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[A phase IIa study of an anti-arrhythmic agent]

[Kin Cheung Choy]

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Department of Pharmacy
Faculty of Pharmacy
Uppsala University

1. Introduction

1.1 Heart arrhythmias and anti-arrhythmia agents

Heart arrhythmias is a description of irregular heartbeat caused by faulty signaling, including tachycardia and bradycardia. Most cases of arrhythmias are not serious, however, some of them may have serious symptoms, such as breath shortness and chest pain, or even life-threatening. There are 4 classes of anti-arrhythmia agents with different mechanism, including sodium-channel blockers, beta-blockers, potassium-channel blockers and calcium-channel blockers. All anti-arrhythmia agents change the cardiac action potentials by altering the membrane ion conductances.

1.2 Drug development and clinical trial simulation

1.2.1 The drug under development and related safety issue

An anti-arrhythmia agent is under development in phase 2a clinical trial and will be given as a single intravenous (i.v.) bolus during surgery. The dose-limiting toxicity is QT-prolongation that may casue life-threatening arrhythmia Torsades de Pointes (TdP).

Electrocardiogram (ECG) (Figure 1) can be used to descript electrical activity of heart by electrocardiography (Bunce et al, 2020). Three main components of ECG include the P wave, which represents the atrial depolarization; The QRS complex, which indicate the depolarization of ventricles and ventricular muscles contraction and the T wave represents the repolarization of the ventricles.

The QT interval is calculated from Q wave to the end of T wave, which indicates the time from the contraction to relaxation of cardiac ventricles. A QT-prolongation (Figure 2) may cause Torsades de Pointes (TdP) which lead to the sudden cardiac death. Noord et al showed that TdP was associated with drug and non-drug factors (Noord et al 2010). A QTc is regarded as abnormal when it is above 450 milliseconds (ms) for males and 470ms for female (Medscape CRM News, 2006). In our study, the safety measure of QTc is below 460ms.

