Child Health Research Institute

University of Nebraska Medical Center

Children's NEBRASKA

Evaluating a physiologically based pharmacokinetic model for predicting the pharmacokinetics of midazolam in pediatric population with obesity

Nusrat Ahmed[1, #], Yashpal S. Chhonker[1], Valentina Shakhnovich[2, 3, *], Daryl J. Murry[1, #].
[1]University of Nebraska Medical Center, Omaha, NE, USA, [2]University of Missouri-Kansas City, Kansas City, MO, USA, [3]Children's Mercy Kansas City, Kansas City, MO, USA, [*]Currently affiliated with Ironwood Pharmaceuticals, [#]The Child Health Research Institute, UNMC

Background: Dosing of drug in children with obesity is challenging due to lack of practical knowledge. Physiologically based pharmacokinetic (PBPK) model can fill the gap of sparse pediatric obese individuals clinical trials and predict the exposure of drugs in them, ensuring safe medications.

Significance of the Problem: According to CDC (Centers for Disease Control and Prevention), in the United States, the prevalence of obesity among children and adolescents aged 2-19 years was 19.7% in year 2017-2020. However, specific dosing guidelines required for pediatric obese individuals are insufficient in prescribing information.

Hypothesis: Pediatric populations differ from adults in terms of physiological development and ontogeny of metabolizing enzymes. Besides, obesity instigates pro-inflammatory state which have influence on CYP3A-mediated drug metabolism. Considering these, we aimed to develop and validate a PBPK model that will allow us to simulate systemic exposure of midazolam (CYP3A substrate) in this special population and will predict specific changes in PK properties; combining both will be advantageous in guiding clinical drug usage.

Experimental Design: Clinical studies evaluating midazolam PK profile were identified and a step-wise strategy was undertaken to developing the intravenous (IV) and oral midazolam PBPK model in adults. We assessed the performance of the model by calculating the mean-fold-error in 2-fold range. Developed model was validated running the simulation with virtual population with similar demographics reported in clinical trials. Later, it was utilized to simulate systemic exposure in pediatric children and adolescents in a clinical study where subjects received 2 mg IV midazolam dose.

Pediatric scaling parameters were utilized, combining drug-specific properties with physiological information. Pediatric PK data were compared with a variety of plasma inflammatory cytokines.

Results: Eighteen different midazolam clinical studies in healthy adults were included. Mean-fold error in predicted PK parameters upon observed PK parameters was within the 2-fold range. Predicted virtual simulation profiles were consistent with the observed clinical data with 90% confidence interval. We successfully extrapolated the developed adult midazolam PBPK model to outline the plasma-concentration time profile of 23 children and adolescents aged between 11.25- 22.33 years, grouped into 4 weight groups based on body mass index (BMI), who received 2mg intravenous MDZ in a clinical setting). In obesity, MDZ Cmax and AUClast correlated inversely with IL1β and IL6 ($R2 \geq 0.5$, $p < 0.05$).

Conclusion: The PBPK model of midazolam for pediatrics with normal vs. obese was successfully developed and validated to provide a rational basis for practical dosing.