture of acetonitrile and deionized water (70:30 vol/vol) was used for the mobile phase, with a flow rate of 0.2 mL/min. Each target analyte was analyzed using electrospray ionization in the negative ion multiple reaction monitoring mode. Celecoxib was monitored at precursor ion *m/z* at 380.1 and product ion *m/z* at 316.2, and celecoxib_d_4 was monitored at precursor ion *m/z* at 384.1 and product ion *m/z* at 320.2. The standard curves for celecoxib were linear over the calibration range of 5−4000 μg/L, with >0.9950 of the coefficient of correlation (back-calculation method). Assay performance was monitored using quality-control samples at concentrations of 15, 200, and 3200 μg/L, and the imprecision and accuracy at all concentrations were ≤7.1% and between 95.9% and 106.6%, respectively.

The standards for moxifloxacin and the IS, moxifloxacin_d_4, were manufactured by TLC Pharmaceutical Standards Ltd (Aurora, Ontario, Canada). An aliquot of 100 μL of plasma was added to a polypropylene tube and mixed with 20 μL of IS solution and 500 μL of acetonitrile. The sample was vortexed for 1 min and then centrifuged for 5 min at 11,000*g*. The supernatant (100 μL) was transferred and mixed with 1 mL of 50% acetonitrile. The 100 μL of mixture was mixed again with 1 mL of 50% acetonitrile and vortexed for 2 min. A 5-μL aliquot thereof was then injected into an LC-MS/MS system. A Waters Atlantis C_{18} column (150 × 2.1 mm, 5 μm internal diameter; Waters, Milford, Massachusetts) was used as an analytical column for chromatography. The mobile phase, a mixture of acetonitrile, deionized water, and formic acid (40:60:0.02 vol/vol/vol), was run at a flow rate of 0.2 mL/min. Each target analyte was analyzed using electrospray ionization in the positive ion multiple reaction monitoring mode. Moxifloxacin was monitored at precursor ion *m/z* at 402.2 and product ion *m/z* at 358.2, and moxifloxacin_d_4 was monitored at precursor ion *m/z* at 406.2 and product ion *m/z* at 362.2. Moxifloxacin was quantified over a theoretical concentration range of 50 to 20,000 μg/L, with >0.9950 of the coefficient of correlation (back-calculation method). Assay performance was monitored using quality-control samples at concentrations of 150, 1600, and 16,000 μg/L, and the imprecision was ≤3.8% and accuracy was between 94.5% and 95.7% at all concentrations.

Pharmacokinetic Analysis

The PK parameters were derived from a noncompartmental analysis using Phoenix WinNonlin version 8.0 (Certara, St. Louis, Missouri). The AUC_{τ} of celecoxib and the AUC_{last} of moxifloxacin were calculated using the linear-up/log-down method. The C_{max}, $C_{max,ss}$, $C_{min,ss}$, T_{max}, and $T_{max,ss}$ parameters were determined from the observed values.

Tolerability Analysis

The investigators closely observed the subjects in consideration of the possibility of adverse events (AEs) throughout the study. AEs were recorded by means of spontaneous reporting by subjects and nonleading questions from the investigators. Physical examinations, vital sign measurements (blood pressure, pulse rate, and body temperature), ECGs, and clinical laboratory tests (hematology, blood chemistry, and urinalysis) were performed at predefined and regular intervals throughout the study. AEs and any abnormalities from investigations were assessed by the investigators, who were not blinded to the interventions.

Statistical Analysis

Statistical analyses were performed using SAS Enterprise Guide version 7.1 (SAS Institute, Cary, North Carolina). All subjects who received any intervention were included in the tolerability analysis, and subjects who had valid ECG data for at least 1 postdosing time point were included in the ECG analysis. The baseline characteristics of ECG were determined by pooling 3 values before dosing in each intervention, and a mixed-design ANOVA was used to identify differences between interventions.

The baseline-adjusted QTcI and QTcF were analyzed using a linear mixed-effects model with repeated measurements assuming the first-order autoregressive covariance structure, in which the time point, sequence, intervention, sex, and intervention by time point interaction and sex by intervention by time point interaction were regarded as fixed effects; the subject as a random effect; and baseline as a covariate. Upper and lower bounds of the 1-sided

95% CIs were calculated for the time-matched least squares mean differences in baseline-adjusted QTcI and QTcF between each study drug and the negative control. A *negative* TQT study was defined as one in which the upper bound of the 1-sided 95% CI for the largest time-matched mean effect of celecoxib on the QTc interval was <10 ms.[10] To establish assay sensitivity, the same linear mixed-effects model was applied. Thus, we determined whether the lower bound of the 1-sided 95% CI for the overall time-matched difference in the QTc interval between moxifloxacin and the negative control was >5 ms.

