Simulation of Midazolam absorption and bioavailability in pediatric patients

Viera Lukacova, Walter S. Wolotsz, Michael B. Bolger
Simulations Plus, Inc. Lancaster, CA
viera@simulations-plus.com

Abstract:
Purpose: To evaluate the accuracy of prediction of midazolam absorption and bioavailability in a pediatric population from in-silico, in-vitro and adult in-vivo data. The significance of scaling the clearance and gastrointestinal tract model parameters to appropriate age was assessed.

Methods: GastroPlus™ 5.0 with the PBPKPlus™ Module was used to simulate the adult human Cp-Time profiles for midazolam in oral solution dosage forms. Simulated Cp-Times were compared to corresponding literature data in order to validate the non-linear dose dependence and bioavailability due to saturable CYPIA4 metabolism. The Population Estimates for Age-Related (PEAR) Physiology™, a part of PBPKPlus™, was used to generate tissue parameters for adult and pediatric patients. Literature data for gut CYP3A4 distribution and in-vivo Km and Vmax values were used along with rat tissue/plasma partition coefficients and in-silico estimation of remaining biochemical and pharmacokinetic properties.

Results: Using the default ACAT model and the observed expression levels of CYP3A4 in liver and gut, PBPK simulations accurately reproduced the non-linear dose dependence for midazolam bioavailability and Cp-Time profiles for po administration of midazolam in adult patients. Using a purely in-silico calculation of pediatric physiology, and scaling of the gastrointestinal tract parameters and metabolism to a pediatric population, pediatric Cmax and Tmax were also accurately simulated.

Conclusions. In-vitro data on in-vivo Cp-Time profiles from an adult population can be successfully used to predict the Cp-Time profiles in pediatric patients if the PEAR Physiology for a given age is accompanied by scaling of the gastrointestinal tract parameters and enterocyte metabolism to the same age.

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