

Original Article**Exposure-response modeling and clinical trial simulation of the effect of tolterodine on QT intervals in healthy volunteers****Kevin R. Sweeney^{1,*}, Marc R. Gastonguay², Lisa Benincosa³, Carol L. Cronenberger¹, Paul Glue⁴, Bimal K. Malhotra⁵**¹ Pfizer Inc., Groton, CT, USA;² Metrum Research Group LLC, Tariffville, CT, USA;³ Hoffmann-La Roche Inc., NJ, USA;⁴ Dunedin School of Medicine, Dunedin, New Zealand;⁵ Pfizer Inc., New York, NY, USA.

ABSTRACT: The objective of this analysis was to explore exposure-response modeling of data from a thorough QT (TQT) study of tolterodine in CYP2D6 extensive (EMs) and poor metabolizers (PMs). Crossover treatments of the TQT study included the recommended (2 mg twice daily) and supratherapeutic (4 mg twice daily) doses of tolterodine, moxifloxacin (400 mg once daily), and placebo. The concentration-response relationships for the QTc effects of moxifloxacin and tolterodine were described using a linear model with baseline effect, placebo effect, and a drug effect. The mixed effects modeling approach, using the first order conditional estimation method, was implemented in NONMEM. Simulated data from 250 trial replicates were used for limited predictive check and to describe the expected extreme responders in this study, under the derived model and point estimates. Modeling results for tolterodine showed linear concentration-dependent increases in QTc interval, with no difference in slopes between EMs and PMs. Model-predicted QTc prolongations for tolterodine and moxifloxacin were consistent with their respective observed mean results. No subjects were predicted to have increases of > 60 milliseconds (ms); the predicted incidence of borderline QTc increases (> 30 and ≤ 60 ms) remained low at the supratherapeutic tolterodine dose in both PMs (9.1%) and EMs (3.9%). In conclusions, this analysis supports our clinical experience that tolterodine does not have a clinically significant effect on QT interval.

Keywords: Tolterodine, QTc prolongation, exposure-response modeling

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1. Introduction

Tolterodine is an antimuscarinic agent approved for the treatment of overactive bladder (1-3). Metabolism by cytochrome P450 (CYP) 2D6 and 3A4 isoenzymes represents the major route of elimination of tolterodine (4,5). Since CYP2D6 is involved in tolterodine metabolism, both extensive (EMs) and poor metabolizers (PMs) of tolterodine have been identified (6,7). Metabolism of tolterodine by CYP2D6 in EMs results in the formation of an equipotent pharmacologically active metabolite, 5-hydroxy-methyltolterodine (DD01), which has been documented to be comparable to tolterodine in its antimuscarinic activity (8,9). In PMs, however, CYP3A4 is involved in the formation of an inactive metabolite.

Systemic exposure to tolterodine following the recommended 4 mg daily dose is substantially different due to the aforementioned metabolism profiles in EMs and PMs. In EMs, the systemic exposures to tolterodine and DD01 are approximately similar, while in PMs, tolterodine concentrations are higher with virtually no detectable DD01 in serum. The observed pharmacologic effects are attributable to both tolterodine and DD01 in EMs and to tolterodine alone in PMs. The unbound fraction of tolterodine and DD01 is 3.7% and 36%, respectively (10,11), and the combined exposure of unbound active moieties is similar in EM and PM subjects (7). Since antimuscarinic activity is not dependent on metabolizer status, a dosage adjustment is not recommended based on CYP2D6 metabolizer status (7). With respect to drug-drug interactions, in CYP2D6 PMs, there is approximately a doubling of exposure following administration of potent CYP3A4 inhibitors, with a recommendation that dose administration be halved (2 mg daily) (8).

An *in vitro* study of the effects of tolterodine on cardiac ion channels showed that tolterodine is a potent inhibitor of both human ether a-go-go-related

gene (HERG) cardiac potassium and L-type calcium channels (12). The HERG inhibitory concentration 50% value (IC_{50}) was reported to be 17 nM, with some inhibition evident at concentrations as low as 3 nM (12). These activities resulted in a prolongation of action potential duration, but not to the extent observed with dofetilide, a pure HERG blocker (12). For drugs like tolterodine and verapamil, it has been hypothesized that blocking the cardiac L-type calcium channel, at least in part, serves to counteract the QT prolonging effects of HERG potassium channel blockade (12).

Despite extensive post-registration clinical experience and a lack of cardiac arrhythmic events potentially related to QT interval prolongation, a thorough QT (TQT) study was deemed to be important for a definitive assessment of the effects of this agent on the QT interval in view of the positive results in the preclinical HERG assay. With few exceptions, regulatory agencies now require a TQT study not only for drug candidates in clinical development, but also for marketed drugs (13). Therefore, a TQT study was performed in healthy subjects to evaluate the potential of tolterodine to alter cardiac electrical conductivity using the recommended and twice the recommended doses.

The results of this tolterodine TQT study have been previously published (14). There were four treatment arms in this crossover study in both CYP2D6 EM and PM subjects: 1) tolterodine immediate release (IR) tablets at the recommended dose (2 mg BID); 2) tolterodine IR at a supratherapeutic dose (4 mg BID); 3) moxifloxacin (400 mg QD) as a positive control and 4) placebo. The supratherapeutic tolterodine dose was selected to provide systemic exposures consistent with the increases in exposures observed following CYP3A4 inhibition. This current work details the exposure-response modeling of data collected as part of this TQT assessment of tolterodine.