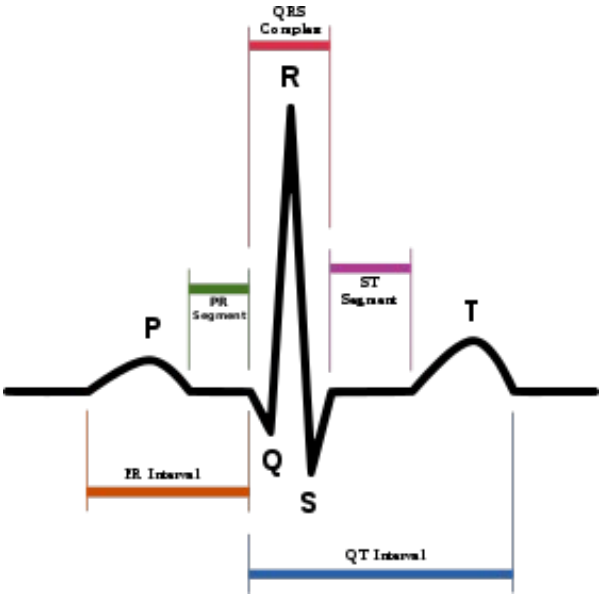


Figure 1: ECG of a heart in normal sinus rhythm

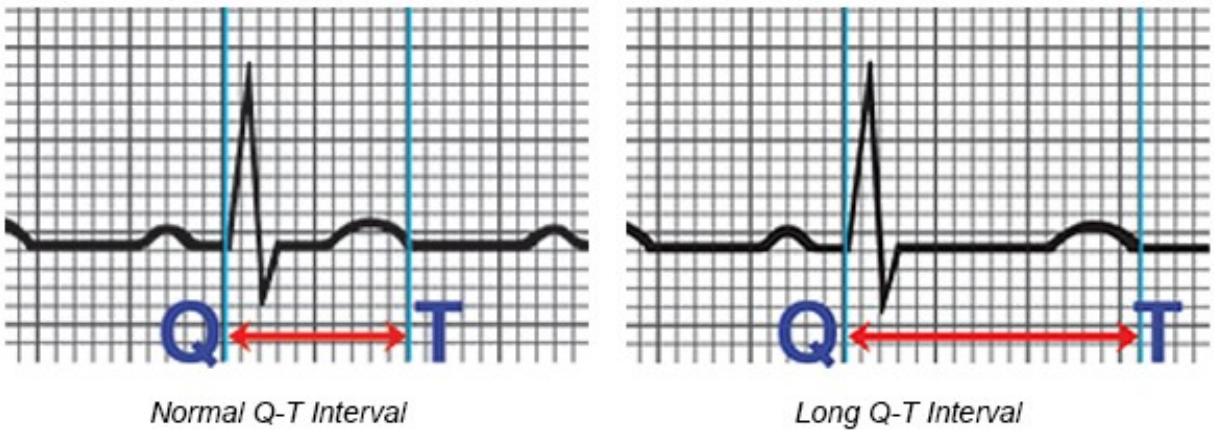


Figure 2: ECG of normal Q-T interval and long Q-T interval

1.2.2 PK and PD (conc-QT) parameters

In phase I study, the pharmacokinetic (PK) of the drug has been studied, 18 – 40 years old healthy male volunteers were given the drug in a dose regimen between 1 – 150 µg. A one-compartment model was used to described the data (Figure 3) and the half-life equation was al showed (Figure 4), including clearance (CL) and volume of distribution (V), 6 L/h and 27 L respectively in the study.

For pharmacodynamic (PD), it depends on maximum additional effect (Emax) and potency, which can be indicated by concentration that gives rise to 50% of the maximal effect (EC_{50}), an Emax model was used to describe concentration-QT relationship for similar drugs (Figure 5). The average baseline QT in the absence of drug ($QT_{baseline}$) and Emax was 382 ms in men and 152 ms respectively. For EC_{50}, it was estimated to a mean value of 0.28 µg/L in preclinical studies in dogs.

1.2.3 clinical trial modelling and simulation

Clinical trial modelling and simulation (M&S) is a tool to design good studies and aims to increase the success rate and lower the expenditure of drug development by optimizing drug effectiveness and safety in trial design (Holford et al 2010). The component of clinical trial simulation (CTS) includes models, covariates and trial design. The PK model can be used to describe trend such as time-course of drug concentration and variability in concentration. PD model describe the relationship between concentration and biomarker (QT in this study).

An effect compartment model was used in the study to show the delay in the effect and the half-life of the effect delay is ln (2) /Ke0. An Emax model with baseline and an effect compartment linked PK and PD Model were described (Figure 5 and 6). The effect compartment account for the delayed drug distribution and was assumed to be the site of action. It was linked by PK and PD model. PK model account for the distribution into the effect compartment by Ke0 and the effect was driven by the Emax model (Sheiner et al, 1979).

Other models account for effect delays includes binding model, indirect response model, transduction model and life-span model (Sheiner et al, 1979; de Witte et al, 2018; Yang et al, 2010; Jusko et al 2005).

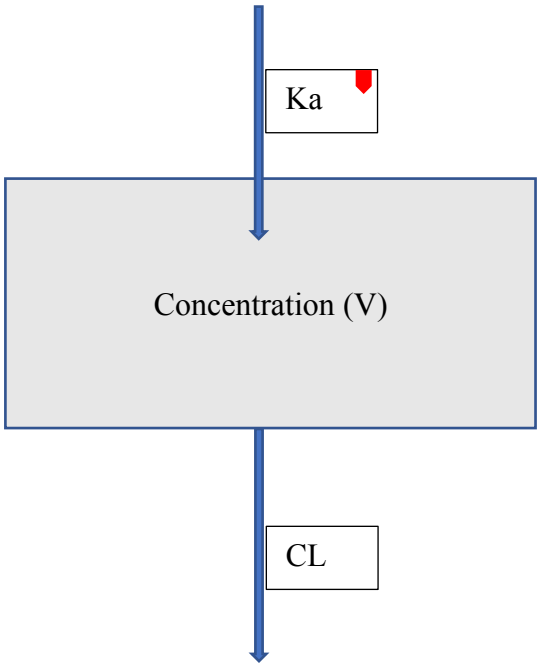


Figure 3: PK One-compartment with 1st order absorption. Ka represents absorption rate constant; V represents volume of distribution and CL represents clearance

