Quantifying the Effects of Frequently Prescribed Antimicrobials with Perceived Potential for QT Interval Prolongation during the COVID-19 Era

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ABSTRACT

Background: Countless diseases and medications have been implicated in the past as causing prolongation of the QT interval. Their unique role through the means of quantifying the definite magnitude of relative risk they contribute during hospitalization still requires further investigation. The aim of this study was to describe the impact of commonly used anti-infectives on the QT interval in hospitalized patients during the COVID-19 era.

Methods: Demographic information, medical history, laboratory data, medication administration history and ECG recording data was collected from the electronic records of adult patients admitted to two urban hospitals. A mixed effects approach with four sub-models for the QT interval comprised of: heart rate, circadian rhythm, gender, and the drug (regressed as the cumulative mg dose administered over time) and disease effects was used. Fixed and random effects with between occasion variability were estimated for the parameters with a Bayesian approach using the STAN software.

Results: Data from 2180 patients were used with baseline characteristics shown in Table 1. Observed vs. predicted plots based on the training (Figure 1.A) and validation data set (Figure 1.B) showed excellent fit. The parameters for QTc0, α, gender, and circadian rhythm were identified within the range previously described (Table 2.). Similarly, the model correctly identified the impact of acute or chronic diseases on the QT interval. Model coefficient estimates [mean (95% CI) of 0.010 (0.006, 0.15) and 0.0045 (0.0013, 0.01100) msec/mg cumulative dose, respectively] suggest that patients treated with conventional regimens of fluconazole and levofloxacin are most likely to present with a QT interval increase > 5 msec, the cutoff threshold of regulatory concern.

Conclusion: The model developed accurately identified the impact baseline risk factors and concomitant medications have on the QT interval. When adjusted for these confounding variables, estimates of QT interval prolongation show that treatment with fluconazole and levofloxacin pose a considerable risk; while treatment with azithromycin or hydroxychloroquine is of moderate risk for QT interval prolongation.

INTRODUCTION AND OBJECTIVES

- In the US, between 300,000-400,000 people die annually of sudden cardiac arrest[1]
- TdP, a potentially fatal polymorphic ventricular tachyarrhythmia, often occurs in association with a prolonged QT interval that may present as sudden death, syncope, dizziness, palpitations, seizures, ventricular tachycardia, or be asymptomatic[1]
- Antimicrobials carry the potential to cause cardiac arrhythmias, from their propensity to bind to the delayed rectifier potassium channel resulting in QT prolongation and risk of TdP or by their frequent interference with the metabolism of other QT prolongers and their susceptibility to metabolic inhibition by commonly used drugs[2,3]
- Those implicated from this class include the macrolides, fluoroquinolones, some antimalarials, pentamidine, hydroxychloroquine, and the azole antifungals[3]
- Despite the long-standing documentation of antibiotic-associated QT prolongation and resultant life-threatening ventricular arrhythmias, little data exists regarding the means of quantifying this risk
- The aim of our study was to develop a linear mixed effects pharmacodynamic model and investigate the impact of cumulative doses of commonly used antimicrobials on the QT interval in hospitalized patients

METHODS

- Demographic, diseases, laboratory, medication administration history and ECG recording data was obtained retrospectively from adult patients hospitalized between 7/2018 and 4/2020.
- A fully Bayesian approach with Markov chain Monte Carlo method was employed for building a linear mixed-effects model using STAN via the brms package in the R® software
- Structural model for QT interval is as follows:

$$QT = QT_{C0} * RR^{\alpha} + A * cos\left(\frac{2\pi}{24} * (t - \emptyset)\right) + \theta_{Azi} * Azi_i + \theta_{Fluc} * Fluc_i + \theta_{Levo} * Levo_i + \theta_{HCQ} * HCQ_i + \theta_{Hal} * Hal_i + \theta_{Met} * Met_i + \theta_{Que} + \theta_{Ami} * Ami_i + \theta_{Ris} * Ris_i + \theta_{Clo} * Clo_i + \theta_{Sep} * Sep_i + \theta_{COPD} * COPD_i + \theta_{CKD} * CKD_i + \theta_{LQT} * LQT_i + \theta_{Tach} * Tach_i + \theta_{Brady} * Brady_i + \theta_{HBloc} * HBloc_i + \theta_{Liv} * Liv_i + \theta_{CAD} * CAD_i + \theta_{ICH} * ICH_i + \theta_{LMg} * LMg_i + \theta_{LK} * LK_i + \theta_{LCa} * LCa_i + \theta_{Age} * Age_i + \theta_{Vfib} * Vfib_i + \theta_{Cov19} * Cov19_i$$