Based on the International Conference on Harmonisation guideline recommendation,[10] the maximum of QTcI in subjects in each intervention was categorized as ≤450 ms, >450−480 ms, >480−500 ms, and >500 ms, and calculated as the frequency and percentage. Likewise, the maximum change from baseline in QTcI in subjects in each intervention was categorized as ≤30 ms, >30 to ≤60 ms, and >60 ms, and calculated as the frequency and percentage.

For an analysis of the relationship between the study drug concentrations and QTcI changes, we plotted the value $QTcI_{d,i} - QTcI_{n,i}$, which was the difference in the change from baseline at time point *i* for QTcI between the study drug and the negative control. The concentration−response analysis was performed using a linear mixed-effects model. Time-matched concentration as a continuous variable was treated in the model as a fixed effect, and a random intercept and slope model were assumed. We explored the adequacy of the model fit, then tested whether the slope of the regression line was significantly different from zero.

RESULTS

Study Population

A total of 28 Korean subjects were randomized, 27 subjects received at least 1 intervention, and 25 subjects completed the study as planned. One subject did not receive any intervention because iron-deficiency anemia was diagnosed just before the first period. Two subjects were withdrawn, one due to noncompliance with the study protocol as judged by the investigator during the first period and the other due to an AE during the first period. The demographic characteristics of the subjects are presented in Table I. Twenty-seven subjects were included in the tolerability analysis, and 26 subjects were included in the ECG analysis since 1 subject had no valid ECG data for postdosing time points (Figure 1).

Drug Effect on QT Interval

The changes from baseline in time-matched mean differences in the QTcI and QTcF values after multiple administrations of celecoxib and single administration of moxifloxacin are depicted in Figure 2. The baseline ECG interval data were similar between interventions (Table II). The largest time-matched mean differences in the QTcI and QTcF values between the celecoxib and negative control occurred at 8 h after administration: +3.7 and +2.7 ms, respectively (Table III). The upper bounds of the 1-sided 95% CIs of the largest time-matched mean effects of celecoxib on the QTcI and QTcF values did not exceed 10 ms. The overall time-matched mean differences from baseline in the QTcI and QTcF values after moxifloxacin administration, meanwhile, were +11.6 and +12.0 ms, respectively. The lower bounds of the 1-sided 95% CIs of the overall effects of moxifloxacin on the QTcI and QTcF values were >5 ms.

Categorical analysis revealed that 0, 2, and 0 subjects who received celecoxib, moxifloxacin, and negative control, respectively, had absolute QTcI prolongations of >450−480 ms (Table IV). There were no subjects with an absolute QTcI of >480 ms after the administration of any of the study drugs. Likewise, there were no subjects with a QTcI increase from baseline of >60 ms. A QTcI change from baseline of >30 ms was observed in 1 subject (4.0%)

Table I. Demographic characteristics of the study subjects, by sex. Data are presented as mean (SD).

Characteristic	Female (n = 12)	Male (n = 16)
Age, y	25.2 (3.2)	25.9 (5.1)
Height, cm	162.0 (5.9)	174.2 (4.6)
Weight, kg	58.1 (6.4)	71.9 (10.1)
BMI, kg/m^2	22.1 (2.3)	23.6 (2.3)

BMI = body mass index.

