Towards unravelling the mechanism of Cardiotoxicity of Citalopram: Utilisation of mechanistic cardiac electrophysiology modelling with Simcyp Cardiac Safety Simulator to explore various hypotheses

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Introduction

Assessment of torsadogenic potential of a drug based only on parent drug and only hERG activity could be misleading as many drugs affect ionic currents other than IKr (hERG channel) and may have electro-physiologically active metabolites. Animal studies may not be a good surrogate in such situations as there are known translational gaps in drug absorption, distribution and metabolism between animals and humans along with cardiac (electro-)physiology variations. Testing all permutations and hypotheses in clinical studies are often practically, ethically and economically infeasible. Physiologically based biophysically-detailed models of human cardiac (electro-)physiology has a potential to bridge translational gap in cardiac safety assessment and allow extrapolation of *in vitro* ion channel activity of a drug to human situation incorporating physiological, demographic, genetic and circadian variability. We have previously shown the utility of such an approach to predict the QT prolongation potential of Tolterodine [1]. Here we address a relatively more complex problem of understanding the mechanism of cardiotoxicity of Citalopram (CT).

Objectives

Understanding the mechanism behind Cardiotoxicity of Citalopram (CT)

 # Hypotheses to be tested
1. What is operating concentration – total plasma, free plasma or heart tissue?
2. Are metabolites or parent responsible – Only CT, Only DDCT or All together?
3. Are multiple ion channels involved – Only IKr, or IKr+ICaL+IKs for all entities?

The foundation for hypotheses

CT, once a most widely prescribed antidepressant drug in the USA had been linked with cardiac toxicity especially in overdose situations resulting in US FDA enforcing restrictions on maximum daily doses in 2011. The cardiac toxicity issues with CT were not new in 2011 but the clinical development of the drug was halted for several years in 1980s due to sudden death of dogs in high dose toxicity studies speculated to be due to high concentrations of cardio-active secondary metabolite didesmethylcitalopram (DDCT) in dogs but not in other species studied. Moreover CT is known to inhibit IKr, IKs, and ICaL cardiac currents and suspected to interfere with INa and IK1 currents. Adding into complexity, the primary metabolite desmethylcitalopram (DCT) and DDCT are also known to inhibit IKr and IKs currents. DDCT is only detectable in human blood at high doses leading to postulations that DDCT is responsible for reported toxicities at high doses. We wanted to test various hypotheses (mentioned above) using mechanistic modelling and validate the tested hypothesis with further data.

Methodology

We collected the *in vitro* ion channel inhibition activity for CT, DCT and DDCT for IKr, IKs and ICaL channels. ten Tusscher 2006 model linked with 1D String model to generate pseudo-ECG signal from single cell level action potential implemented within the Cardiac Safety Simulator version 2.0 [2] was used for simulating pseudoECG traces with various operating concentrations, responsible moieties and involved ion channels. Mechanistic models are very powerful tools in assessing hypotheses and understanding mechanisms of toxicity which are otherwise difficult or practically impossible to study *in vivo* for example difficulty in studying effect of pure CT as CT gets converted to DCT via multiple metabolic pathways once in the body and DCT gets quickly transformed to DDCT hence all three entities exist simultaneously and they all can block multiple ion channels. Thus understanding impact of individual processes are very challenging. On the other hand properly parameterised and appropriately validated physiologically based models can allow various simulations to answer what-if questions for understanding the mechanisms. Drug exposure and clinical ECG data were obtained for multiple time points from suicidal overdose case report of 46 year old female subject [3]. The same demographics and physiology (heart rate, plasma K^+, Na^+, Ca^{2+} ion concentrations) were simulated with reported drug concentrations. The heart tissue concentrations were calculated from reported heart to plasma partition coefficient for drug and metabolites from cadavers. The metabolite concentrations were estimated from parent concentration using known parent/metabolite ratios. Free plasma concentrations were estimated from plasma protein binding information of parent and metabolite. The developed model was further tested with clinical data at therapeutic dose of CT (20mg) and two more reports of life threatening arrhythmia/TdP cases [4-6].

Results and Discussion

We tested free plasma concentrations of drug and metabolite for four different scenarios using Unterecker 2012 and Tarabar 2008 data: (1) only IKr activity of only CT, (2) IKr+IKs+ICaL activity of only CT, (3) IKr activity of CT+DCT+DDCT, and (4) all entities and all ion channels. We found that only when all three entities (CT, DCT and DDCT) and all ion channels were considered, we could explain the clinically observed QT prolongation data at all time points using our simulations.

Table 1. Simulated results compared with clinically reported data; Arr. means unstable and dysrhythmic pseudoECG signals in simulated results

Clinical Reference	CT conc. (ng/mL)	OBSERVED			All Molecules All Ion channels — Total Plasma		All Molecules All Ion channels — Total Heart		All Molecules All Ion channels — Free Plasma		Free Plasma — All Molecules Only IKr		Free Plasma — Only CT Only IKr		Free Plasma — Only CT All Channels	
		QT (msec)	RR (sec)	QTcB (msec)	QT	QTcB	QT	QTcB	QT	QTcB	QT	QTcB	QT	QTcB	QT	QTcB
Unterecker 2012	1231	460	0.74	535	532	618	703	817	463	538	430	499	414	481	416	484
	922	460	0.83	505	524	576	645	708	451	495	424	465	412	452	414	455
	796	440	0.74	511	506	589	677	787	441	513	418	486	407	473	409	475
	491	420	0.78	476	473	536	570	645	427	483	364	413	357	404	357	404
	0	380	0.78	430	387	438	387	438	387	438	387	438	387	438	387	438
Tarabar 2008	477	NA	0.4-0.59 (0.48)	572-600	Not Performed as proven above				412	597	400	577	392	566	394	569
US FDA TQT (20mg)	63 (mean)	dQTcF (mean)		8.5	21.93 (mean)		Not Performed		9.53 (mean)		Not performed as the above two studies already established the importance of all entities and all ion channels					
Loitier 2011	5880	440	0.531	604	Arr.	Arr.	Arr.	Arr.	Arr.	Arr.						
	2420	600	0.8	671	660	737	Arr.	Arr.	574	641						
	2400	420	0.428	642	Arr.	Arr.	Arr.	Arr.	Arr.	Arr.						

There are contrasting reports exist on the operating drug concentration. We calculated total heart tissue concentrations from plasma concentrations using the total tissue partition coefficient reported from post-mortem analysis of human cadavers. Then we tested all entities and all ion channels with (1) total plasma; (2) free plasma and (3) estimated heart tissue concentrations as operating concentrations and found that only when free plasma concentrations all entities and all ion channels were considered the simulated results were in good agreement with the clinical measured data (Table 1). It would be difficult to accept the hypotheses based only on the one clinical study data hence we tested battery of other clinical studies – [1] A thorough QT trial of CT (20mg dose) and two more cardiotoxcity case reports of overdose of CT (Loitier 2011 and Tarabar 2008) found that consideration of all entities and all ion channels with free plasma concentration as operating concentration is crucial in prediction of cardiotoxic profile of citalopram.

References

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