$$Half\ Life = \frac{\ln 2 * CL}{AUC}$$

Figure 4: Equation of Half life

$$QT = QTbaseline + \frac{Emax * Concentration}{Concentration + EC50}$$

Figure 5: Emax model showing concentration-QT relationship

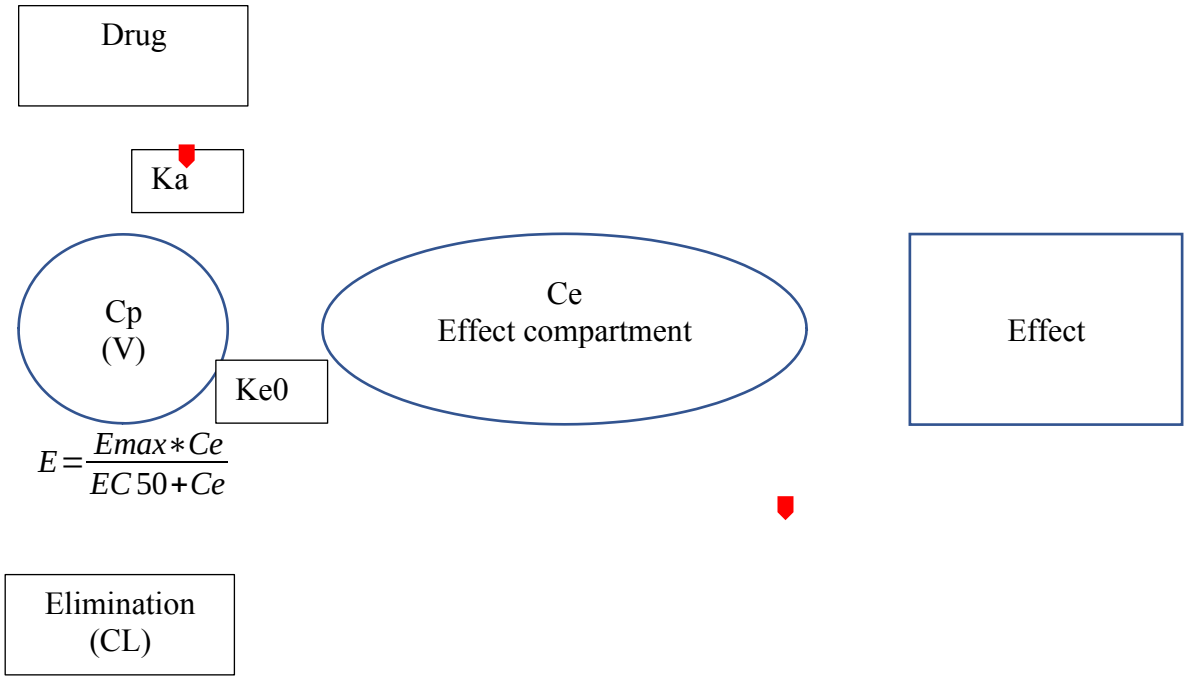


Figure 6: Illustration of an effect compartment linked PK and PD Model. PK represent the PK model with PK parameters Ka, CL and V, Cp represents the given drug plasma concentration; PD represents the PD model with PD parameters Emax and EC_{50}; Ce represents effect compartment and Ke0 represents the rate constant of effect delay.

2. Aim and objectives

The aim was to indicate the concentration-QT relationship of the anti-arrhythmic agent that under development in order to optimize the best drug effectiveness and safety. The report was provided to help the clinical drug development team understand the assumptions and basis for the simulations.

3. Methods

3.1 Clinical trial modelling and simulation

Shiny application (v[redacted]was used to build the PK and QT-model, simulated without between-subjects variability (BSV) and with BSV respectively. An effect compartment model was included to simulate effect delay (Figure 6). All the parameters v[redacted]described in section 1.2.2 and 1.2.3. The Emax model with equation that demonstrated the concentration-QT relationship was illustrated (Figure 5).

