Development of a population pharmacokinetic meta-model for everolimus from simulated database

Nanga TM.[1], Bouriah S.[1], Woillard JB.[2], Rousseau A.[1], Marquet P.[2], Musuamba FT.[3], Prémaud A.[1]

[1]IPPRITT UMR-1248 INSERM, Université de Limoges - Limoges (France)
[2]IPPRITT UMR-1248 INSERM, CHU de Limoges, Université de Limoges - Limoges (France)
[3]Federal Agency for Medicines and Health Products - Brussels (Belgium)

Background.
Everolimus is a selective mTOR inhibitor used to prevent organ rejection and in the treatment of certain types of cancers. Published population pharmacokinetic (popPK) models were developed in small homogeneous patient groups with given diseases. Our objective was to develop a popPK meta-model appropriate for all solid-organ transplanted patients.
Methods.
First, patient datasets (concentrations, body weight, dose, …) were independently simulated using 5 published popPK parameters (mean and variance). Then these simulated datasets were evaluated and pooled. Secondly a non-specific popPK model was developed from the pooled dataset. This model was externally validated in an independent dataset of 499 observed concentrations collected in 89 kidney, liver, or heart recipient patients. Simulations and nonlinear mixed effects modeling were performed using NONMEM 7.3.
Results.
A total of 5636 concentrations were simulated for 271 patients from these 5 models and served to the development of a 2 compartment-model with first-order absorption and lag time. Body weight and dose were found to influence the clearance. Apparent clearance, central compartmental volume, intercompartmental clearance, absorption first-order rate and absorption lag-time were respectively 23.42 L.h-1, 46.01 L.h-1, 183.5 L, 5.434 h-1 and 0.6329 h for a 60kg patient taking 2mg twice daily. The model parameters were estimated with acceptable precision (i.e. <20%, except for the absorption rate). External validation provided satisfactory results.
Conclusions.
A popPK meta-model appropriate together for kidney, liver and heart transplant patient was developed and validated using simulation from published model in small homogeneous patient groups. This model needs further validation in oncology. Such meta-model could be useful in under-documented patient-groups.
Keywords.
Everolimus, meta-model, population pharmacokinetic, simulation.