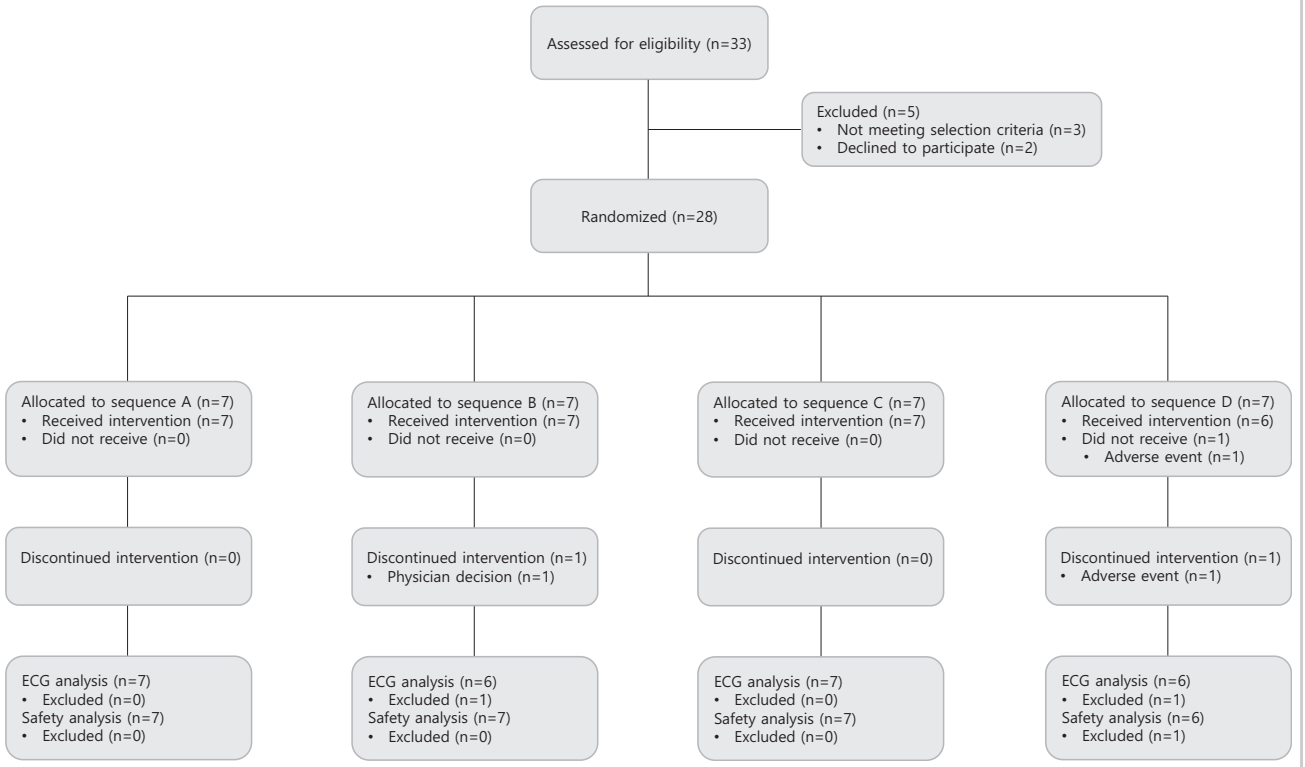

Figure 1. CONSORT flow chart. Sequence A: celecoxib − moxifloxacin − negative control; sequence B: celecoxib − negative control − moxifloxacin; sequence C: moxifloxacin − negative control − celecoxib; sequence D: negative control − moxifloxacin − celecoxib.

after celecoxib administration and in 5 subjects (20.0%) after moxifloxacin administration.

Pharmacokinetic Analysis and Relationship With QT Interval

The PK properties of celecoxib and moxifloxacin are summarized in Table V and the plasma concentration−time curves of the study drugs are shown in Figure 3. Both celecoxib and moxifloxacin showed rapid absorption after oral administration, with a median $T_{max,ss}$ value of celecoxib and T_{max} of moxifloxacin of 3 and 2 h, respectively. The female subjects showed relatively greater exposure to both celecoxib and moxifloxacin than did the male subjects.

The relationships between the plasma concentrations and baseline-adjusted time-matched differences in QTcI are shown in Figure 4. Based on a plot of standardized residuals versus fitted values and the Anderson-Darling test, no significant departures from model assumptions were observed. There was no positive correlation of celecoxib in the concentration range up to ~2700 μg/L (mean [90% CI] slope: −0.0026 [0.0052−0.0000]; $P = 0.1028$) (Figure 4A). A further analysis by sex revealed that the slope of the relationship tended to be greater in female than male subjects (−0.0006 vs −0.0055), although statistical significance was not reached. However, the baseline-adjusted time-matched difference in the QTcI was positively related to the plasma concentration of moxifloxacin (mean [90% CI] slope: +0.0033 [0.0010−0.0055]; $P = 0.0199$) (Figure 4B). Additionally the relationships between the study drug exposures and QTcI are shown in Figure 5.

Tolerability

No serious AEs were reported. It was during the negative control period that 1 subject was withdrawn due to an AE (migraine). A total of 11 AEs occurred