2. Materials and Methods

2.1. Study design

This was a positive- and placebo-controlled, multiple-dose, 4-way crossover study conducted at 2 centers. This study evaluated the single-dose and steady-state QTc effects of the recommended (2 mg twice daily) and supratherapeutic (4 mg twice daily) doses of tolterodine IR and the positive control, moxifloxacin (400 mg once daily), each compared with placebo. Treatments were administered for 4 days (morning dose only on Day 4), with a washout period of ≥ 5 days between periods. Moxifloxacin was included as a positive control to confirm the sensitivity of the study to detect small increases in the QTc interval. Moxifloxacin is frequently used in TQT studies because it has a well-defined QTc prolongation effect, usually about 6 to 12 ms.

A total of 48 subjects were enrolled for this study. At the time of study enrollment, subjects were categorized as either extensive metabolizers (EM, $N = 26$) or poor metabolizers (PM, $N = 22$) for CYP2D6, as assessed by genotyping (14). Eligible study participants were men and women between the ages of 18 and 55 years, with a body mass index of 18 to 30 kg/m². All subjects reported to the clinic two days prior to initiation of dosing in each treatment period. During each period, baseline and on-treatment ECGs were obtained in triplicate at pre-specified time points, with the consecutive replicates about 2 min apart.

Electrocardiograms were obtained within 1-hour predose on the mornings of Days 1-4 in each period. In addition, ECGs were obtained at 0.5, 1, 2, and 4 h postdose on Day 1 and at steady state (Day 4) at 0.5, 1, 2, 3, 4, 6, 9, and 12 h postdose. Baseline ECGs were performed on Day 0 at the same times of the day (time-matched) as those on Day 4. All ECG data used in the PK/PD analysis were machine-read (GE Marquette's MAC 1200[®] ECG recorders, GE Medical Systems, Milwaukee, WI, USA), and obtained in triplicate. Malhotra *et al.* have published additional information on ECG collection and study conduct (14).

2.2. ECG data

An initial graphical assessment was performed to assure that pre- and post-treatment heart rate (HR) distributions were similar prior to generation of heart rate adjusted data. After verifying the similarity of the distributions, corrected QT interval (QTc), period- and subject-specific baseline-subtracted QTc interval (Δ QTc or Δ QTc) data were generated.

All QT intervals were adjusted to a HR of 60 beats/minute (bpm). Methods used to generate heart rate corrected QTc values from QT and RR intervals were the Fridericia ($QTcF = QT/RR^{0.33}$), Bazett ($QTcB = QT/RR^{0.50}$), and study-specific population ($QTcP = QT/RR^{0.41}$) correction formulae (15), where RR equals 60/HR and 0.41 represents the mean study-specific correction factor across the four baseline periods. The exponent for RR in the study-specific population correction formula was determined as the slope of the regression of $\ln(QT)$ versus $\ln(RR)$. In addition to the population-specific correction factor, an individual-specific correction factor was generated. This factor was obtained in similar fashion to the population-specific factor outlined above except that a correction factor was generated from each individual's baseline data. Therefore, this correction factor is individual-specific and period-specific. QTcI denotes the heart-rate adjusted QT interval using the individual correction.

Following application of the correction formulae to pre- and post-treatment QT interval data, Δ QTc data were derived as corrected QT interval minus the period- and subject-specific, time-matched baseline data. Plots

of corrected QT interval (QTcF, QTcB, QTcP and QTcI) versus HR data were constructed to assess the adequacy of each heart rate correction factor. Acceptable correction was defined as no apparent relationship between corrected QT interval and heart rate.

2.3. Concentration data

During each treatment, 2 sets of blood samples were obtained at the same time point as the ECGs. One set of samples was processed for the analyses of tolterodine and DD01 in serum and the other for moxifloxacin in plasma, as described by Malhotra *et al.* (14).

Since pharmacologic activity is a function of unbound drug concentration, and there is a significant difference in the free fraction of active moieties (16), period- and subject-specific unbound fractions for tolterodine ($f_{u,Tolterodine}$) and DD01 ($f_{u,DD01}$) were calculated from alpha₁-acid glycoprotein (AAG) concentrations using the following formulae (17):

$$f_{u,Tolterodine} = 1/(1 + (2100 \cdot AAG/42))$$

$$f_{u,DD01} = 1/(1 + (130 \cdot AAG/42))$$

Individual concentration-time data for tolterodine, DD01 and moxifloxacin on Days 1 and 4 were analyzed by a standard non-compartmental approach using WinNonlin Enterprise (Pharsight Co., Mountain View CA, Version 3.2) (14). Maximum observed concentrations (C_{max}) and time of C_{max} (T_{max}) were obtained by direct observation of the experimental data. Area under the concentration-time curve (AUC) was calculated using the linear-log trapezoidal rule.

2.4. Concentration- Δ QTc analysis

The concentration-response relationships for moxifloxacin and tolterodine were modeled using machine-read QT interval data which were collected at baseline (Day 0), after the first dose (Day 1), pre-dose on Days 2 and 3, and at steady state (Day 4). This dataset provided the most complete and comprehensive range of exposures for modeling the concentration-response relationships. For heart-rate correction, the population-corrected Δ QTcP data were used as the population correction appeared to best eliminate the QT dependence on heart rate, as evidenced by the slope closest to zero in Figure 1. This model characterized the relationship between Δ QTcP interval and concentration, accounting for placebo, baseline, and drug effects. For the tolterodine- Δ QTcP effect modeling, contributions to the observed QTc prolongation were assumed from both the parent drug and its primary active metabolite, DD01.