Two study arms on active treatment and one placebo arm (not included in the report as the placebo arm will not affect QT) were simulated. A lower dose was suggested to be 1/3 to 1/2 of the highest dose level. A suitable sampling schedule (5 time points) was also performed (1 sample wa[redacted]en at baseline, t = 0h). The dose selection and sampling time were evaluated in different simulation scenario. The target population was patients up to 70 years of age and study duration was 24 hours. The limit of quantification for the drug assay was 0.04 µg/L.

3.2 Simulations without BSV

The BSV of $QT_{baseline}$ (ms), EC_{50} (µg/L) and Emax (ms) were not considered in this case, therefore, only one individual was included. Two different doses selection in 2 study arms were first determined by maximum QT (520 ms) and the safe line (460 ms) was ignored (until section 3.4). Sampling schedule was based on the limit of quantification (same strategies for dose and sampling time selec[redacted]were performed in all scenarios, section 3.2 – 3.4). A few parameters (EC_{50}, CL and QT) were changed in different scenarios in order to demonstrated the relationship with dose selection as well as sampling schedule and 6 scenarios were investigated in this study (Table 1).

3.3 Simulations with BSV

The BSV of $QT_{baseline}$ (ms), EC_{50} (µg/L) and Emax (ms) were included and changed in different scenarios to account for the effect of variability on dose selection and sampling schedule. Thirty patients in each arm with 10 simulation trials per each scenario were also being studied (<10% of simulated patients at QT > 520 ms). Totally 3 scenarios were investigated (Table 1).

3.4 Simulations with effect compartment

An effect compartment model was included in this study (Figure 6) and the half-life of the effect delay is ln (2) /Ke0. Ke0 was modified in each scenario to demonstrated the relationship between Ke0 and the PK and QT models as well as the time of the peak and 3 scenarios were investigated with modified dose and sampling time selection (Table 1).

4. Results

4.1 Simulations without BSV

For scenario 1.1, two dose levels were selected (70 µg and 30 µg) based on QT (< 520 ms) (Table 1 and Figure 7A). The maximum QT value was expected to be around 530 ms for infinite dose. Time at 0.5h, 1.5h, 5h, 10h and 14h were chosen as sampling time (figure 7B and Table 1). the last sampling time point was above the red dash line in order to give the best des ion of Time-Course of drug concentration (Figure 7B). The half-life in healthy volunteers was calculated by ln2 * Vd / CL, which was around 3

For scenario 1.2a and 1.2b, which EC_{50} was 50% higher and lower, 120µg and 50µg, 40µg and 20µg were chosen for 2 study arms respectively (Table 1). For higher EC_{50}, a hig dose can be selected which indicated the increases of EC_{50} may lower the QT, on the other hand, a lower EC_{50} may increase it (Figure 8). There was no obvious changes in time course of PK by changing EC_{50}. The last sampling time was shortened from 17h to 12h in scenario 1.2b as the dose decreased (Table 1).

For scenario 1.3 to 1.5, the effect of CL and $QT_{Baseline}$ on dose selection and sampling time was showed (Table 1). The changed of CL (scenario 1.3) from 6 L/h to 4 L/h did not show obvious change in dose selection but the longer last sampling time (from o 21h). The changed of $QT_{Baseline}$ from 382ms to 393ms showed obvious changes in the higher dose selection (from 70µg to 40µg). For the worse case scenario (decreased in CL and increased in baseline of QT), the higher dose selection was similar to that in scenario 1.4 but the last sampling time was longer (from 12h to 18h) (Table 1). For scenario 1.3, the half-life was expected to be 4.6h which indicated that the lower the CL, the higher the half-life.

4.2 Simulations with BSV

In scenario 2.1 – 2.3, BSV in $QT_{Baseline}$, EC_{50} and Emax were considered (3%, 20% and 16% respectively) (Table 1). The higher dose selcetion compared to scenario 1.5 decreased (from 40µg to 25µg) if 3 % CV of $QT_{Baseline}$ was considered. It was found that the higher dose selection decreased even more (from 25µg to 20µg and 13µg) if more parameters with BSV were

considered (20% and 16% CV of EC_{50} and Emax). However, the sampling time was similar in scenario 2.1 – 2.3 and a bit faster in last sampling point compared to scenario 1.5 (Table 1).