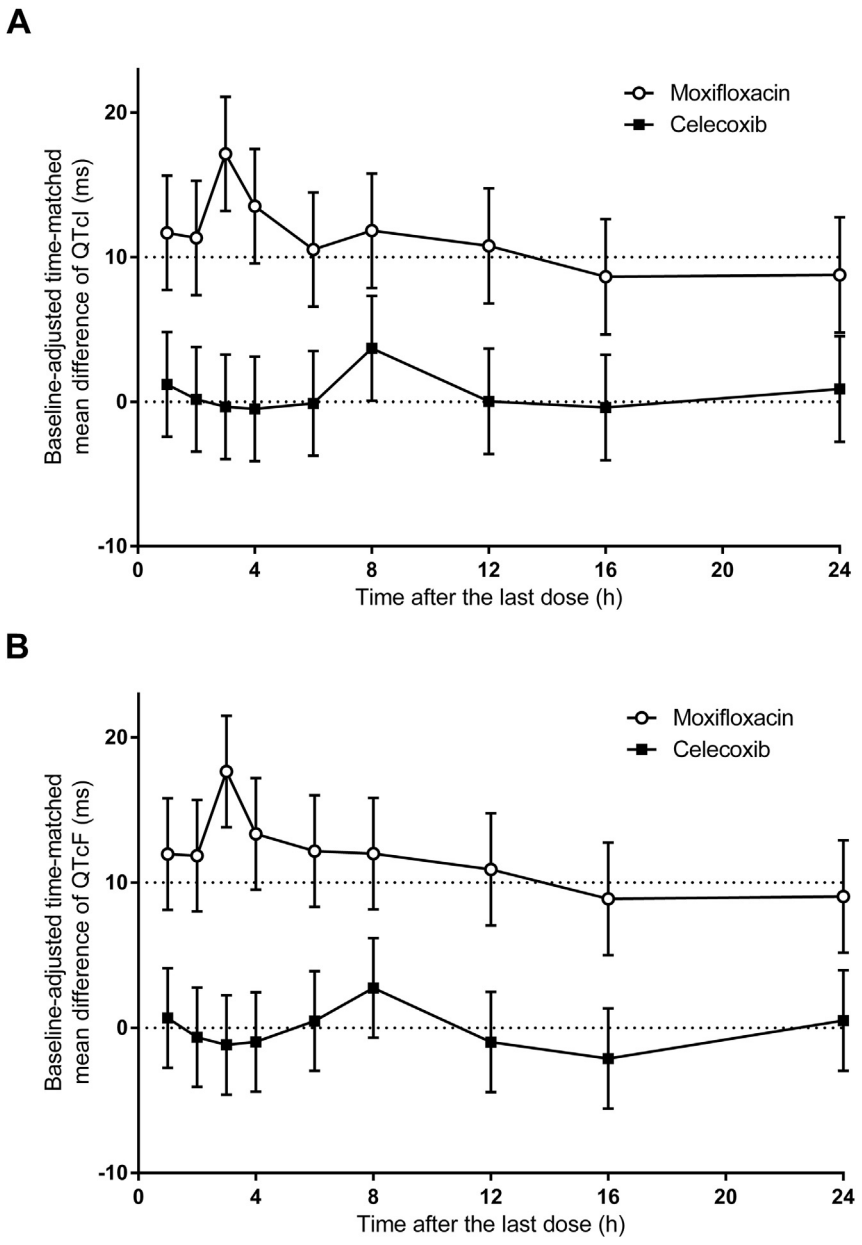

Figure 2. Baseline-adjusted time-matched least squares mean (2-sided 90% CI) differences compared to the negative control in QTcI (A) and QTcF (B) after multiple administration of celecoxib for 6 days and single administration of moxifloxacin in healthy subjects (N = 26). QTcF = Fridericia method-corrected QT interval; QTcI = individually RR-corrected QT interval.

in 8 subjects. Two subjects reported AEs with celecoxib, 3 subjects with moxifloxacin, and 3 subjects with the negative control. The most common AE was headache, which occurred in 3 subjects. All of the AEs were mild or moderate in severity, and those were resolved without sequelae.

Table II. The baseline characteristics of electrocardiogram in each intervention. Data are given as mean (SD) milliseconds.

Parameter	Celecoxib*	Moxifloxacin*	Negative Control	p
RR				
All patients (n = 26)	1030.2 (147.5)	1024.8 (141.4)	1033.5 (155.3)	0.8565
Female (n = 11)	937.1 (92.0)	951.2 (122.0)	934.3 (120.8)	—
Male (n = 15)	1092.3 (146.8)	1073.9 (135.0)	1106.3 (138.8)	—
QT				
All patients (n = 26)	404.1 (24.6)	404.7 (20.6)	406.3 (22.4)	0.8579
Female (n = 11)	402.8 (17.3)	406.6 (15.6)	403.6 (18.5)	—
Male (n = 15)	405.0 (29.0)	403.5 (23.9)	408.3 (25.4)	—
QTcI				
All patients (n = 26)	402.6 (17.5)	404.8 (16.2)	404.6 (16.4)	0.4738
Female (n = 11)	414.1 (13.0)	417.2 (12.4)	415.4 (14.9)	—
Male (n = 15)	395.0 (16.1)	396.5 (13.0)	396.7 (12.9)	—
QTcF				
All patients (n = 26)	401.1 (16.9)	402.8 (15.3)	403.0 (15.1)	0.5973
Female (n = 11)	412.4 (12.3)	414.4 (12.0)	413.5 (12.1)	—
Male (n = 15)	393.5 (15.5)	395.1 (12.2)	395.2 (12.3)	—

QTcF = Fridericia method-corrected QT interval; QTcI = individually RR-corrected QT interval.
* A total number of subjects was 25 since 1 female subject who had data only for negative control was excluded.

Table III. The baseline-adjusted time-matched mean differences in QTcI and QTcF. Data are given as least squares mean (2-sided 90% CI*) milliseconds.

