1521-0103/389/S3/supplement: ASPET 2024 Annual Meeting Abstract
The Journal of Pharmacology and Experimental Therapeutics

dx.doi.org/10.1124/jpet.404.938920
J Pharmacol Exp Ther 389: June 2024

Development of a Physiologically Based Pharmacokinetic Model for Predicting Midazolam Pharmacokinetics in a Pediatric Population with Obesity

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Abstract ID 93892 **Poster Board 404**

Background: Drug dosing in children with obesity is challenging due to a lack of clinical guidelines. Physiologically based pharmacokinetic (PBPK) models can fill the gap of limited clinical trials with obese pediatric individuals and help guide drug dosing to ensuring the safe and efficacious use of medications in this population.

Significance of the Problem: The prevalence of obesity among children and adolescents aged 2-19 years was 19.7% according to the CDC for the years 2017-2020. However, specific guidelines required for drug dosing in obese pediatric individuals are limited.

Hypothesis: Pediatric populations differ from adults in terms of physiological development and ontogeny of metabolizing enzymes. Obesity instigates a pro-inflammatory state which may influence CYP3A-mediated drug metabolism. We aimed to develop and validate a PBPK model that will allow us to simulate systemic exposure of the CYP3A substrate, midazolam (MDZ), in this special population.

Experimental Design: Previously published clinical studies evaluating MDZ PKs 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 of predicted and observed PK parameters. The developed model was validated using a virtual population with similar demographics. Subsequently, the model was utilized to simulate MDZ systemic exposure in pediatric and adolescents following MDZ administration (2mg IV). Pediatric scaling parameters were utilized, combining drug-specific properties with physiological information. Finally, dosing simulations were performed using the same midazolam dosing in adults and children. MDZ exposure (AUC) and other PK parameters (volume of distribution, Vd and clearance, CL) were compared across children stratified into 4 weight groups based on body mass index (BMI); normal, overweight, obese and morbidly obese.

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 PK parameters within the 90 % confidence interval. We successfully extrapolated the developed adult midazolam PBPK model to outline the plasma-concentration time profile of 23 children and adolescents receiving MDZ aged between 11.25-22.33 years, grouped into 4 BMI based weight groups. Midazolam Vd differed significantly in obese and morbidly obese groups, with an increase over 51.68 - 69.28 % and 178.73 – 182.70 % range in obese and morbidly obese individuals respectively compared to normal children ($p < 0.01$). Compared to the healthy children, MDZ clearance decreased 24.61 – 31.35 % and 13.89 – 48.81 % range in obese and morbidly obese individuals respectively ($p < 0.05$).

Conclusion: Our midazolam PBPK model was successfully developed and validated to provide a rational basis for practical dosing of drugs in children with obesity.