4.3 Simulations with effect compartment

There was no obvious changes in effect delay if ke0 i[redacted] h^{-1}. The decreased in ke0 from 100 h^{-1} to 2 h^{-1} decreased the QT as well as the plasma concentrations (Cmax) (Figure 9). The time reach the peaks was delayed too (Figure 9). The higher dose selection changed from 13 to 18µg and the last sampling time was longer (from 12 to 14 h) (Table 1).

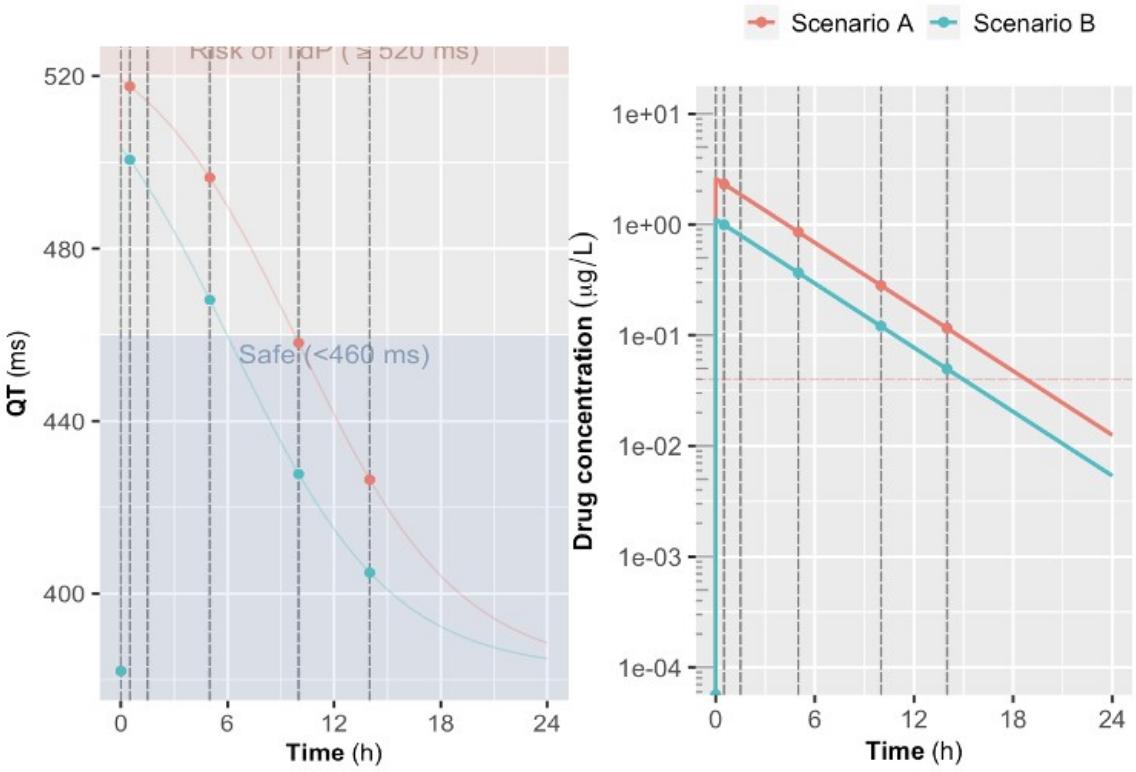
In scenario 3.2, ke0 was changed to 0.2 h^{-1} and the changes were similar to scenario 3.1 but greater. The higher dose selection changed from 18 to 30µg but the last sampling time was similar (Table 1).

In scenario 3.3, the safety line was considered (<460 ms) and parameters were similar to that in scenario 3.1. The maximun dose was 10µg (Figure 10) and the sampling time were 0.5h, 1.5h, 6h, 8h (indicate maximum dose resulting when QT was below 460ms at 8 hours) and 10h (Table 1). The half-life of the effect delay was around 0.[redacted]

Table 1 Illustarion of all the PK, QT parameters, dose selection and sampling time in all simulation scenarios