Drug/Time After Last Dose	QTcI	QTcF
Celecoxib		
1 h	+1.2 (−2.4 to 4.8)	+0.7 (−2.8 to 4.1)
2 h	+0.2 (−3.4 to 3.8)	−0.6 (−4.1 to 2.8)
3 h	−0.3 (−4.0 to 3.3)	−1.2 (−4.6 to 2.2)
4 h	−0.5 (−4.1 to 3.1)	−1.0 (−4.4 to 2.5)
6 h	−0.1 (−3.7 to 3.5)	+0.5 (−3.0 to 3.9)
8 h	+3.7 (0.1 to 7.3)	+2.7 (−0.7 to 6.2)
12 h	0.0 (−3.6 to 3.7)	−1.0 (−4.4 to 2.5)
16 h	−0.4 (−4.0 to 3.3)	−2.1 (−5.6 to 1.3)
24 h	+0.9 (−2.8 to 4.5)	+0.5 (−3.0 to 4.0)
Moxifloxacin (overall)	+11.6 (9.7 to 13.4)	+12.0 (10.2 to 13.7)

QTcF = Fridericia method—corrected QT interval; QTcI = individually RR-corrected QT interval.
* The upper and lower bounds of a 2-sided 90% CI are equivalent to the upper and lower bounds of a 1-sided 95% CI.

Table IV. Summary of categorical analysis of QTcI data. Data are given as number (%) of subjects.

Intervention	Absolute QTcI Prolongation			Change from Baseline in QTcI		
	≤450 ms	>450–480 ms	>480 ms	≤30 ms	>30–60 ms	>60 ms
Celecoxib*	25 (100)	0	0	24 (96.0)	1 (4.0)	0
Moxifloxacin*	23 (92.0)	2 (8.0)	0	20 (80.0)	5 (20.0)	0
Negative control	26 (100)	0	0	26 (100.0)	0	0

QTcI = individually RR-corrected QT interval.
*The total number of subjects was 25 because 1 female subject who had data only for negative control was excluded.

DISCUSSION

This research represents the first published TQT study of celecoxib. The findings from the present TQT study show that the largest time-matched mean effects of celecoxib on the QTcI and QTcF values were <5 ms and that the upper bounds of the 1-sided 95% CIs of those effects did not exceed 10 ms, with the result being termed *negative* according to the guideline.[10]

The assay sensitivity was established based on the finding that the overall time-matched mean effects of the moxifloxacin on the QTcI and QTcF values were >10 ms and also the lower bounds of the 1-sided 95% CIs of those effects were >5 ms. Moreover, a previous study reported that QTcI showed a maximum shortening at 3.5 h from the start of breakfast of 5.6 ms (95% CI, 3–8) and that this effect of food on the QTc interval could be used to demonstrate assay sensitivity in a TQT study.[19] In the present study, a QTcI at 2 h after lunch was shortened by 6.8 ms (90% CI, 4.0–9.5) compared to that just before lunch in the negative control. Although the QTcI shortening was not observed at a matched time point, this finding may be supportable evidence that the present study was capable of detecting a 5- to 10-ms change in QTc interval.

If the TQT is negative but the available nonclinical data are positive, it is recommended to consider the power of the results from nonclinical studies.[10,20] Based on findings from the nonclinical studies, celecoxib inhibited the hERG channel with a 50% inhibitory concentration of 6 μmol/L, which is equivalent to 2286 μg/L, and the mechanism of hERG inhibition appeared to be modification of gating properties rather than direct channel block.[9] In the present TQT study, the mean $C_{max,ss}$ of celecoxib was 1210.5 μg/L, and the highest concentration of celecoxib identified among all of the subjects was 2610.1 μg/L. Although the celecoxib dose of 400 mg seems to be sufficient for achieving the hERG 50% inhibitory concentration, particularly in women, the following should be noted. First, total

Table V. Pharmacokinetic parameters of study drugs. Data are given as mean (SD), except for $T_{max,ss}$ and T_{max} as the median (range).

Intervention/Parameter	All Patients (N = 25)	Female (n = 10)	Male (n = 15)
Celecoxib			
AUC_{τ}, h · μg/L	10,954.2 (6341.5)	14,827.8 (7977.1)	8371.8 (3188.9)
$C_{max,ss}$, μg/L	1210.5 (601.8)	1540.0 (600.0)	990.9 (510.2)
$T_{max,ss}$, h	3 (1–6)	3 (1–4)	3 (1–6)
$C_{min,ss}$, μg/L	158.1 (146.5)	225.8 (202.5)	113.0 (70.3)
Moxifloxacin			
AUC_{last}, h · μg/L	27,072.7 (4451.9)	29,906.0 (3501.1)	25,183.8 (4066.8)
C_{max}, μg/L	2338.6 (436.6)	2636.6 (306.3)	2139.9 (400.9)
T_{max}, h	2 (1–4)	3 (1–4)	2 (1–4)

