Systemic pharmacotherapy support during chronic kidney disease using a novel conceptual framework

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Objectives: The complex set of physiological and pathological interactions reveals the need to characterize the systemic nature of chronic kidney disease (CKD) by applying a quantitative systems pharmacologic (QSP) approach. This approach should be tested as a framework to evaluate the effect vs. side effect relationship during a pharmacotherapy of CKD patients.

Methods: A comprehensive literature search was conducted to inform the altered renal and hepatic physiological, pathological and metabolic conditions for CKD patients. Findings were pooled according to the CKD classification and analyzed in order to allow dynamic fractional changes along the staging system in the Open Systems Pharmacology Suite. Age- and disease-related alterations were distinguished and the uncertainty of each parameter was defined by using a Taylor series. Physiologically based pharmacokinetic (PBPK) models for paradigm compounds were assessed to quantify relevant parametric changes with increasing pharmacokinetic complexity. Finally, the exposure of lidocaine and two sequential metabolites were predicted for every CKD stage. Its complex metabolism and elimination property served as an external model qualification to assess the renal-hepatic elimination interplay. The prediction bias and error were quantified using the mean absolute error (MAE) and the root-mean-square error (RMSE).

Results: Identified hepatic, portal and renal perfusion changes were incorporated along with protein level and renal volumetric alterations. CYP1A2 activity changes were captured and finally applied to describe the exposure of lidocaine and its metabolites successfully. Estimation of MAE and RMSE revealed a clear prediction improvement.

Conclusions: The model framework has been qualified internally and externally. Although, the exposure of lidocaine is not significantly altered under CKD conditions, the prolonged half-life of the sequential metabolites was well captured. Since both metabolites are likely to contribute to the lidocaine-assigned cardiovascular toxicity, changes in the pharmacotherapy can be assessed based on this conceptual framework.