Evaluation of the Relationship between Changes in PK Parameters and its Corresponding Change on Steady-State Drug Exposure

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Objectives: Identification of clinically relevant covariates/factors in Population PK analysis (PPK) is often based on the magnitude of their effects on PK parameters. A >20-25% effect on PK parameter is commonly considered clinically relevant. However, the translation of a covariate effect from on PK parameters to on steady-state exposure is not well understood and not always straightforward. The current analysis aims to evaluate the PK-to-exposure translation for a covariate effect.

Methods: The values of PK parameters of 74 drugs with 1-compartment and 51 drugs with 2-compartment kinetics were obtained from literatures and were used to predict the change in steady-state exposures, ie, trough (Cminss) and peak (Cmaxss) concentrations, assuming a 20% change in PK parameters. All drugs were orally administered (either QD or BID). The relationship between changes in exposure and change in PK parameters was assessed.

Results: Exposure was mostly influenced by apparent clearance (CL/F); 20% change of CL/F could lead to a substantial change of Cminss (ΔCminss; up to a few folds), particularly for compounds whose half-life (T1/2) is shorter than the actual dosing interval. ΔCminss decreased with increasing T1/2 and reached plateau when T1/2 was large. However, 20% change in Ka, Vp/F and Q/F had only minimal impact on exposure (<20%). Additional subgroup analysis showed similar pattern of PK-to-exposure translation across all four Biopharmaceutics Classification System classes, indicating that this translation may be independent of drug's physicochemical properties.

Conclusions: The PK-to-exposure translation could be more than proportional for some compounds. When assessing clinical relevance of covariates in PPK analysis, their influence on steady-state exposure should be taken into consideration.