Linear Mixed-Effects Model of QTc Prolongation for Olmesartan Medoxomil

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Keywords

olmesartan, angiotensin receptor blocker, cardiac safety, QTc interval, hypertension

Olmesartan medoxomil is a selective angiotensin II receptor antagonist indicated for the treatment of hypertension.[1] In the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP; ClinicalTrials.gov identifier: NCT00185159) study and the Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy Trial (ORIENT; ClinicalTrials.gov identifier: NCT00141453), patients with type 2 diabetes mellitus (T2DM) received either olmesartan medoxomil 40 mg or placebo on a background of other antihypertensive agents to determine if treatment with olmesartan medoxomil would either prevent or delay onset of microalbuminuria and subsequently provide protection against renal disease (ROADMAP) or reduce the incidence of end-stage renal disease (ORIENT).[2,3] An unexpected finding in both the ROADMAP and ORIENT studies was a greater number of deaths from a cardiovascular cause (heart attack, sudden death, or stroke) in patients administered olmesartan medoxomil compared with patients receiving placebo. In ROADMAP, a significantly greater proportion of patients in the olmesartan medoxomil group experienced a fatal cardiovascular event compared with placebo (0.7% vs 0.1%, respectively; $P = .01$), whereas in ORIENT a numerically greater, but not statistically significant, proportion of patients had a fatal cardiovascular event (3.5% vs 1.1% patients, respectively). Therefore, a thorough QTc study was conducted to definitively assess the effects of olmesartan medoxomil on cardiac conduction.[4]

QTc measurements are highly influenced by heart rate and are measured as the interval RR (ie, 60/heart rate) on the electrocardiogram. The conventional corrections include Bazzet's (QTcB) and Fridericia's (QTcF); however, they may not always optimally correct QTc for heart rate. The purpose of this analysis was to explore the relationship between olmesartan plasma concentrations and QTc prolongation potential using (1) a population-optimized RR correction method (QTcP) and (2) a linear regression model with placebo and baseline corrected RR ($\Delta\Delta$RR) and olmesartan effects on QTc, QTcF, and QTcP changes in the thorough QTc study.

Methods

Study Design

A thorough QTc study was conducted as a phase 1, single-center, randomized, single-dose, double-blind, double-dummy, placebo and active-controlled, 4-period crossover study to evaluate the effect of olmesartan medoxomil on QTc prolongation in accordance with the ICH E14 Guidance.[5] The study enrolled 56 healthy male and female subjects (demographics, eligibility criteria, and full methodology details have been previously published). Each subject received single oral doses of 40 mg of olmesartan medoxomil, a 160-mg dose of olmesartan medoxomil, placebo, and 400 mg of moxifloxacin according to the randomization schedule. Blood samples were collected for determination of plasma olmesartan concentrations over 72 hours, and electrocardiograms (ECGs) were measured at the same times up to 24 hours postdose.

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Study Subjects and ECG Data

Fifty-six subjects (28 men, 28 women) were randomized, and 51 subjects completed the study. Mean age of the subjects was 31.9 years (range, 19–45 years) with a mean body mass index of 26.2 kg/m^2 (range, 19.1–30.6 kg/m^2). The primary end point was the baseline-adjusted with time-matched placebo corrections for QTc interval using Fridericia's formula ($\Delta\Delta$QTcF) for therapeutic and supratherapeutic plasma exposures to olmesartan. The Cardiodynamic Analysis Set included 55 subjects who received at least 1 dose of study medications (olmesartan medoxomil, moxifloxacin, or placebo) and had valid baseline and postdose QT/QTc data from at least 1 study period. The Pharmacokinetic Analysis Set included 55 subjects who received at least 1 dose of olmesartan medoxomil and did not have any clinically significant events that may have compromised the integrity of the pharmacokinetic results. Assay sensitivity was demonstrated because the lower limit of the 1-sided 95% confidence interval (CI) was >5 milliseconds of $\Delta\Delta$QTcF for moxifloxacin at the specified times.