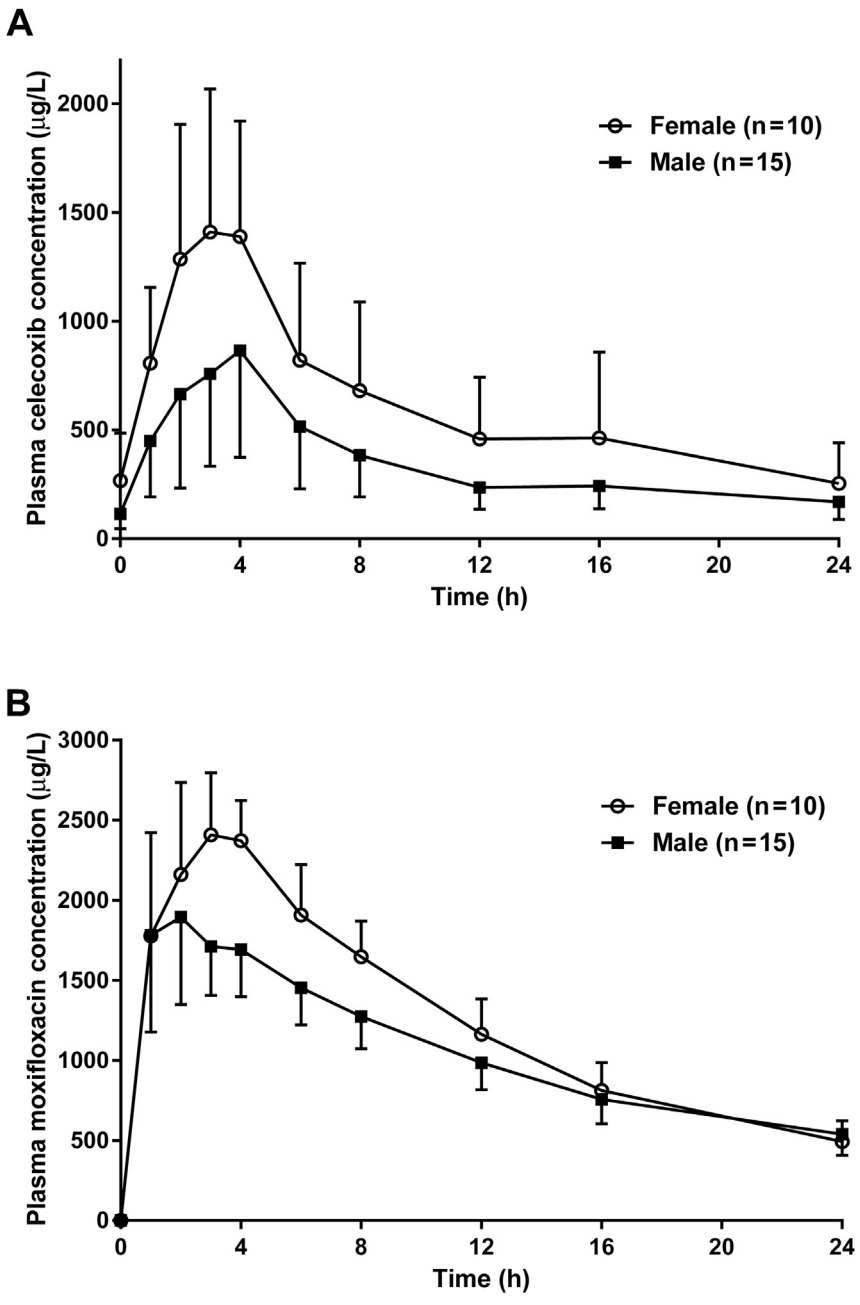

Figure 3. Mean (SD) plasma concentration–time curves of celecoxib (A) and moxifloxacin (B).

concentration in plasma generally does not reflect that in cardiac tissue expressing hERG channel, and high plasma protein binding but a large volume of distribution of celecoxib makes it difficult to predict the free concentration in cardiac tissue.[12] Second, several channels besides hERG are involved in drug-induced TdP, although direct block of the hERG channel is predominantly considered to be crucial.[8] To overcome these drawbacks, the new paradigm of comprehensive *in vitro* proarrhythmia assay was proposed.[21,22] Lastly, Park et al[23] reported that hERG assay demonstrated robust sensitivity but low