QT_{c0} individually corrected baseline QTc; RR, interval between successive R waves;α, individual heart rate correction factor; A, amplitude of circadian rhythm; T, clock time; Φ, phase; θ_i, typical value of the specific parameter effect; X_i indicator for the specific parameter treatment; Azi, azithromycin; Fluc, fluconazole; Levo, Levofloxacin; Cipr, ciprofloxacin; HCQ, hydroxychloroquine; Hal, haloperidol; Met, methadone; Que, quetiapine; Ami, amiodarone; Ris, risperidone; Clo, clozapine; Sep, sepsis, COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; Tachy, tachycardia; Brady, bradycardia; Hbloc, heart block, Liv, liver disease; CAD, coronary artery disease; ICH, intracranial hemorrhage; LMg, magnesium ≤ 1.8 mEq/L; LK, potassium ≤ 3.5 mEq/L; LCa, calcium ≤ 8.6 mEq/L; Age, age > 65 years; Vfib, ventricular fibrillation; Cov19, COVID-19 infection

Mathematical model adapted in this analysis

RESULTS

Parameters	Training set (n=1521)	Validation set (n=659)	P value
Age (years)	65.9 (15.7)	66.9 (15.7)	0.84
Sex, male (%)	58.7	53.2	0.02
QT (ms)	376 (68.7)	380 (65.3)	0.15
QTc (ms)x	445 (66.3)	450 (57.4)	0.06
Disease states (%)			
Age >65 years	43.5	43.4	1.00
Sepsis	17.6	16.5	0.60
COPD	7.4	7.6	0.96
CKD	14.2	14.1	1.00
Liver disease	1.0	0.6	0.45
Cardiac arrest	1.3	2.5	0.06
Long QTc syndrome	7.6	5.6	0.11
Atrial fibrillation	8.6	7.6	0.44
Ventricular fibrillation	0.26	0.0	0.32
Bradycardia	0.79	0.0	0.02
Heart block	2.4	2.5	0.95
Hypertension	38.9	37.3	0.51
CAD	13.5	13.7	0.96
Heart failure	11.4	11.2	0.98
Acute MI	15.1	15.8	0.73
ICH	0.6	0.3	0.52
Stroke	0.0	0.07	1.00
COVID - 19	40.2	36.4	0.10
Known QT risk treatment (%)			
Azithromycin	42.4	41.9	0.89
Fluconazole	0.4	0.1	0.16
Levofloxacin	0.9	1.2	0.76
Hydroxychloroquine	21.7	20.6	0.83
Haloperidol	2.3	2.6	0.76
Methadone	0.15	0.17	0.80
Quetiapine	0.76	0.53	0.12
Amiodarone	0.30	0.17	0.01
Risperidone	0.15	0.17	0.67
Clozapine	0.07	0.30	0.01

Data presented as mean (SD) unless otherwise indicated; COPD, chronic obstructive pulmonary disease; CDK, chronic kidney disease; CAD, coronary artery disease; MI, myocardial infarction; ICH, intracranial hemorrhage