Olmesartan Bioanalytical Methods

Plasma olmesartan concentrations were analyzed by Celerion (Lincoln, Nebraska) using a validated liquid chromatography with tandem mass spectrometry method developed by Celerion. An aliquot of human plasma (ethylenediaminetetraacetic acid) containing the analyte and internal standard was extracted using a liquid–liquid extraction procedure. Quantitation was determined using a weighted linear regression analysis (1/concentration^2) of peak area ratios of the analyte and internal standard. The following sets of calibration standards (10 concentrations ranging from 2.5 to 1500 ng/mL), and quality control samples (at 7.5, 37.5, 375, 1150, and 5000 ng/mL) were used for the analysis of clinical samples.

QTc Corrections for Heart Rate

QTc values were plotted versus RR, where RR is 60/heart rate (HR) × 1000 (milliseconds), and was obtained directly from the ECGs by digital extraction of the Holter monitor recording. Correction methods for HR were assessed by identifying the lowest slope of the linear regression and loess lines. The standard correction method used was Fridericia's (QTcF) as QT/RR$^{0.33}$. In addition, the optimal correction factor for the study population was evaluated (QTcP) in the analysis after characterization of population-based RR correction coefficients based on a mixed-effects model.

Evaluation of Population QT Correction Coefficients

Population QTc (QTcP) correction coefficient was evaluated by optimizing the correction coefficient (CC) with 3 decimal points to demonstrate a near-0 slope for RR and QTcP, where QTcP = QT/RR$^{1/CC}$. The correction coefficient estimated for QTcP in this study was 3.265.

Exposure–Response Model

QTc modeling is a good alternative method to assess potential drug-induced cardiac effects in cases when it is not possible to perform such as an analysis in healthy volunteers.[6] The advantage of using an exposure–response analysis for a thorough QT study is that a single model uses all the data across the entire range of plasma concentrations, which results in an improvement in the precision of the estimated QTc effect.[7]

QTc values were corrected for each individual QTc using 3 separate predose measurements at each olmesartan treatment period, denoted as ΔQTc. The ΔQTc values for the olmesartan treatments were further corrected as the difference between time-matched placebo QTc for each individual ($\Delta\Delta$QTc). Similarly, RR values were corrected for each individual RR using 3 separate predose measurements at each olmesartan treatment period, denoted as ΔRR. The ΔRR values for the olmesartan treatments were further corrected as the difference between time-matched placebo RR for each individual ($\Delta\Delta$RR).

Linear regression models for olmesartan plasma concentrations and $\Delta\Delta$QTc were assessed for the 2 olmesartan treatments using a linear mixed-effects model in NONMEM (version 7.1.0; ICON plc, Ellicott City, Maryland). The NONMEM data processing and plots were done in S-Plus. The first-order conditional estimation with interaction method was used. The minimum of the NONMEM objective function value (OFV), typical goodness-of-fit diagnostic plots, and an evaluation of the precision of parameter and variability estimates were used to discriminate between models during the model-building process. The difference of 3.84 in OFV, which follows an asymptotic chi-square distribution, was considered significant (chi-square, $df = 1$, $P < .05$).