Scenario	CL (L/h)	V (L)	QTBase (ms)	Emax (ms)	EC50 (µg/L)	Ke0 (h-1)	BSVQTBase (%CV)	BSVEmax (%CV)	BSVEC50 (%CV)	DoseArm1 (µ g)	DoseArm2 (µ g)	Sampling time (h)
1.1	6	27	382	152	0.28	-	-	-	-	70	30	0.5 1.5 5 10 14
1.2 a	6	27	382	152	0.42	-	-	-	-	120	50	0.5 1.5 5 11 17
1.2 b	6	27	382	152	0.14	-	-	-	-	40	20	0.5 1.5 5 8 12
1.3	4	27	382	152	0.28	-	-	-	-	70	30	0.5 1.5 5 12 21
1.4	6	27	393	152	0.28	-	-	-	-	40	20	0.5 1.5 4 8 12
1.5	4	27	393	152	0.28	-	-	-	-	40	20	0.5 1.5 6 12 18
2.1	4	27	393	152	0.28	-	3	-	-	25	12	0.5 1.5 6 10 12
2.2	4	27	393	152	0.28	-	3	-	20	20	10	0.5 1.5 6 10 12
2.3	4	27	393	152	0.28	-	3	16	20	**13**	**6**	0.5 1.5

												6 10 12
3.1	4	2 7	393	152	0.28	**2**	3	**16**	20	**18**	**9**	0.5 1.5 6 9 14
3.2	4	2 7	393	152	0.28	**0.2**	3	**16**	20	**30**	**15**	0.5 1.5 6 9 14
3.3	4	2 7	393	152	0.28	**2**	3	**16**	20	**10**	**5**	0.5 1.5 6 8 10



A B

Figure 7: (A) Time-Course of QT in scenario 1.1 (B) Time-Course of drug concentration (PK) in scenario 1.1 Scenario A and B represented arm1 and arm2 study respectively which was showed in red and green lines. Black dash line represented sampling time. Red dash line indicated the limitation of quantification.

