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Toward Unravelling the Mechanism of Cardiotoxicity of Citalopram: Utilization of Mechanistic Cardiac Electrophysiology Modelling with Simcyp Cardiac Safety Simulator (CSS) to Explore Various Hypotheses

Nikunjkumar Patel[1], Masoud Jamei[1], Sebastian Polak[1,2]

nikunj.patel@certara.com

[1]Simcyp Limited, a Certara Company, Sheffield, UK; [2]Faculty of Pharmacy, Jagiellonian University Medical College, Poland

PURPOSE: Exploring the mechanism behind cardiotoxicity of Citalopram (CT)

Hypotheses to be tested

1. What is the operating concentration – total plasma, free plasma or heart tissue?
2. Are the metabolites or parent responsible – Only CT, Only DDCT or all together?
3. Are multiple ion channels involved – Only I_{Kr}, or I_{Kr}+I_{CaL}+I_{Ks} for all entities?

Background to the hypotheses

CT, once a most widely prescribed antidepressant drug in the USA had been linked to 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 I_{Kr}, I_{Ks}, and I_{CaL} cardiac currents and suspected to interfere with I_{Na} and I_{K1} currents. Adding into complexity, the primary metabolite desmethylcitalopram (DCT) and DDCT are also known to inhibit I_{Kr} and I_{Ks} 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 investigated various hypotheses (mentioned above) using mechanistic modelling and validate these hypothesis with external data.

METHODOLOGY

In vitro ion channel inhibition activity data for CT, DCT and DDCT for I_{Kr}, I_{Ks} and I_{CaL} channels were collected. The ten Tusscher 2006 model linked with one dimensional (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 using various operating concentrations, responsible moieties and involved ion channels. Mechanistic models could be useful 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 underlying 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 the therapeutic dose of CT (20mg) and two more reports of life threatening arrhythmia/TdP cases [4-6].

RESULTS & DISCUSSION

Simulated results showed that only when all three entities (CT, DCT and DDCT) and all ion channels were considered, simulations could explain the clinically observed QT prolongation data at all time points. 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 clinically observed data (Table 1). To improve confidence we tested the model with battery of other clinical studies – QT at therapeutic dose of 20mg and two more cardiotoxicity case reports of overdose of CT (Loitier 2011 and Tarabar 2008) and verified that the consideration of all entities and all ion channels with free plasma concentration as operating concentration is crucial in prediction of cardiotoxicity profile of citalopram.

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			PREDICTED											
					All Molecules All Ion channels						Free Plasma as Operating Conc.					
					Total Plasma		Total Heart		Free Plasma		All Molecules Only IKr		Only CT Only IKr		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.						

References [1] Patel et al. 2013 http://abstracts.aaps.org/Verify/aaps2013/postersubmissions/T3221.pdf; [2] Polak et al. Drug Discov Today. 2014 Mar;19(3):275-81; [3] Unterecker et al. Pharmacopsychiatry. 2012 Jan;45(1):30-4; [4] Tarabar et al. J Med Toxicol. 2008 Jun;4(2):101-5; [5] http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm; [6] Loitier & Coudore Drug Chem Toxicol. 2011 Oct;34(4):420-3. **ENCORE**: The presented work here has, in part, been presented at 15th Annual Safety Pharmacology Society Meeting in Prague, September 2015.