Pharmacokinetics can be predicted through pre-dose Metabolomic profiling

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Introduction

Genetic heterogeneity alone cannot explain and predict individual's response to drugs; as it doesn't consider environmental and other external contributions to individual's biological condition. So, possible alternative can be measuring and statistically modeling the metabolic phenotype of an individual before drug administration and use it to predict post-dose pharmacokinetic response. In this study, we demonstrate ability of pre-dose urinary metabolite profile through PLS multivariate modeling to predict pharmacokinetic parameters of tacrolimus in healthy human subjects. Tacrolimus, a drug routinely being used during organ transplantations as immunosuppressant, has a narrow therapeutic index and high degree of individual variation in blood drug concentration. Therefore, it is of considerable interest to predict individual variation in pharmacokinetics of tacrolimus prior to its administration to avoid adverse drug effects and therapeutic failures like organ rejection.

Methods

Clinical trial has been conducted on 29 healthy Korean male volunteers. Pre-dose urine samples were collected during 24 hrs before tacrolimus drug dose (0.075mg/kg). The tacrolimus blood concentration was measured up to 72hrs using UPLC-MS/MS and AUC (area under curve) was calculated.

Results

Using only 117 metabolite ions from initial PLS analysis which significantly correlate with AUC having (VIP>1.5) we have built final PLS model for prediction of AUC and Clearance. This two component PLS model shows statistically significant results as $R^2=0.92$, $Q^2=0.79$ and Eigen-value= 4.2. This model shows excellent internal and cross-validation results which validates it for prediction of pharmacokinetics in new sample sets without risk of data overfitting. Identification of those metabolite ions (VIP>1.5) reveal that amino acids, sterols, glycoprotein and nucleoside metabolic pathways are responsible for early drug intervention of tacrolimus. Finally, by integrating the results from both PLS and hypothesis network analysis, we selected four major network modules describing metabolic pathways in which the key metabolites are involved and can affect pharmacokinetics of tacrolimus.

Conclusion

We proposed an integrative approach for predicting the individualized pharmacokinetics. The application of this approach to tacrolimus allowed us to identify a metabolic phenotype predictive of the individualized pharmacokinetics of tacrolimus using pre-dose urinary metabolic profile. The proposed approach can be also extended to other drugs having complex responses and high degree of individual variation.