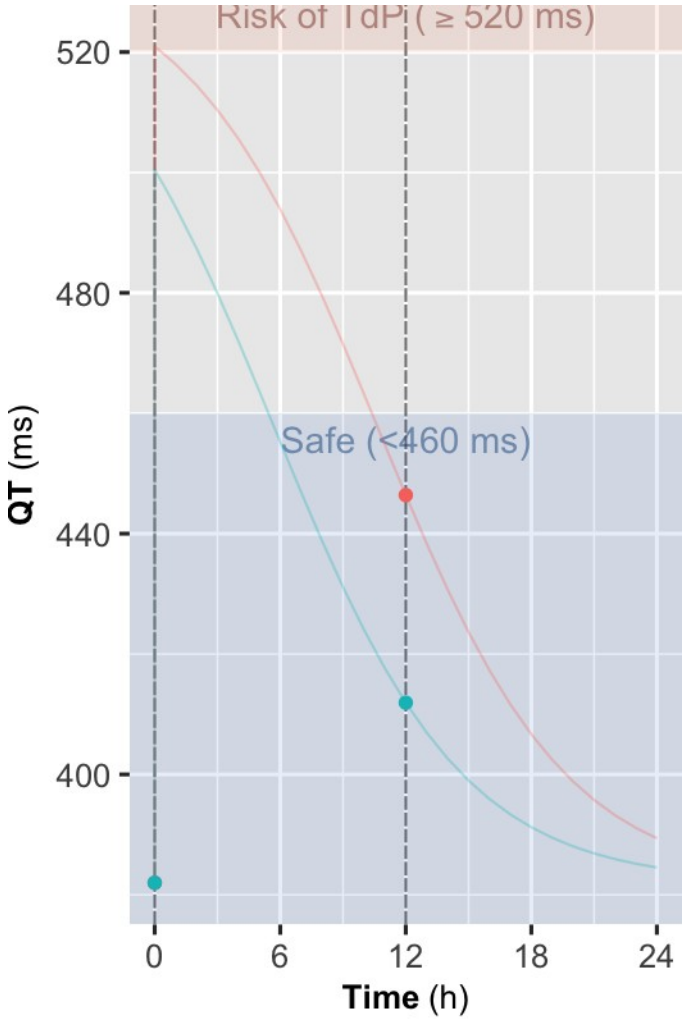
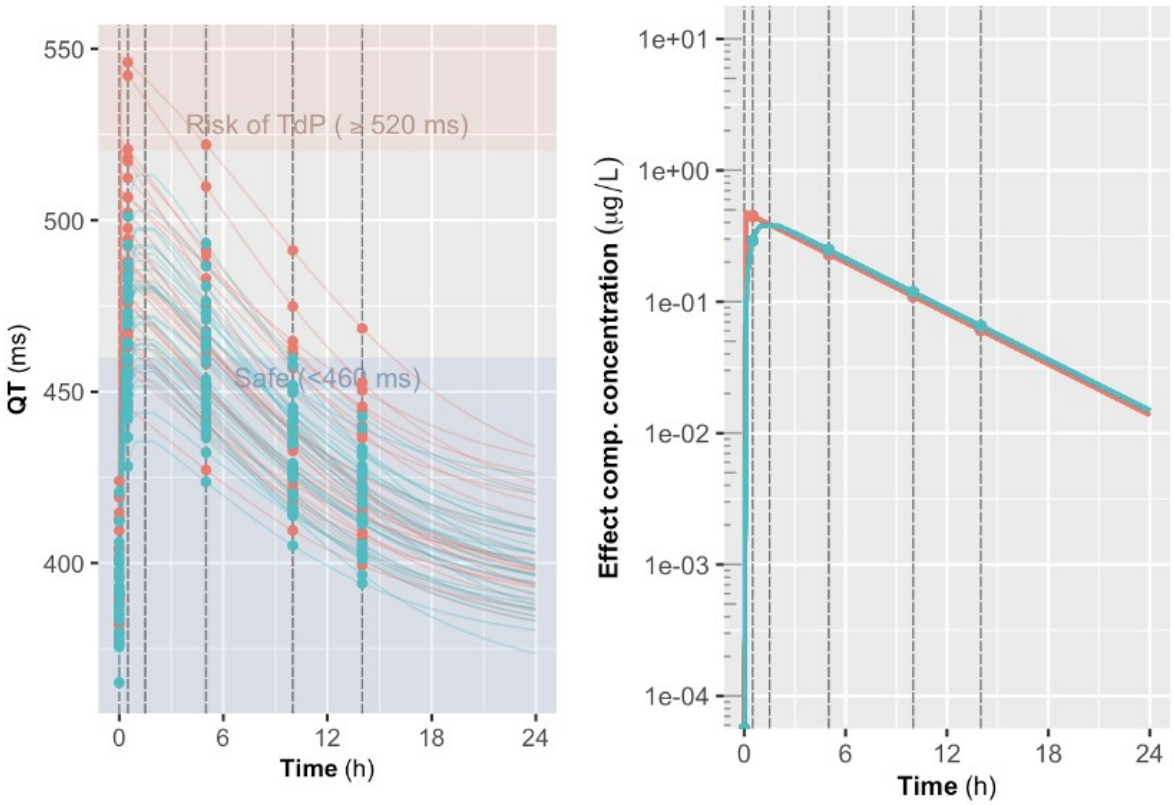


Figure 8: Time-Course of QT in scenario 1.2a and 1.2b Red dot at t = 12 represents the QT in lower EC_{50}; Green dot at t = 12 represents the QT in higher EC_{50}. All the parameters except EC_{50} remained unchanged.



A B

Figure 9 (A) Comparision of time-course of QT when ke0 is 100 h^{-1} (Red line) and 2 h^{-1} (Green line). (B) Comparision of time-course of when ke0 is 100 h^{-1} (Red line) and 2 h^{-1} (Green line) All the other parameters remain unchanged except ke0