Since there is an approximately 10-fold difference in unbound fraction of DD01 compared with tolterodine, the pharmacokinetic/pharmacodynamic (PK/PD)

analysis was performed using the sum of unbound serum concentrations along with a modeled relative potency factor of IKr-channel antagonism *in vivo* by both tolterodine and DD01. A similar model was fitted to Δ QTcP interval versus moxifloxacin total plasma concentration data. Because there was no apparent nonlinearity when the data were graphically displayed, a population mixed effects modeling approach using linear models was employed to characterize the concentration- Δ QTcP relationship. The mixed effects modeling approach was implemented in NONMEM Version V Level 1.1 (ICON Development Solutions, Ellicott City, MD, USA and NONMEM Project Group, UCSF, San Francisco, CA, USA) using the first order conditional estimation method.

2.5. Δ QTc model definition

The relationship between Δ QTcP interval and tolterodine/DD01 serum concentration was described using a linear model with baseline effect, placebo effect, and a drug effect. The placebo parameter ($PCBO_i$) describes the average offset of Δ QTcP that can be attributed to the placebo treatment. The baseline parameter ($BSLN_i$) describes the average Δ QTcP interval in the absence of any drug-induced effect for each individual contributing data (predose, Day 0 data). The slope parameter (SLP_i) describes the dependence of Δ QTcP interval on serum concentration for each individual following tolterodine administration. The potency (POT) parameter accounts for the potential difference between tolterodine and DD01 metabolite in ability to block IKr channels. The model with $BSLN_i$, $PCBO_i$, SLP_i and POT parameters, and associated variances, is presented below:

$$PCBO_i = \theta 1 + \eta 1$$

$$BSLN_i = \theta 2 + \eta 1$$

$$SLP_i = \theta 3 + \eta 2$$

$$POT = \theta 4$$

$$\Delta QTcP_{i,j} = PCBO_i + BSLN_i + SLP_i \times (C_{tolterodine_{i,j}} + POT \times C_{DD01_{i,j}}) + \epsilon_{i,j}$$

In these equations, $\Delta QTcP_{i,j}$ is the j^{th} Δ QTcP observation for the i^{th} individual, $\theta 1$ represents the population mean estimate of the placebo effect, $\theta 2$ represents the population mean estimate of the baseline Δ QTcP, $\theta 3$ represents the population mean estimate of the slope describing concentration effect, $\theta 4$ represents the population mean estimate of the relative potency between tolterodine and DD01 metabolite, $\eta 1$ represents the inter-individual random effect for the placebo and baseline parameters, assumed to be a normal, independent, identically distributed random variable with zero mean and variance ω_1^2 (\sim NIID(0, ω_1^2)), and $\eta 2$ represents the inter-individual random effect of the slope parameter (\sim NIID(0, ω_2^2)). The $\epsilon_{i,j}$

parameter represents the j^{th} residual error for the i^{th} individual and is assumed to be a normal, independent, identically distributed random variable with zero mean and variance σ^2 ($\sim \text{NIID}(0, \sigma^2)$). An additive model (constant variance) was used for the inter-individual random effect distributions, allowing for these effects on ΔQTcP interval to be positive or negative across individuals.

A similar analysis was conducted on the observed $\text{DQTcP}_{i,j}$ versus moxifloxacin plasma concentration data. The difference from the model presented above is that total concentration of moxifloxacin was used, as there is no active metabolite. The equation used is as follows:

$$\begin{aligned}\text{PCBO}_i &= \theta_1 + \eta_1 \\ \text{BSLN}_i &= \theta_2 + \eta_1 \\ \text{SLP}_i &= \theta_3 + \eta_2 \\ \Delta\text{QTcP}_{i,j} &= \text{PCBO}_i + \text{BSLN}_i + \text{SLP}_i \times (C_{\text{MOXI},i,j}) + \varepsilon_{i,j}\end{aligned}$$

In this equation, all terms are as defined above, with the difference that $\Delta\text{QTcP}_{i,j}$ values are associated with the respective moxifloxacin concentration and no potency parameter was necessary since there is no active metabolite of moxifloxacin.

2.6. Model evaluation

A linear model was fitted to ΔQTcP data using the first order conditional method of estimation. Bootstrap analysis was employed to generate a 95% CI constructed about each of the parameters in the final model. Model estimates and associated CI were used to characterize the magnitude and estimate confidence (precision) of parameters in the linear model, even those that may be associated with "no effect".

Model performance was assessed by performing a predictive check using the final model and final parameter estimates, generating distributions of simulated maximum ΔQTcP values by tolterodine dose and genotype status, with the respective observed mean maximum ΔQTcP value by tolterodine dose level and genotype status superimposed onto the appropriate distribution. A total of 250 replicates of this study were simulated.