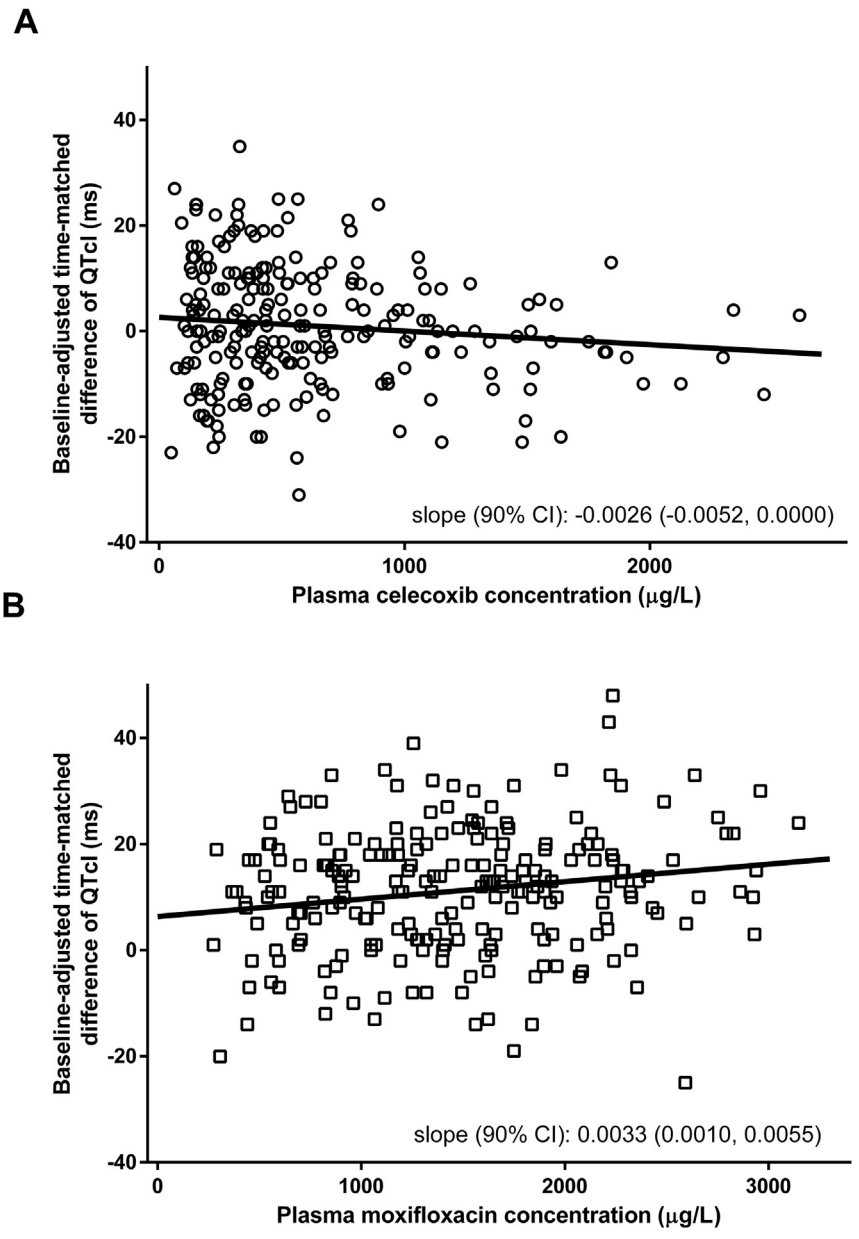

Figure 4. Relationship between plasma concentrations and baseline-adjusted time-matched differences in QTcI with celecoxib (A) and moxifloxacin (B). Lines represent regression. QTcI = individually RR-corrected QT interval.

positive predictive value at clinically relevant exposures for predicting the results of clinical TQT studies. In view of the low positive predictive value, the present study results can be interpreted as a similar phenomenon. However, the above explanations for the discrepancy between clinical and nonclinical results cannot be the basis to exclude the possibility of QT/QTc interval prolongation in patients with hepatic failure or with the use of supratherapeutic doses.

The main elimination pathway of celecoxib is hepatic metabolism, following biotransformation via

