Poster

[P25-8] P25-8: Immunosuppressive drugs (3): Biomarkers and pharmacokinetics

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Mon. Sep 25, 2017 12:30 PM - 1:30 PM Annex Hall (1F)

(Mon. Sep 25, 2017 12:30 PM - 1:30 PM Annex Hall)

[P25-8-10] Drug-drug interaction risk assessment using PBPK modeling: inhibitory magnitude of diltiazem and its metabolite on sirolimus disposition

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Keywords: Drug-drug interaction, Risk assessment, PBPK modeling, Sirolimus, Diltiazem

Background

Sirolimus is an inhibitor of the mammalian target of rapamycin (mTOR) used in renal transplantation. Since sirolimus is predominantly metabolized by the CYP3A pathway, the concentration-time profile could be altered by co-administration of CYP3A inhibitors. The quantitative and mechanism-based prediction approach for the drug-drug interaction (DDI) risk on sirolimus disposition would be beneficial to avoid concentration-related adverse effects of sirolimus, such as hyperlipidemia, thrombocytopenia, and leucopenia. The aim of this study was to demonstrate the utility of physiologically-based pharmacokinetic (PBPK) modeling for DDI risk assessment. Diltiazem, a calcium-channel blocker administered in renal transplant patients, was used as a CYP3A inhibitor to predict the potential inhibitory magnitude on sirolimus PK profile.

Methods

PBPK models of sirolimus, diltiazem, and its metabolite, desmethyldiltiazem, were developed using Simcyp Simulator (version 13, Certara). Drug-specific information was collected from *in-house* data and the literature: physicochemical parameters; *in-vitro* kinetic parameters for CYP3A-dependent drug reactions; and *in-vitro* CYP3A inhibition parameters (reversible and time-dependent inhibitions) for diltiazem and desmethyldiltiazem. Each drug compound file with anatomical and physiological system parameters was evaluated using reported clinical time-concentration profiles in healthy volunteers, before conducting the *in-silico* DDI risk assessment.

Results

Three PBPK models demonstrated reasonable time-concentration profiles in healthy volunteers, which were comparable to reported clinical observations. Predicted AUC values were within a 2-fold range of observed data after single administration of each drug. In the *in-silico* DDI simulations using three PBPK models, the predicted increase in sirolimus AUC was 1.55 fold during co-administration of diltiazem, which was similar to clinical observations (1.60 fold, Bottiger *et al., Clin. Pharmacol. Ther.*, 2001). The PBPK modeling approach identified potential dosing regimens which could minimize DDI risks in sirolimus PK.

Conclusions

The *in-silico* DDI risk assessment using PBPK modeling reasonably predicted the magnitude of sirolimus AUC increase during co-administration of diltiazem. The confidence in PBPK model-informed dosing regimens to minimize DDI risk on sirolimus PK would be improved through clinical confirmation in kidney transplant

patients. This study demonstrates the potential utility of PBPK modeling as a clinical application.