A variety of QTc-derived ECG indices may be analyzed to evaluate the effect of a drug on ventricular repolarization and the potential clinical risk of torsades de pointes (TdP). In addition to the population-based mean increase in placebo-corrected maximal QTc interval, a frequently used index is the number of subjects with a > 60 ms increase in QTc interval from baseline (13,19). Therefore, a second simulation with uncertainty around all parameter estimates was performed to provide insight into extreme responder individuals (e.g. individuals identified with ΔQTcP values defined as borderline or prolonged) and to make

a statement about model performance. To address the question of extreme responder individuals, the median percentage of individuals with ΔQTcP values in the following categories were tabulated by tolterodine dose level and genotype status:

- ≤ 30 ms (Normal)
- > 30 and ≤ 60 ms (Borderline)
- > 60 ms (Prolonged)

These categories were selected based on the recommendations in the ICH-E14 guidance (13). Additionally, the 95% confidence interval for each of these values was also generated and reported.

3. Results

3.1. Tolterodine and DD01 exposures

Tolterodine was quickly absorbed and systemic exposure increased proportionally between the 2 and 4 mg doses. The tolterodine C_{max} and AUC were approximately 3-5 and 10 times greater, respectively, in PMs than in EMs. In EMs, DD01 exposure increased proportionally with dose, consistent with exposure of tolterodine. The systemic exposure of DD01 in PMs was 6-7 times less than that of EMs (14).

3.2. Corrected QT interval

The observed heart rates in baseline (Day 0) and respective treatment periods were similar in range and distribution. The range of heart rates for baseline ($n = 1,286$), placebo ($n = 752$), tolterodine 4 mg/day ($n = 768$) and tolterodine 8 mg/day ($n = 768$) and moxifloxacin ($n = 543$) groups were 41-105, 45-101, 45-97, 40-97 and 43-101 bpm, respectively. Correction methods previously described (15) were applied to the QT data in an effort to eliminate the QT interval dependence on heart rate, and permit the use of a linear model for analysis. Graphical representation of baseline QTc interval versus baseline heart rate is presented for each correction method (Figure 1).

The study-specific population correction (bottom left panel) appeared to best correct QT interval over the observed heart rate range. All other correction methods did not appear to adequately correct the observed dependence of QT interval on heart rate. This is represented by the non-horizontal pattern of the data.

Following the regression of $\log(\text{QT})$ on $\log(\text{HR})$, the population correction factors for each of the four Day 0 baseline periods were: Period 1, 0.414; Period 2, 0.423; Period 3, 0.407; and Period 4, 0.394. These period-specific correction factors were then used to generate heart rate adjusted QTc interval data using the population correction method described previously, and appropriate baseline data were then used to

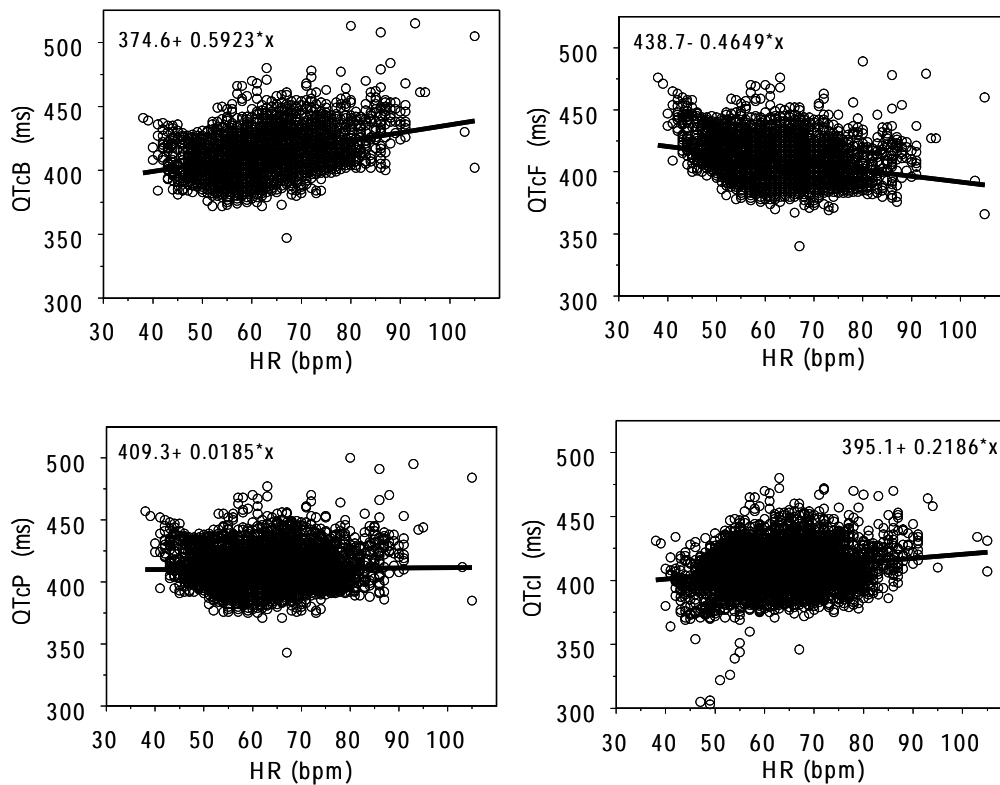


Figure 1. Corrected baseline (Day 0) QT interval (fridericia, bazett, population and individual correction) versus baseline (Day 0) heart rate.

generate Δ QTcP. Analysis of the effect of tolterodine/DD01 concentration on Δ QTcP was performed and conclusions drawn from subsequent results.

