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Virtual Clinical Trial Toward Polytherapy Safety Assessment: Combination of Physiologically Based Pharmacokinetic/Pharmacodynamic-Based Modeling and Simulation Approach With Drug-Drug Interactions Involving Terfenadine as an Example

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ABSTRACT

A Quantitative Systems Pharmacology approach was utilized to predict the cardiac consequences of drug-drug interaction (DDI) at the population level. The Simcyp *in vitro–in vivo* correlation and physiologically based pharmacokinetic platform was used to predict the pharmacokinetic profile of terfenadine following co-administration of the drug. Electrophysiological effects were simulated using the Cardiac Safety Simulator. The modulation of ion channel activity was dependent on the inhibitory potential of drugs on the main cardiac ion channels and a simulated free heart tissue concentration. ten Tusscher's human ventricular cardiomyocyte model was used to simulate the pseudo-ECG traces and further predict the pharmacodynamic consequences of DDI. Consistent with clinical observations, predicted plasma concentration profiles of terfenadine show considerable intra-subject variability with recorded C_{max} values below 5 ng/mL for most virtual subjects. The pharmacokinetic and pharmacodynamic effects of inhibitors were predicted with reasonable accuracy. In all cases, a combination of the physiologically based pharmacokinetic and physiology-based pharmacodynamic models was able to differentiate between the terfenadine alone and terfenadine + inhibitor scenario. The range of QT prolongation was comparable in the clinical and virtual studies. The results indicate that mechanistic *in vitro–in vivo* correlation can be applied to predict the clinical effects of DDI even without comprehensive knowledge on all mechanisms contributing to the interaction.

Introduction

Providing a safe, reliable, and effective drug to the patient population is the ultimate goal of drug design and development. Establishing a safety regime is a stepwise, data-driven, rigorous and comprehensive process initiated during the early phases of drug development. Every compound approved for market release must go through this process to authenticate the developed drug. This safety testing strategy is invaluable in screening out any toxic compounds. However despite the strict regulations, the process cannot fully predict safety for the entire population of patients who will ultimately receive a drug. In the early 1990s, a series of blockbuster drugs were withdrawn from the pharmaceutical market because of their potential life-threatening adverse effects (i.e., a QT interval prolongation and Torsade de Pointes [TdP] arrhythmia). This significant event highlighted the inadequate safety strategy that was in place in the existing drug development process. Since then and until very recently, functional cardiotoxicity (especially proarrhythmia risk) was one of the main causes of late-stage attrition in drug development and a major contributor to withdrawals, restrictions, and relabeling of marketed drugs. In 2005, the International Conference on Harmonization issued 2 guidance documents to address the drug-induced proarrhythmia hazard. A battery of preclinical and clinical tests proposed in S7B and E14 ICH guidelines, and adopted soon after by the pharmaceutical industry, were based on the observation that most TdP cases are preceded by QT interval prolongation. In parallel, it was concluded that almost all prolongations of QT can be traced back to inhibition of the cardiac channel for potassium ions (Kv11.1, IKr[1]) encoded by the hERG (human ether-a-go-go-related gene). This approach is adequate for

