Population pharmacokinetic modeling as a tool to identify covariates important for drug dosing

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Population pharmacokinetic (pop PK) modeling offers an advantage of identification of predictive covariates of a drug's PK variability. Identification of predictive covariates in a pop PK model represents a scientific base for creating personalized dosing regimens customized to individual patients. The aim of this habilitation thesis was to describe PK of drugs during specific therapeutic modalities in pediatric, neonatal, and adult population, to identify predictive covariates, and to propose optimal dosing of drugs during these specific therapeutic modalities. This thesis represents a commented set of 7 original publications. I will present 3 publications. The details can be found below.

1. In the first study, a pop PK model of phenobarbital in neonates undergoing extracorporeal membrane oxygenation (ECMO) was developed. ECMO was found to rapidly increase the clearance (CL) of phenobarbital, while no changes in the volume of distribution (Vd) of phenobarbital were identified. CL increased linearly with time during ECMO. We performed model simulations that suggested that the current recommended maintenance dose (MD) of 5 mg/kg/day for neonates aged 0–14 days and 6 mg/kg/day for neonates aged 15–28 days might not be appropriate for older neonates and neonates on ECMO for extended periods. Therefore, we recommended a new optimal dosing regimen that provides the desired target levels of phenobarbital. It consists of a 20 mg/kg loading dose (LD) and a MD = 4 mg/kg/day, divided into two doses, with an increase of 0.25 mg/kg every 12 hours throughout the duration of ECMO treatment.
2. In the second study, a pop PK model of vancomycin was developed in patients with end-stage renal disease (ESRD) treated with peritoneal dialysis. Our analysis revealed that maintenance of diuresis and estimated glomerular filtration rate (eGFR, a marker of renal function) were the primary factors influencing vancomycin CL, while body weight served as a significant covariate for Vd. Furthermore, model-based simulations suggested that current International Society for Peritoneal Dialysis (ISPD) dosing recommendations did not achieve the desired drug exposure targets in the peritoneal compartment in majority of the patients with preserved diuresis. Therefore, we proposed a new dosing regimen consisting of intraperitoneal LD = 20 mg/L for the continuous dosing regimen, followed by MD = 50 mg/L in the each exchange. This strategy ensures an adequate peritoneal exposure from the start of treatment.
3. A pop PK model of fondaparinux was developed in ESRD patients undergoing high-flux (HF) and low-flux (LF) hemodialysis, and in one patient on peritoneal dialysis. Based on the results of the study, the CL of fondaparinux increased 2.26-fold during HF hemodialysis, while LF hemodialysis and peritoneal dialysis did not affect the CL of

fondaparinux. Model-based simulations suggested that an initial LD = 5 mg should be recommended to achieve steady-state levels of anti-Xa activity, which would ensure fully effective anticoagulation from the start of treatment.

References:

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