3.3. Moxifloxacin plasma concentration- Δ QTcP analysis

Moxifloxacin was included in this study as a positive control to validate the ability to detect a positive signal when present (13). The slope (%SE) from this analysis was 0.00300 (0.000475) ms/ng/mL, with a 95% CI constructed about slope of 0.00207 to 0.00393 ms/ng/mL. Given the exclusion of zero in this CI and the good precision of the parameter estimate (%SE = 15.8), the slope estimate was sufficiently robust for making clinical inferences. The observed C_{max} on Day 4 was 3,610 ng/mL, translating to a Δ QTcP prolongation of 10.8 ms, consistent with historical data describing the effects of moxifloxacin on QT interval prolongation.

3.4. Tolterodine/DD01 serum concentration- Δ QTcP analysis

Results from the concentration- Δ QTc model fitted to the Δ QTcP interval versus unbound serum concentration data are provided in Table 1. As a measure of precision of model estimates, the asymptotic relative standard errors (%SE) of the placebo, baseline, slope and potency, and associated inter-individual variance (IIV)

Table 1. Modeling results of the study-specific population Δ QTcP interval vs. unbound serum tolterodine and DD01 concentration analysis

Parameter	Parameter Estimate	%SE ^a	95% CI ^b
Placebo (ms)	0.362	216	-1.32 to 1.98
Baseline (ms)	0.321	241	-1.31 to 1.72
Placebo/Baseline IIV ^c (ms ²)	3.62	34.5	–
Slope (ms/ng/mL)	13.4	26.7	6.90 to 21.9
Slope IIV ^c (ms/ng/mL) ²	118	37.1	–
Potency	0.140	48.7	-0.306 to 0.227
Residual Variances (ms ²)	67.3	10.3	–

^a%SE (precision) of the parameter estimate = 100*SE/Mean; ^b95% CI based on Bootstrap Analysis; ^c Inter-individual variance; ^d Intra-individual (residual) variance.

parameters were generated. Precision of slope was very good, as evidenced by the low %SE (26.7). Precision of placebo and baseline was not precisely estimated given the rather high %SE (216 and 241, respectively). Residual error was low (67.3 ms², or 8.20 ms expressed as a standard deviation) and precisely estimated (%SE = 10.3). The 95% CI on slope (6.90 to 21.9) did not contain zero and is consistent with the good precision of the slope estimate. The 95% CI for placebo, baseline and potency parameters all enclosed zero, consistent with the large %SE associated with each of these parameters.

Figure 2 presents a plot of Δ QTcP interval versus unbound tolterodine and DD01 serum concentration,

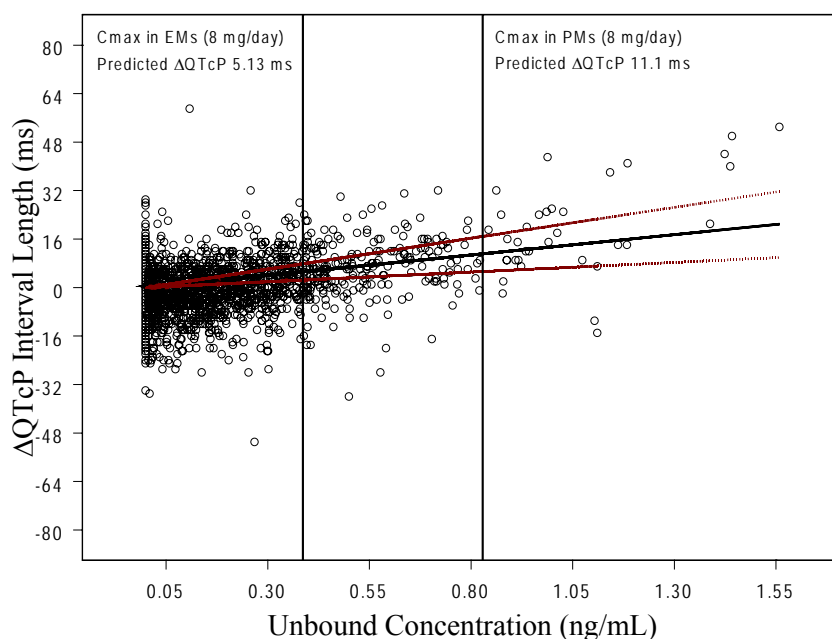


Figure 2. Population Δ QTcP interval versus unbound tolterodine/DD01 serum concentration following twice-daily oral administration of tolterodine immediate release tablets. Lines denotes NONMEM population model predicted slope and 95% CI estimates.

Table 2. Summary of mean unbound concentrations of tolterodine and DD01 metabolite and model-Predicted prolongation at T_{max} , by genotype and administered dose

Group	Unbound Tolterodine (ng/mL)	Unbound DD01 (ng/mL)	Normalized Concentration ^a (ng/mL)	Predicted Prolongation (ms)
EM 2 mg BID ^b	0.0790	0.814	0.193	2.59
EM 4 mg BID ^c	0.159	1.60	0.383	5.13
PM 2 mg BID ^d	0.392	0.102	0.406	5.44
PM 4 mg BID ^e	0.793	0.230	0.825	11.1
Study Population 2 mg BID ^f	–	–	–	3.90
Study Population 2 mg BID ^f	–	–	–	7.87

