Abstract

The aim of this dissertation thesis was to study the factors affecting drug distribution and elimination and to use these factors to individualize dosing. The work consists of three thematic areas: estimation of the volume of distribution and subsequent dosing of selected drugs (vancomycin, amikacin, phenobarbital) using body size descriptors; estimation of clearance and subsequent dosing of selected drugs (vancomycin, amikacin, phenobarbital, perindopril) using renal function status markers; and the impact of drug interactions on the distribution and elimination of phenobarbital. The thesis summarizes original papers on these topics.

Individual pharmacokinetic parameters were calculated for each patient based on their demographic and clinical characteristics, dosing records and measured serum drug levels. The relationships between distribution volume/drug clearance and body size descriptors/renal functional status markers were examined by regression analysis.

Vancomycin volume of distribution was best predicted by the total body weight. Loading dose of 10.7 mg/kg of total body weight was optimal in patients taking continuous vancomycin and would lead to reducing of median time to reach target concentrations from 17 to 1 hour. On the contrary, amikacin volume of distribution was most associated with the body surface area, although the adjusted body weight was practically just as good predictor. The optimal single dose of amikacin was 517 mg/m^2 and 14 mg/kg of adjusted body weight, respectively. The distribution volume of phenobarbital in asphyxiated newborns was related with weight, body surface area and length. The optimal loading dose for this cohort was 15 mg/kg.

The clearance of both vancomycin and amikacin most closely corresponded to the estimation of glomerular filtration rate using the CKD-EPI equation. We designed nomograms for estimation of the optimal continuous vancomycin maintenance dose and for estimation of the optimal amikacin dosing interval using the CKD-EPI equation. Phenobarbital clearance did not relate with any of the examined characteristics in asphyxiated newborns. Therefore, a fixed maintenance dose of 9 mg/day appeared to be optimal, corresponding to a weight-normalized dose of 3 mg/kg/day. Perindoprilat clearance related better with cystatin C than with creatinine. Differences in prediction performance of the individual equations using cystatin C were minimal.

Frequently used co-medication (vasoactive drugs, furosemide, phenytoin, tramadol, sufentanyl, midazolam) did not affect phenobarbital pharmacokinetics in asphyxiated newborns in real clinical settings.