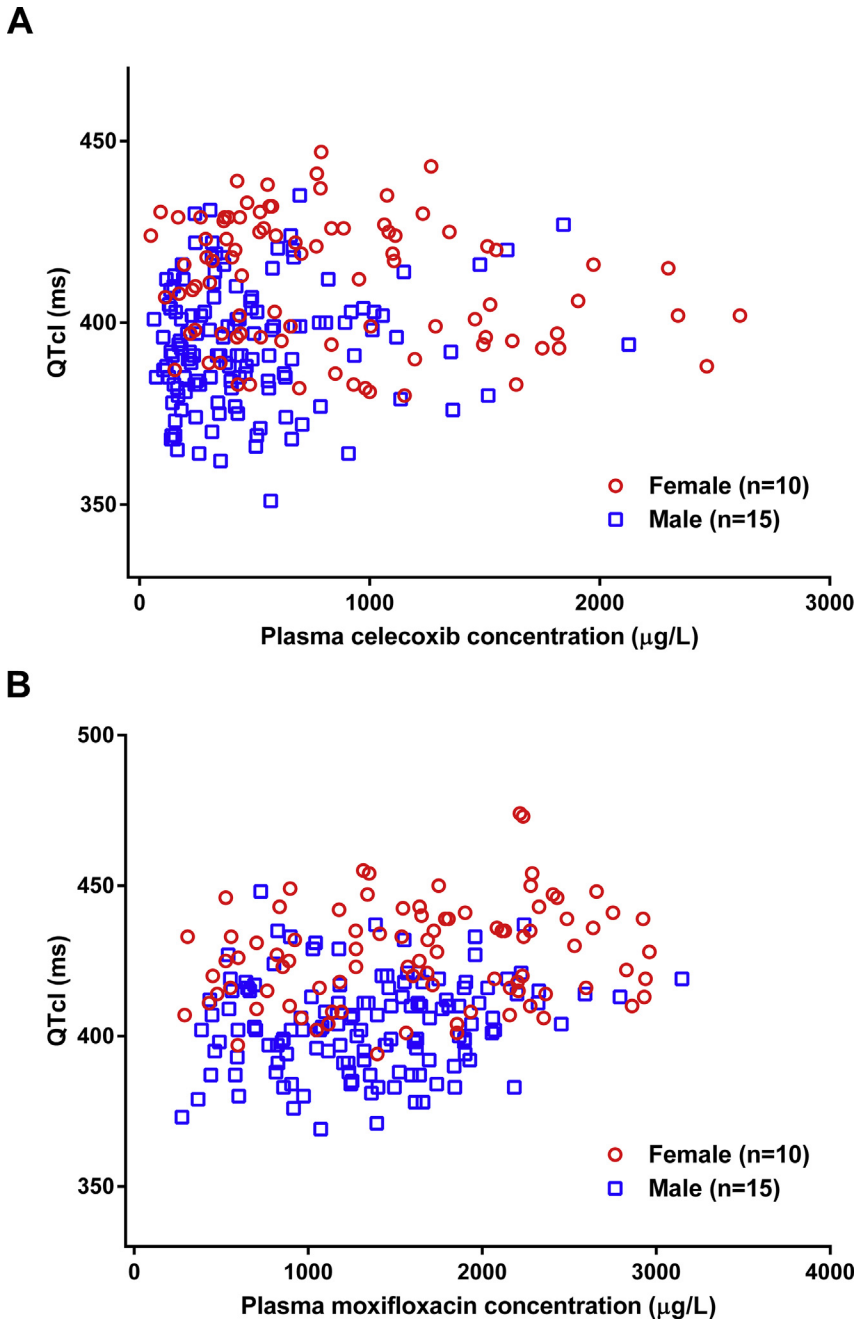

Figure 5. Relationship between plasma concentrations and absolute QTcI, by sex, with celecoxib (A) and moxifloxacin (B). QTcI = individually RR-corrected QT interval.

the cytochrome P450 (CYP) 2C9 isozyme to metabolites that are excreted in urine and feces.[12] A polymorphism that affects CYP2C9 activity in Koreans is known as CYP2C9*3,[24] and subjects with CYP2C9*3 show reduced CYP2C9 enzyme activity.[25] Since the allele frequency of CYP2C9*3 in Koreans is only 1.1%,[24] and the exposure to celecoxib in the homozygote carriers of CYP2C9*3 was more than fivefold that in the others,[26] the results from the present study are unlikely to be

associated with the homozygote carriers of CYP2C9*3. Considering that celecoxib exposure is linearly related to dose within the clinical range of 100−600 mg, the PK parameters of celecoxib in the present study were comparable with those in a previous study that assessed the steady-state PK properties after multiple administrations of celecoxib 200 mg, with similar T_{max} and half of $C_{max,ss}$ and AUC_{τ}.[15] Compared with higher exposure to celecoxib in the female than in the male subjects, there was no significant difference in body weight−normalized apparent clearance between women and men. This finding implies that smaller body weight could contribute to a slower elimination and/or faster absorption of celecoxib. As for moxifloxacin, the PK characteristics in the present study were similar to those in the previously reported TQT studies in healthy Korean subjects.[13,14]

The present study showed that the baseline-adjusted time-matched difference in the QTcI was not correlated with the plasma concentration of celecoxib up to ~2700 μg/L. Similarly, the baseline-adjusted time-matched mean difference in the QTcF for celecoxib decreased until $T_{max,ss}$ and tended to increase after $T_{max,ss}$. On the contrary, there was a positive linear relationship between the plasma concentration of moxifloxacin and the baseline-adjusted time-matched difference in the QTcI, with a slope of 0.0033 ms/μg/L. This slope was comparable to that in the previously reported data, in which the mean (90% CI) slope of the linear relationship between the baseline-adjusted time-matched mean difference in QTcF and concentration was estimated to be +0.0031 ms/μg/L (0.0028−0.0033) from the QTc model for moxifloxacin, which was developed by pooling data from 20 TQT studies.[27] Also, Kim et al[13] reported that the slope of the baseline-adjusted time-matched mean difference in QTcI versus the concentration of moxifloxacin was +0.0032 ms/μg/L in healthy Korean subjects.

The female subjects tended to have a longer QTc interval in the baseline ECG than did male subjects, and this finding is consistent with a known sex difference.[28] However, the relationship between the study drug exposure and QTcI change in women was not statistically different from that in men, except that the QTcI tended to be longer in women than in men given the same concentration of the study drug. Thus, sex difference in the effect of celecoxib on the QT/QTc interval may not be anticipated.

CONCLUSIONS

The present TQT study conducted in healthy subjects revealed that celecoxib caused no clinically relevant prolongation of the QT/QTc interval at the maximum dose level used in current practice settings. Moreover, the methodology of this study was valid and sensitive enough to establish the effect of celecoxib on the QT/QTc interval.

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DISCLOSURES

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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