^a Unbound Tolterodine Concentration + POT*Unbound DD01 Concentration; ^b Extensive metabolizers administered 2 mg every 12 h (4 mg/day); ^c Extensive metabolizers administered 4 mg every 12 h (8 mg/day); ^d Poor metabolizers administered 2 mg every 12 h (4 mg/day); ^e Poor metabolizers administered 4 mg every 12 h (8 mg/day); ^f (Study population genotype-specific mean prolongation*respective number of individuals)/total number of individuals in the study.

including the 95% CI constructed about the slope estimate. In Figure 2, the vertical reference lines denote the mean unbound C_{max} in EMs and PMs receiving the tolterodine supratherapeutic dose, and the corresponding QTc prolongations are noted for each C_{max} . Table 2 presents mean tolterodine and DD01 unbound concentration by dose level and genotype (EM = extensive metabolizer, PM = poor metabolizer), along with estimates of predicted QTc interval at T_{max} . Additionally, prolongation estimates by dose group in

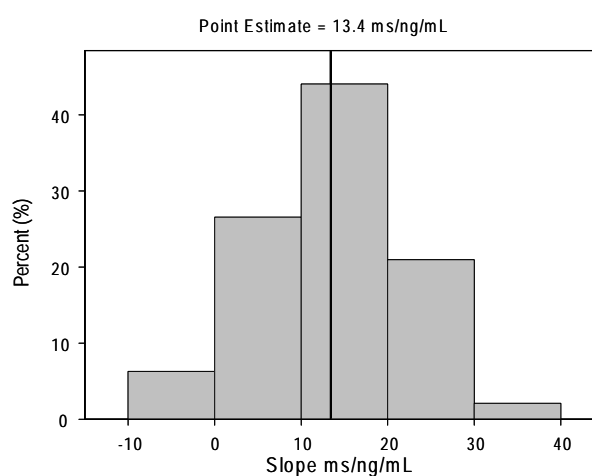


Figure 3. Population distribution of slopes from describing Δ QTcP interval versus unbound tolterodine/DD01 serum concentration following twice-daily oral administration of tolterodine immediate release tablets.

the pooled study population (enriched for PMs) were calculated.

A histogram distribution of slope across the 48 individuals in the study is presented in Figure 3. The range of slopes by genotype was as follows: EM, -7.66 to 27.7 ms/ng/mL; PM, 0.24 to 31.9 ms/ng/mL. The highest observed slopes were comparable in the EM and PM subgroups (31.9 ms/ng/mL and 27.7 ms/ng/mL, respectively). The similarity of slope ranges between EM and PM subjects suggested that there was

no difference by CYP2D6 genotype in sensitivity to tolterodine/DD01 with respect to QTc prolongation.

3.5. Δ QTcP simulation

A simulation of 250 trial replicates was performed and a limited predictive check was conducted using the simulated data as a measure of model performance. Final parameter estimates of the model were used to generate simulations of Δ QTcP interval values as a function of random noise and unbound concentration of tolterodine and DD01 metabolite. Five distributions of simulated maximum Δ QTcP were generated: EM subjects at the 2 and 4 mg BID dose level, PM

subjects at the 2 and 4 mg BID dose level, and placebo. The respective mean observed maximum DQTcP in the study was superimposed on each of the five distributions identified above. In each of the five groups, the observation of mean maximum Δ QTcP fell within the distribution: 11, 16, 16, 20 and 9 ms for the 2 mg BID EM, 4 mg BID EM, 2 mg BID PM, 4 mg BID PM and placebo subjects, respectively. Overall performance of the model as a Monte Carlo simulation tool was acceptable, but some over-prediction was evident for the placebo group. These distributions are presented in Figure 4.

Additionally, the simulation with uncertainty (250 trial replicates) was used to describe the expected