Results

Correction Methods for QTc

The plots for the individual values of QT, QTcF, and QTcP versus RR are shown in Figure 1, panels 1–3. Although QTcF and QTcP best corrected for HR resulting in a QTc versus RR slope approaching 0, the higher heart rates (ie, lower RR values) were still poorly corrected as observed in the divergence of the loess curve (shown in blue; Figure 1, panels 2 and 3) from the linear regression line (shown in red; Figure 1, panels 2 and 3). Figure 1 panels 4–6 show the influence of $\Delta\Delta$RR on $\Delta\Delta$QT, $\Delta\Delta$QTcF, and $\Delta\Delta$QTcP. RR uncorrected QT and $\Delta\Delta$QT are linearly correlated with RR and $\Delta\Delta$RR (Figure 1, panels 1 and 4). QTcF and $\Delta\Delta$QTcF showed a slightly negative corelationship (slight
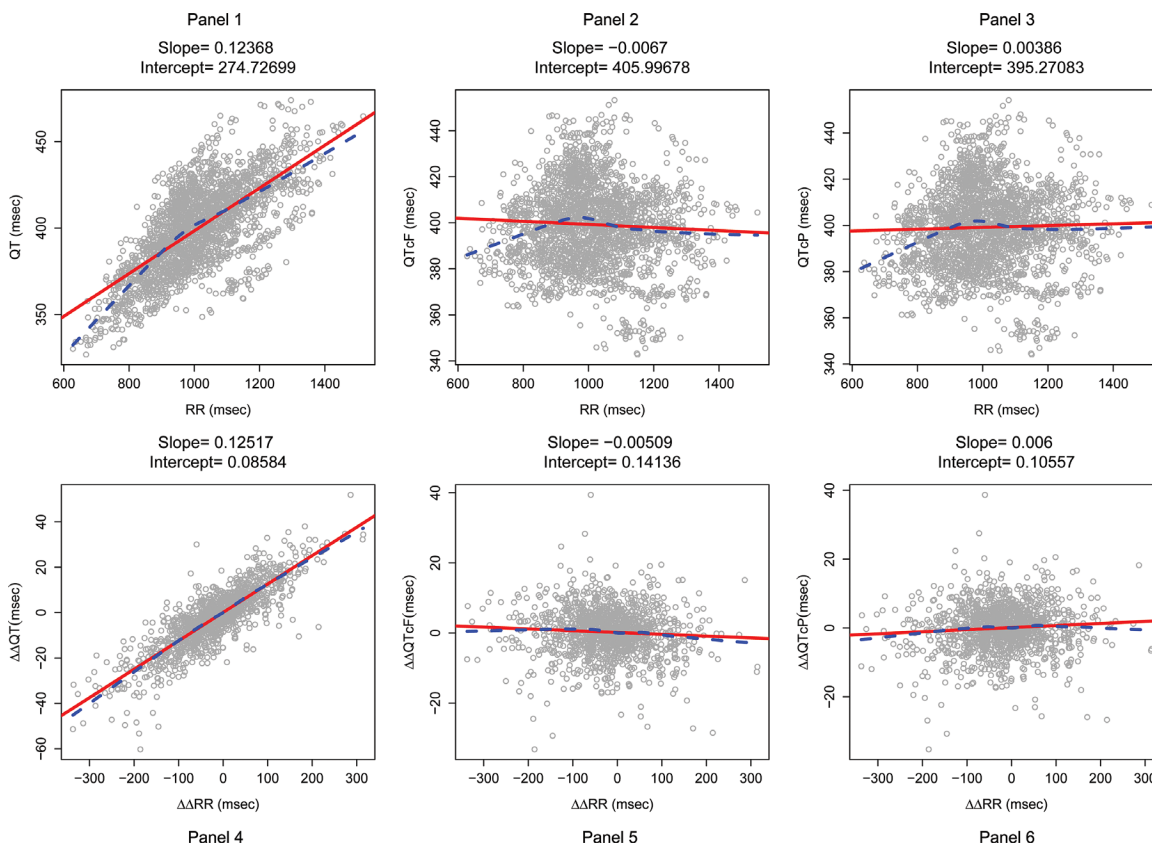
Figure 1. The relationships between QT (in milliseconds) and RR (in milliseconds), panel 1; QTcF (milliseconds) and QTcP (milliseconds) and RR (milliseconds), panels 2 and 3; baseline-corrected, placebo-adjusted RR (ΔΔRR), panels 4, 5, and 6. Blue, loess curve; red, linear regression slope; QT, uncorrected QT interval; QTcF, corrected QT interval using Fridericia's formula; QTcP, population-based corrected QT interval; RR, RR interval in milliseconds; ΔΔRR, baseline-corrected, placebo-adjusted RR; ΔΔQT, baseline-corrected, placebo-adjusted QT; ΔΔQTcF, difference in baseline-adjusted Fridericia's formula-corrected QT interval between placebo and olmesartan; ΔΔQTcP, difference in baseline-adjusted, population-corrected QT interval between placebo and olmesartan.

overcorrection) with RR and ΔΔRR (Figure 1, panels 2 and 5). QTcP and ΔΔQTcP showed a near-zero and slightly positive corelationship (slight undercorrection) with RR and ΔΔRR (Figure 1, panels 2 and 5). It should be noted that there still remain RR influences in the interpretation of QTcF and QTcP prolongation potential. Therefore, there is a methodological advance needs to minimize RR influences on QT prolongation potential independent of RR correction methods.

