Model-informed precision dosing of levetiracetam in pediatrics population

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Abstract

Aims: Assessing the suitability and safety of doses of levetiracetam in pediatrics using physiologic-based pharmacokinetic (PBPK) modeling. Methods: A PBPK model of levetiracetam was developed and validated for healthy adults and scaled for children (0.5 to 12 years old). Prediction of levetiracetam exposure at steady- state, were carried out for different therapeutic regimens to achieve the target of Cmax values within the therapeutic range of 5 to 46 μg ml-1. Then, a multivariate linear regression analysis (MLR) was applied to correlate the simulated data with covariates: dose, therapeutic regimen, sex, age and body weight (BW), to describe the best model prediction for the initial dosing in pediatrics. Results: The results indicated the suitability of the PBPK model for adults and pediatrics. For children aged 0.5 to 6 y.o. the dose range capable of reaching the pharmacokinetic target is between 10 and 100 mg kg-1 day-1, for 7 to 9 y.o. doses between 20 and 90 mg kg-1 day-1, and for 10 to 12 y.o. doses between 20 to 80 mg kg-1 day-1. Further, the MLR related Cmax to dose, therapeutic regimen, and BW. Conclusions: For 3 daily administrations, it is suggested that maximum daily doses of 80 mg kg-1 could be used for ages between 0.5 and 6 y.o. and 100 mg kg-1 for ages above 7 years old, since they weigh below 50 kg. The PBPK model lumped to MLR could be very supportive for clinical decisions to safety and effectiveness of prescription of levetiracetam along the titration phase.

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