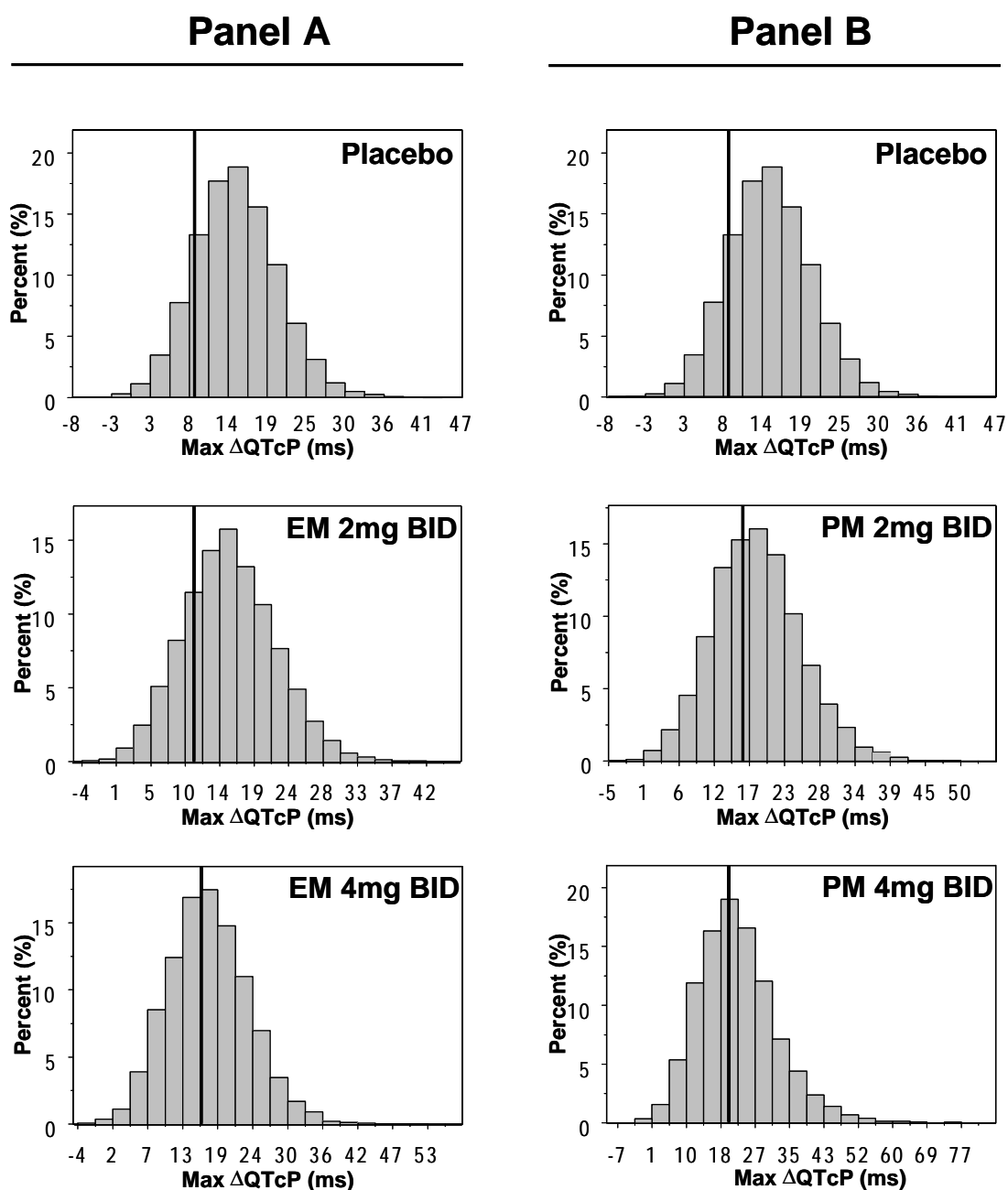


Figure 4. Simulated distributions and observed mean (solid line) maximum Δ QTcP interval by dose group and genotype following twice-daily oral administration of tolterodine immediate release tablets. Panel A: Extensive metabolizers. Panel B: Poor metabolizers.

Table 3. Trial simulation results for median percent (95% CI) of subjects predicted to exhibit prolongation, stratified by tolterodine dose level and genotype status

Dose Group	Genotype	% Subjects Predicted for Categorical Increases in Δ QTcP		
		Normal (≤ 30 ms)	Borderline (> 30 and ≤ 60 ms)	Prolonged (> 60 ms)
Placebo	EM/PM	100 (93.6 to 100)	0 (0 to 0)	0 (0 to 0)
2 mg BID	EM	100 (92.3 to 100)	1.92 (0.0962 to 3.75)	0 (0 to 0)
4 mg BID	EM	96.2 (88.5 to 100)	3.85 (0.192 to 7.50)	0 (0 to 0)
2 mg BID	PM	95.5 (81.8 to 100)	4.55 (0.227 to 8.86)	0 (0 to 0)
4 mg BID	PM	81.8 (63.6 to 95.5)	9.09 (0.455 to 17.7)	0 (0 to 4.55)

extreme responders in this study, under the derived model and point estimates. A categorical tabulation of median percent maximal prolongation with associated 95% CI by dose level and genotype was generated, with values less than or equal to 30 ms, greater than 30 and less than or equal to 60 ms, and greater than 60 ms reported. These simulated values were consistent with observations made during the conduct of the study. Results are presented in Table 3.

4. Discussion

A thorough QT study was conducted to investigate the potential effect on the QTc interval following oral administration of tolterodine (2 and 4 mg BID, 4 and 8 mg/day total dose, respectively). Based on the statistical analyses of the machine-read QTcF data for the pool of EM and PM subjects combined, a negative TQT conclusion could be made for both recommended and supratherapeutic doses of tolterodine (14). The modeling results also predicted only small increases in QTc interval following tolterodine administration and were consistent with the traditional statistical analysis. Concentration-QTc modeling approaches were used to further investigate the effects of tolterodine on QTc interval in EMs and PMs separately. An estimation approach was employed, using bootstrap estimates to make inference regarding model parameters.

The systemic exposures and pharmacokinetic profiles of tolterodine and DD01 were consistent with those previously reported in both EM and PM subjects, suggesting that the results of the PK/PD analysis of a potential QT effect would be indicative of the population at large (5). Additionally, exposure observed in PMs receiving twice the recommended daily dose (4 mg BID) approximated that observed in PMs administered the recommended daily dose (2 mg BID) allowing the concentration-response relationship to be descriptive of PMs whose tolterodine exposure is inadvertently increased by concomitant dosing with a potent CYP3A4 inhibitor. The moxifloxacin exposure in this study was consistent with values reported in the product label (18).

