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COMMENTARY

Predicting QTc Prolongation in Man From Only *In Vitro* Data

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Mishra *et al.*[1] in their article "Interaction between domperidone and ketoconazole: toward prediction of consequent QTc prolongation using purely *in vitro* information" describe the use of physiologically based pharmacokinetic (PBPK) modeling and pharmacodynamic models of cardiac repolarization to predict clinical data from preclinical data. Eliminating the risk of cardiac arrhythmias through delayed repolarization often relies on preclinical data during compound selection. Although there are some limitations, there appears to be significant promise in using this modeling approach.
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As the authors point out compounds associated with the cardiac arrhythmia torsade des pointes (TdP) in man are dominated by those which block the human ether-a-go-go-related gene (hERG) potassium current. An *in vivo* surrogate for this proarrhythmic liability is QTc prolongation in animals and man, and the *in vitro* surrogate is the potential to block the hERG current. This has led to the common practice of selecting compounds based on potency and relative selectivity in blocking hERG potassium currents. There are two key issues which then emerge, both of which could be addressed by physiologically based pharmacokinetic (PBPK)-QTc modeling.

First, many compounds have the potential to block the hERG channel, only a smaller number will ever be associated with TdP in man. Three key publications illustrate this. In the first, Webster *et al.*[2] demonstrated that for a modest-sized group of 28 compounds, all had hERG inhibitory potencies measured and published but only some had been associated with TdP. This paper was the first to suggest that a margin of 30-fold between hERG IC_{50} and unbound therapeutic plasma concentrations separated those which were associated with TdP from those which were not. These authors also suggested that only a small amount of hERG block was required to appreciably prolong the QTc interval in man. This latter point was subsequently confirmed through PK/pharmacodynamic modeling with the selective hERG blocker dofetilide.[3] The second publication, expanded on the Webster analysis by adding more compounds (n = 53) and adding subcategories: antiarrhythmic drugs, drugs withdrawn for TdP/QTc prolongation, those probably associated with TdP, those possibly associated with TdP, and those not associated with TdP.[4] Again all compounds, including those not associated with TdP, blocked the hERG channel. The previously described 30-fold margin between hERG potency and therapeutic plasma concentration generally held true, however, it was apparent that in this analysis the hERG margin was not a perfect predictor of the classification. Some compounds not believed to be associated with TdP had a margin less than 30-fold, while others which were associated with TdP had margins greater than 30-fold. In a more recent publication, again examining compounds that were all hERG blockers but separated in to 33 compounds associated with TdP and 22 not believed to be associated with TdP, the 30-fold margin was shown to be an imperfect predictor.[5] The sensitivity and specificity of this 30-fold margin for the prediction of TdP were 81 and 65%, respectively. This and the earlier publication illustrate the potential utility for a PBPK-QTc modeling technique. Clearly, a margin calculation is dependent on a numerator, the hERG potency, and a denominator, the unbound plasma concentration. The latter has usually been taken as the mean unbound efficacious maximum plasma concentration. This often does not take into account the concentrations, which may result from drug–drug interactions, overdose, cardiac accumulation, or the impact of metabolites, which also block the hERG potassium current. The article by Mishra and colleagues is an illustration of how PBPK modeling can be used to improve predictions of attainable active exposures. Considered further, Kramer and colleagues described 55 hERG blocking compounds divided into proarrhythmic and non-proarrhythmic categories. Agnostic to exposure values, the hERG potency assay could be described as 100% sensitive but 0% specific in predicting proarrhythmia. In adding specificity to the assessment by incorporating an exposure value, the sensitivity was eroded considerably. PBPK modeling to simulate potential exposures may offer an opportunity to increase the specificity without losing the sensitivity by estimating exposures under conditions of drug–drug interaction and other situations rather than using the mean efficacious therapeutic level. This would optimize the detection of true positives and negatives while minimizing false negatives and false positives. Minimizing false positives in the assessment of proarrhythmic potential is receiving considerable scrutiny.[6] The activities at additional ion channels are often cited as a means of improving specificity; it may, however, be more important to consider the multiple influences on exposure, which could now feasibly be addressed with a PBPK modeling technique. Indeed, in the discussed impact of domperidone on QTc prolongation,[1] at the exposures described and with the given potencies, it is difficult to imagine a contribution from the ion channels other than hERG.

A cautionary note is necessary. Estimation of hERG potency can be variable.[7] In addition, state dependence and

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kinetics of block can be very relevant.[8] This may impact the numerator in the margin calculation. Current hERG channel protocols may be biased toward the most sensitive and stable recording configurations. Consideration of the reproducibility and statistical power of the assay formats is also relevant. If the experimental design offered 80% confidence that the measured IC_{50} was within threefold of the true IC_{50}, then the variability in the hERG potency estimate could sometimes (20% of cases) be as substantial as any increase in exposure triggered by a drug–drug interaction. These latter considerations of reproducibility are relevant too for the *in vitro* metabolism estimates in the PBPK modeling. This suggests that the experts in the fields of ion channel assessments and metabolism assays may need to consider sharing best practice experience to improve predictivity and reproducibility. Sharing of best practice has already taken place for *in vivo* studies;[9] this is especially important since it appears that the absolute change in QTc (in msec) is smaller in most laboratory animal species than in man.[10]

The second issue which PBPK-QTc modeling could address is the high cost of a false negative in the preclinical and clinical assessment of proarrhythmia. Previously, TdP was detected postapproval after significant patient exposure to drugs. This high impact and cost created a tolerance to an assessment paradigm with an appreciable false-positive rate. Elimination of false negatives is paramount. However, the study by Mishra and colleagues illustrates now that a compound such as terfenadine—an archetype in proarrhythmia assessment—would proceed very differently. The hERG assessment would identify that it had the potential to prolong QTc and perhaps be associated with TdP. The PBPK assessment would give an estimate of the likely efficacious C_{max} concentrations and highlight the potential for a drug–drug interaction with a CYP3A inhibitor. The PBPK-QTc modeling would likely suggest an appreciable QTc prolongation with terfenadine alone and a dramatic QTc prolongation in the presence of ketoconazole—mirroring described clinical experience.[11] If such a compound were to be selected for testing in man, it is likely that modern phase I study designs would test the concentration effect on QTc alone and in a ketoconazole interaction in healthy volunteers. The proarrhythmic potential would be detected in phase I. This dramatically alters the cost of false negatives from the nonclinical testing and reshapes the tolerance of false negatives and false positives in proarrhythmia testing overall.

In summary, although Mishra and colleagues point out some limitations in the fidelity of prediction, their illustration of the application of PBPK-QTc modeling offers the ability to minimize both false positives and false negatives in proarrhythmia testing. This could occur at a stage of development most compatible with efficiently minimizing this safety liability. Further exploration of the technique would serve to confirm this promising utility. Next steps likely involve examples where the QTc prolongation in man is driven by metabolites or metabolites plus parent. Examples where other ion channels may plausibly make a contribution would also be valuable. In refining the techniques, some attention to the translation and reproducibility of the experimental protocols used to gather the *in vitro* information will be necessary. These considerations would allow this technique to be a key component of the revised proarrhythmia testing paradigm.[6]

Conflict of Interest. D.J.L. is an employee and stockholder of Eli Lilly and Company.

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