Exposure–Response Analysis

The effect of the relationship between olmesartan plasma concentrations and ΔΔQT, ΔΔQTcF, and ΔΔQTcP was described by a linear mixed-effects model using the stepwise addition of intercept ΔΔRR and olmesartan concentration (OM$_{conc}$).

$$\Delta\Delta QTc_{ij} = \theta_1 * (1 + \omega_1) + \theta_2 * \Delta\Delta RR_{ij} * (1 + \omega_2) + \theta_3 * OM_{Conc, ij} * (1 + \omega_3) \quad (1)$$

where ΔΔQTc$_{ij}$ is the *j*th observation for individual *i*, θ_1 is the mean value for the intercept for QTc, θ_2 is the mean

value of the coefficient for ΔΔRR for the *j*th observation for the individual *i* included as a covariate, θ_3 is the mean value of the slope for olmesartan concentrations (OM$_{conc}$), and ω^2 is the interindividual variability associated with each parameter. The equation was also used for simulations. The inclusion of intraindividual variability using the additive model below further improved the model fit:

$$\Delta\Delta QTc_{pred} = \Delta\Delta QTc_{ipred} + \sigma_i \quad (2)$$

The stepwise model building with the associated minimum OFV is presented in Table 1. The goodness-of-fit plots (ie, individual predicted vs observed, predicted vs observed, and predicted vs weighted residual) show that the final model for the 3 measures of QTc (ie, QTc, QTcF, and QTcP) resulted in unbiased predictions, as shown in Supplemental Figure 1. The final parameter estimates are presented in Table 2. The slopes for the effect of olmesartan concentrations were similar across QTc (0.000807 ± 0.000390 ms/[ng/mL]), QTcF (0.000816 ± 0.000382 ms/[ng/mL]), and QTcP

Table 1. Stepwise Minimum Objective Function Changes for Linear Mixed-Effects Model for the Dependent Variables ΔΔQTc, ΔΔQTcF, or ΔΔQTcP

Model	Base	Step 1	Step 2	Step 3	ΔΔQTc	ΔΔQTcF	ΔΔQTcP
1	Intercept				13 540.84	10 266.05	10 260.91
2		+ΔΔRRij			9927.30	9875.62	9867.78
3			OM$_{conc}$+ΔΔRRij		9732.14	9678.30	9670.34
4				No intercept	9753.20	9699.51	9691.05
5		+OM$_{conc}$			13 272.47	10 044.93	10 053.12

ΔΔQTc, difference in baseline-adjusted QTc between placebo and olmesartan; ΔΔQTcF, difference in baseline-adjusted Fridericia's formula-corrected QT interval between placebo and olmesartan; ΔΔQTcP, difference in baseline-adjusted population-corrected QT interval between placebo and olmesartan; OM$_{conc}$, olmesartan concentrations; ΔΔRRij, baseline-adjusted QTc for the time-matched placebo value of the *j*th observation for individual *i*.

Table 2. Parameter Estimates for the Linear Mixed-Effects Model for the Effect of Olmesartan Plasma Concentrations (OM$_{conc}$) and Baseline-Corrected, Placebo-Adjusted Heart Rate (ΔΔRR) on ΔΔQTc

Parameter	QTc		QTcF		QTcP	
	Estimate	SE	Estimate	SE	Estimate	SE
Intercept (ms)	−0.15	0.134	−0.129	0.129	−0.156	0.134
θ_3OM$_{conc}$(ms/[ng/mL])	0.000807	0.000390	0.000816	0.000382	0.000800	0.000381
θΔΔRR (ms)	0.128	0.00601	0.000336	0.0000618	0.00646	0.00538
$\omega^2_{Intercept}$	4.81	4.28	−5.73	5.75	4.63	4.02
$\omega^2_{\beta OMconc}$	3.37	1.58	3.27	1.48	3.31	1.52
$\omega^2_{\Delta\Delta RR}$	−0.315	0.0487	−108	2.61	−5.58	4.74
σ^2	4.03	0.208	3.99	0.209	3.99	0.209

QTc, corrected QT interval; QTcF, corrected QT interval using Fridericia's formula; QTcP, population-based corrected QT interval; SE, standard error, θ_3, slope of olmesartan concentration on QTc; θΔΔRR, coefficient for the effect of the baseline-adjusted, time-matched placebo correction for RR on QTc; ω^2, interindividual variability; σ^2, intraindividual variability.