Four correction methods were investigated to eliminate the dependence of QT on heart rate. The

study-specific population method was determined to be the best method for generation of QTc data, as the Fridericia, Bazett and Individual methods retained some bias. Following appropriate correction of the observed QT data, Δ QTc data were generated using time-matched and period-specific Day 0 baseline data. The Δ QTcP data were used as the primary endpoint in this modeling analysis. A linear model characterized the relationship between Δ QTcP and concentration, accounting for placebo, baseline and drug effects. Since the DD01 metabolite is reported to be pharmacologically active, and there is an approximate 10-fold difference in unbound fraction when compared to tolterodine, the analysis was performed using unbound serum concentrations with a potency correction for DD01 metabolite based on observed differences in IKr channel blocking activity *in vitro*. A similar model was fitted to Δ QTcP interval *versus* moxifloxacin total plasma concentration data. The differences were that total concentration was used and no potency correction factor was necessary.

Results of the moxifloxacin analysis were consistent with generally accepted prolongation values, validating the sensitivity of study conduct. The global mean concentration of moxifloxacin was 3,610 ng/mL. The slope describing QTc prolongation in this study was 0.00300 ms/ng/mL, translating to an average prolongation of 10.8 ms. There was a high degree of confidence in this value since the 95% CI constructed about the moxifloxacin slope was relatively narrow and did not include zero (0.00207 to 0.00393 ms/ng/mL).

Results of the tolterodine/DD01 analysis indicated a population slope estimate (95% CI) of 13.4 (6.90 to 21.9) ms/ng/mL. This parameter was well-estimated as evidenced by the relative standard error of 26.7%. CI constructed about the placebo and baseline model parameters enclosed the null value, suggesting that these were essentially zero. Additionally, the potency parameter 95% CI also enclosed zero, but this was retained in the model as there are pre-clinical data supporting differences in HERG blockade between tolterodine and DD01 metabolite. This result was most likely due to the relatively small numbers of subjects in the study. Residual variability was low, 8.20 ms when expressed as a standard deviation.

The current analysis of tolterodine/DD01 data indicated that tolterodine administration elicited only a small effect on the QTc interval. However, since PM subjects exhibited higher concentrations of tolterodine, they potentially represent a group with greater QTc interval prolongation. Separating the population of subjects by genotype, an estimate of prolongation was determined for EM and PM subjects by dose level, by identifying the respective dose-specific mean C_{max} . Tolterodine appeared to cause a small QTc interval prolongation which is at or below the threshold of clinical significance in EM subjects, irrespective of dose (2.59 and 5.13 ms for the 2 and 4 mg BID doses, respectively). This statement is supported by the current ICH E14 concept paper suggesting that a mean change of "around 5 ms" in the QT/QTc interval is viewed as clinically not important (13).

PM subjects administered the recommended dose of tolterodine appeared to exhibit a small QTc interval prolongation (5.44 ms) which is at the threshold of clinical significance; the model-predicted magnitude of effect in EMs given the suprathreshold dose is similar to that in PMs given the recommended dose of tolterodine. The suprathreshold dose of tolterodine was predicted to prolong QTc interval in PM subjects by 11.1 ms. Although the effect in PMs receiving the suprathreshold tolterodine dose was above 5 ms, it remained well below the 20 ms threshold above which drugs have a substantially increased likelihood of being proarrhythmic, and might have clinical arrhythmic events captured during drug development (13,19). Overall, the results of this analysis support a conclusion that tolterodine administration at recommended doses (2 mg BID) to all subjects or twice the recommended dose to EM subjects appears to have a low potential for QT prolongation.

Model performance was assessed and validated by a predictive check. Essentially, this method of validation assessed the ability of the model to reproduce the observed data. A particular characteristic of the data, maximum $\Delta QTcP$ in this study, was summarized from both observed and simulated data. Concordance of these summaries is an indication of acceptable model performance. Following simulation of 250 trial replications, maximum $\Delta QTcP$ distributions by dose level and genotype were constructed. The respective mean observed maximum $\Delta QTcP$ was then superimposed onto each distribution. Since the observation of maximum $\Delta QTcP$ by dose level and genotype was positioned centrally in each distribution, the model performed very well, validating conclusions drawn from the modeling effort.

Lastly, simulations of expected extreme responders support above statements on prolongation potential. The categorical analysis of these data indicates that the median percentage of subjects predicted to exhibit borderline prolongation (> 30 and ≤ 60 ms) was small

following administration of the recommended dose of 2 mg BID, irrespective of genotype status (1.92% and 4.55% for EM and PM subjects, respectively). The percentage of EM subjects predicted to show borderline prolongation at the suprathreshold dose was also small (3.85%), indicating minimal prolongation potential. A somewhat greater percentage of PM subjects (9.09%) were predicted to have borderline prolongation upon administration of the suprathreshold dose. QTc interval prolongation of clinical concern (> 60 ms) was not predicted at either dose, irrespective of metabolizer status, as median percent of subjects predicted to exhibit prolongation was zero. Based upon these simulations, there appears to be minimal potential of any subject being classified as an extreme responder to tolterodine and DD01 metabolite.

In conclusion, the systemic exposures of tolterodine, its DD01 metabolite and moxifloxacin were consistent with previous reported results. Based on the exposure-response analysis of data collected from a thorough QT study, tolterodine appears to have a low potential for QT prolongation. Model-predicted mean changes in QTc for both tolterodine and moxifloxacin were consistent with the corresponding statistical estimates. Based on simulation of 250 trials, no subjects were predicted to have increase of > 60 ms; the predicted incidence of borderline QTc increases (> 30 but less than ≤ 60 ms) remained low at the suprathreshold tolterodine dose in both PMs and EMs. These analyses confirm our clinical experience that tolterodine does not have a clinically significant effect on QT interval.

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