Table 1. Baseline characteristics

Parameter	Population Mean (95 % CI)	BSV	BOV
α	0.44 (0.44, 0.44)	0.06	0.04
Gender (male)	-8.15 (-8.59, -8.02)	NE	NE
QT_{c0}	440.45 (438.11, 441.83)	17.49	5.09
A	4.37 (4.11, 4.56)	3.00	5.23
Φ (h)	4.68 (2.91, 6.92)	3.16	7.88
Azithromycin*	0.0005 (0.0002, 0.0021)	0.0044	0.00
Fluconazole*	0.010 (0.006, 0.15)	0.14	0.13
Levofloxacin*	0.0045 (0.0013, 0.01100)	0.0085	0.00
Hydroxychloroquine*	0.0028 (0.0013, 0.0037)	0.0035	0.00
Haloperidol*	0.20 (0.08, 0.54)	0.40	0.45
Methadone*	0.12 (0.00, 0.26)	0.22	0.25
Quetiapine*	0.004 (0.0015, 0.0084)	0.02	0.02
Amiodarone*	0.006 (0.0011, 0.0231)	0.01	0.02
Risperidone*	6.23 (1.73, 22.39)	6.65	11.80
Clozapine*	27.58 (3.08, 51.52)	9.11	27.33
Sepsis	1.00 (0.23, 1.89)	2.59	3.46
COPD	2.28 (0.87, 5.50)	7.04	2.95
CKD	5.49 (3.56, 8.61)	5.07	2.47
Tachycardia	3.73 (0.99, 11.19)	9.51	4.85
Bradycardia	1.23 (0.27, 2.21)	15.84	7.01
Heart block	10.97 (8.17, 15.46)	9.08	10.52
CAD	7.88 (6.01, 11.13)	5.59	2.35
COVID -19	0.33 (0.08, 1.18)	1.59	2.71
Liver disease	6.05 (1.30, 9.73)	21.08	14.61
Long QT syndrome	17.88 (13.20, 21.28)	3.03	2.93
Ventricular fibrillation	22.58 (0.38, 77.89)	36.62	44.26
ICH	4.95 (0.82, 15.43)	16.40	3.70
Magnesium ≤ 1.8 mEq/L	4.13 (2.04, 6.69)	1.69	18.32
Potassium ≤ 3.5 mEq/L	3.49 (1.5, 8.08)	4.95	5.45
Calcium ≤ 8.6 mEq/L	0.66 (0.29, 1.95)	1.38	0.75
Age > 65 years	4.99 (3.85, 6.41)	8.79	5.73

All data presented in milliseconds unless otherwise indicated; * coefficient is presented as milliseconds/mg cumulative dose of the drug administered; α, individual heart rate correct factor, dimensionless parameter; ϕ, phase; A, amplitude of circadian rhythm; QT_{c0}, intercept for the QT-RR relationship; COPD, chronic obstructive pulmonary disease; CDK, chronic kidney disease; CAD, coronary artery disease; MI, myocardial infarction; ICH, intracranial hemorrhage, CI, credible interval; BSV, Between subject variability; BOV, between occasion variability; NE, not estimated

Table 2. Model Parameter estimates

RESULTS

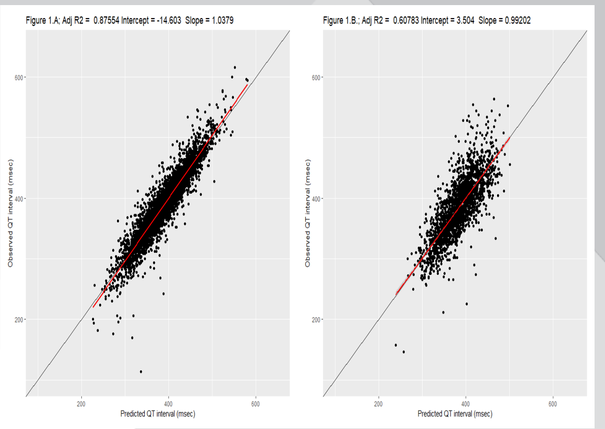

Figure 1. Observed versus predicted QT intervals, training (A) and test (B) data set

CONCLUSION

- The mixed-effects model developed accurately described the impact of baseline characteristics on the QT interval resulting in the magnitude of estimates that are similar to those in the published literature.
- Based on the results, patients treated with fluconazole and levofloxacin are likely to present with longer QT interval as compared to those treated with hydroxychloroquine and azithromycin, which may put them at higher risk for adverse events associated with QT interval prolongation.
- Further work to quantify the impact of maximum doses of the medication received, the effects of concomitant administration of medications known to prolong the QT interval, the consequence of suspected drug-drug interactions, and the role of these factors as the function of time combined with covariate interactions is on going.

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