(0.000800 ± 0.000381 ms/[ng/mL]). The coefficient of variation among these 3 slope estimations is 0.99%. The model further identified a significant impact of RR correction represented by 380-fold and 20-fold higher slope of the effect of ΔΔRR for QTc compared with QTcF and QTcP. These evaluations suggest that the mixed-effects model could adequately differentiate the effect of ΔΔRR and perpetrator on QTc prolongation potential, independent of QTc correction methods.

Based on the final model, the predicted mean (1-sided 95%CI or 2-sided 90%CI) ΔΔQTc was 1.815 milliseconds (0.024–3.606 milliseconds) for the highest observed olmesartan plasma concentration associated with the supratherapeutic dose (160 mg) in the thorough QTc study (ie, 2440 ng/mL). In addition, ΔΔQTc values for olmesartan concentrations up to 4500 ng/mL were predicted, and all upper bounds of the 95%CI were <10 milliseconds. Therefore, the QTc effects associated with olmesartan, even at concentrations far surpassing those observed for the supratherapeutic dose, do not reach the pharmacologic threshold effect for QTc prolongation.

Discussion

Results from the ROADMAP and ORIENT studies conducted in patients with T2DM showed numerical imbalances between the treatment groups in these studies in that the olmesartan medoxomil group had an increased number of adjudicated cardiovascular-related deaths compared with those in the placebo group, even though the number of adjudicated nonfatal cardiovascular events was balanced.[2,3] Consequently, data analyses and clinical studies have been recently conducted to provide additional information in regard to the cardiovascular risks and/or benefits of olmesartan medoxomil treatment.[8–10] The present study investigated the effect of therapeutic and supratherapeutic plasma exposures of olmesartan on the duration of the QTc interval after the administration of single oral doses of olmesartan medoxomil in healthy subjects.

The exposure–response relationship between plasma olmesartan concentrations and ΔΔQTc was assessed using a linear mixed-effects model to describe the linear slope for olmesartan concentrations. Terms for interindividual variability and intraindividual variability were included in the mixed-effects model. QTc was adjusted for HR using the standard correction, QTcF, and using QTcP, which was based on the population-fitted slope for QTc and RR to provide a study-specific correction for each subject. Although both QTcF and QTcP provided reasonable corrections for RR, the corrections at high HRs (ie, low values of RR) overpredicted QTc values.

Therefore, the baseline-adjusted and placebo time-matched correction of RR ($\Delta\Delta$RR) was used as a covariate in the regression model to provide more consistent correction, with a slope of approximately 0 across all values of HR (ie, RR). The linear mixed-effects models were established for QTcF, QTcP, and QTc as the dependent variables. The inclusion of $\Delta\Delta$RR as a covariate in the linear mixed-effects model provided adequate evaluation of QTc prolongation potential of olmesartan independent of RR, as manifested by similar slope values for olmesartan concentration and the goodness-of-fit plots. This mixed-effects method or the inclusion of $\Delta\Delta$RR may be helpful, especially in cases in which standard corrections for QTc values do not consistently correct across all ranges of HR, particularly for cardiovascular drugs.[11–13]

Conclusion

Linear regression of QTc versus the baseline-adjusted, time-matched, placebo-adjusted RR ($\Delta\Delta$RR) provided the best correction method of QTc for HR, particularly at the highest values. The linear mixed-effects model used to describe the relationship between olmesartan concentrations and $\Delta\Delta$QTc included $\Delta\Delta$RR as a covariate. The model adequately fit the observed data. The results of this exposure–response analysis confirmed the results from the thorough QTc study, which showed that olmesartan, at both therapeutic and supratherapeutic concentrations, does not prolong the QTc interval.

Declaration of Conflicting Interests

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Supporting Information

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