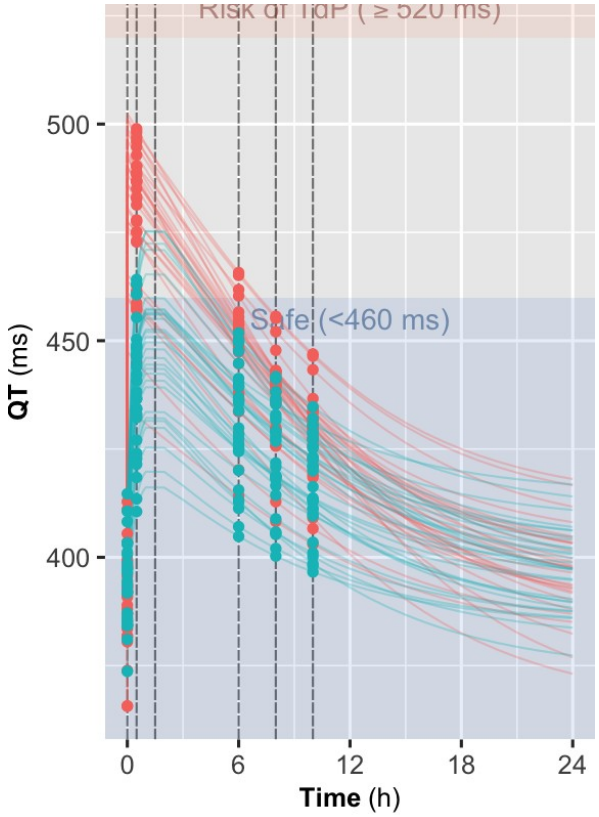


Figure 10 Time-Course of QT in scenario 3.3

5. Discussion

5.1 Factors affecting exposure responses in CTS

5.1.1 PK and PK-QT parameters

The sensitivity of parameters were tested which included CL, EC_{50} and baseline of QT. The drug half-life increases while the CL decreases, in order words, the drug exposure increases, therefore, the sampling time could be longer (slope of time course concentration decreases). For EC_{50}, the lower of it, the less the concentration needed to give responses (the lower the EC50, the higher the max.QT if the dose was unchanged), therefore, the decreased EC_{50} resulted in lower dose while increases of it lead to higher dose selection. For the baseline of QT, a lower dose should be selected in a higher baseline of QT if the desired QT (Max. QT) remain unchanged.

5.1.2 Individual difference (BSV)

In section 5.1.1, it was assumed that all patients have the same PK and PK-QT parameters, however, if BSV in the parameters were included, the exposure responses was found to be different, the more the variability added, the lower the dose was selected (number of patients with QT > 520ms increases).

5.1.3 Delay effect

An effect compartment explained the delay effect. It was assumed that the plasma unbound drug concentrations is the same at the site of action and the response related to it. An equilibration half-life (ln(2)/ke0) was used to show course of equilibration between the plasma and effect compartments, the lower the ke0, the greater the delay. The delay was around 0.3h in the study (ke0) = 2 h-1) , it was a delay due to distribution rather than a mediator turnover (physiological) as the delay was in minutes rather than hours (Holford, 1982). Therefore, a slower equilibration half-life (low ke0) resulted in slower rate of drug exposure and response and lead to slower rate of administrative and higher dose selected (Figure 9 and Table 1).

5.2 Application of CTS and limitation of study

From 5.1, CTS provides a good view on good studies design by building model with parameters (PK-QT model and effect compartment model) and explains variability in parameters (BSV), resulted in different scenarios with dose selection and sampling time, we are able to predict the best dosing regimen and sampling time to maximize the drug effect and safety depends on the different factors affecting CTS and assumptions in different scenario.

Based on the assumption, 10% population were allowed to reach QT > 520ms (highest dose), no other serious side-effects were found and concentration should be as high as possible. The effect delay may be ignored as it is hard to determine the exact value of ke0 (no obvious changes if ke0 is high, e.g. 100 h-1). Moreover, it is assumed that the binding to the active site is rapid and does not contribute much to the delayed drug effect. Therefore, the final design will be Scenario2.3(T 1). Besides, the limitation of study included the neglected consideration of sample variability (plasma), covariates (patients characteristics and parameters) and uncertainty in models and parameters, therefore, it would still be difficult to have an informative design without simulation in further study.

6. Conclusions

It was found that PK and PK-QT parameters, BSV and delay effect were the factors affecting the decision in CTS. The final design will be Scenario2.3 (higher and lower dose are 13μg and 6μg respectively with sampling time 0.5h,1.5h,6h,10h,12h). Both male and female were included with reduced CrCL and increased QT baselines, no effect delay but with BSV in all Emax-model parameters.

7. References

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