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some drugs due to their relatively simple pharmacokinetic and pharmacodynamic characteristic which permits such direct *in vitro–in vivo* extrapolation. For example, dofetilide is a selective IKr blocker and has a predictable impact on the QT interval length and TdP risk with a direct concentration-effect relationship.[2,3] Conversely, for many drugs risk assessments based on hERG liability alone can be misleading, because hERG-connected arrhythmogenic potential of a drug can be counterbalanced by the simultaneous effects on other cardiac ion currents resulting in a reduction or elimination of the presented torsadogenic risk.[4-7] Furthermore, the correlation between proarrhythmia and drug-induced QTc prolongation is a complex phenomenon related not only to the properties or dose of a particular drug, but also to a variety of patient-specific factors, which can influence the individual response of the heart electrophysiology. Potentially crucial factors that have an impact on QT prolongation and proarrhythmia include the concomitant administration of specific drugs. Unlike dofetilide, terfenadine is an example of a compound for which *in vitro–in vivo* extrapolation is not straightforward and therefore requires a systemic analysis approach, utilizing a wide range of preclinical data acquired from multiple experiments. In addition, terfenadine represents a drug for which both proarrhythmic risk and potential clinical usefulness are likely to be discounted. This is because the ionic current disruption and the complex pharmacokinetics for the drug need to be clearly understood to allow for an accurate and informative safety assessment. Terfenadine is a very potent IKr current inhibitor, but its biotransformation (triggered by the CYP3A enzyme) is close to complete in physiological conditions. The first-pass metabolism results in the very low systemic concentration of the parent compound, but clinically relevant concentration of its main metabolite—fexofenadine. Fexofenadine has no significant effect on the cardiac cell membrane potential and QT interval. Combining these 2 elements together creates a picture of a complex pharmacology—a prodrug, efficiently metabolized by 3A4 with significant affinity to hERG and a safe metabolite responsible for the pharmacodynamic activity. The relatively large volume of distribution of terfenadine suggests peripheral tissue penetration which adds another level of complexity, because the concentration of the drug in the plasma does not reflect the actual concentration at the site of action—specifically the heart as the target organ.[8,9] The lack of significant cardiac clinical effects of terfenadine administered alone to treat hay fever symptoms to otherwise healthy people resulted in a long and successful market life of the drug.[10] However, when either the repolarization reserve is reduced (because of the genetic or iatrogenic reasons) or when CYP3A activity is compromised (i.e., by diseases or genetic factors), the total cardiac effect can cross the safety threshold and result in a life-threatening ventricular arrhythmia. Similarly, concomitant administration of other QT-prolonging drugs (pharmacodynamic interaction) or potent CYP 3A4 inhibitors including erythromycin, itraconazole, or ketoconazole (pharmacokinetic interaction) can potentially lead to increased level of unmetabolized terfenadine in the systemic circulation and provoke adverse clinical effects. A precise assessment of these effects resulting from drug-drug interactions (DDIs) becomes imperative especially for compounds which present such complex pharmacology. However, a number of drug combinations possibly implicated in QT prolongation is practically infinite, so it is infeasible to comprehensively assess their potential DDIs during the clinical trial process. *In silico* modeling may offer an alternative approach with the capacity to overcome the limitations associated with current clinical trial design. The terfenadine scenario exemplifies challenges faced by the drug safety specialists during the drug development process as well as clinicians dealing with polytherapy, and makes terfenadine a good example for the case study investigating the potential of employing computational approaches to assess the effects of DDIs on the safety of a compound.

In this study, we integrate knowledge accumulated from multiple disciplines including drug pharmacology, systems biology, electrophysiology/physiology, and mathematics. Various techniques and data sources used include physiologically based pharmacokinetic (PBPK) models, biophysically detailed cardiac models, and *in vitro* patch clamp data; therefore, it can be considered as an example of the Quantitative Systems Pharmacology approach utilized for the prediction of the cardiac consequences of DDIs at the population level.[11] Following recent achievements in the practical

Table 1
Physicochemical and Pharmacokinetic Parameters of Terfenadine Used for DDI Simulations

Variable	Parameter Value	Source and Comments
Parameter type		
Log *P*	5.69	[15]
pKa	9.5	[17]
Fraction unbound in plasma	0.03	[18,19]
Absorption		
Model	ADAM	
Peff,man (10^{-4} cm/s)	1.26	Simcyp predicted based on Caco-2 data
Fa	0.787	Simcyp predicted based on phys-chem data
ka (1/h)	0.52	Simcyp predicted based on phys-chem data
Caco-2 permeability ($\times 10^{-6}$ cm/s)	5.47	[20]
Apical pH:basolateral pH 7.4:7.4	For propranolol: 21.29	
Distribution		
Model	Full PBPK	Perfusion limited model for all organs
V_{ss} (L/kg)	4.43	Simcyp predicted Poulin and Theil method with the Berezhkovskiy correction[21]
K_p heart:plasma	3.91	Simcyp predicted Poulin and Theil method with the Berezhkovskiy correction[21]
Elimination		
rCYP 3A4	$K_m = 9$; $V_{max} = 1257$	[22]
	$Fu_{mic} = 0.2$	Fitted manually
rCYP 3A4	$K_m = 13$; $V_{max} = 206$	[22]
	$Fu_{mic} = 0.2$	Fitted manually
Additional clearance liver (HLM)	800	Estimated from total HLM clearance[16] after CYP3A4 and 2D6 clearance deduction
	$Fu_{inc} = 0.3$	Fitted manually
Additional clearance intestine	1650	[16]
	$Fu_{inc} = 0.075$	Fitted manually
Active uptake into hepatocyte	0.85	Fitted manually

ADAM, advanced dissolution absorption metabolism; HLM, human liver microsomes.