

**Title:** Simulation of Midazolam Absorption and Bioavailability in Pediatric Patients

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**Objectives:** To evaluate the possibility of predicting Midazolam absorption and bioavailability in pediatric population from pure *in silico* inputs or from available adult *in vivo* data. The significance of clearance and gastrointestinal tract scaling to the appropriate age for accurate predictions was assessed.

**Methods:** GastroPlus™ 5.3 with the PBPKPlus™ Module (Simulations Plus, Inc., Lancaster, CA) was used to simulate adult human plasma concentration time profiles (Cp vs. time) observed for Midazolam in peroral (“po”) solution dosage forms. Simulations were compared to corresponding literature data [1-3] in order to validate the nonlinear dose dependence and bioavailability due to saturable gut and liver CYP3A4 metabolism. The built-in Population Estimates for Age-Related (PEAR) Physiology™ was used to calculate organ weights, volumes, perfusion rates, and tissue-plasma partition coefficients for an average human male adult and the pediatric patients. *In vitro* values for gut distribution and *in vitro*  $K_m$  and  $V_{max}$  values [4] for CYP3A4 were used along with *in silico* estimation of biopharmaceutical and pharmacokinetic properties. For the simulations of a pediatric population, the gut parameters and the liver clearance were scaled from adult values to the lower patient weight. The resulting data were compared to the clinical data from the literature [5].

**Results:** Using the default ACAT model and the observed expressions of CYP3A4 in liver and gut, GastroPlus PBPK simulations accurately reproduced the nonlinear dose dependence for Midazolam bioavailability and Cp vs. time profiles for po administration of Midazolam solution from 7.5 mg to 30 mg in adult patients. Using a purely *in silico* calculation of pediatric physiology, and scaling the gastrointestinal tract parameters and metabolism to a pediatric population, the pediatric  $C_{max}$ , and  $T_{max}$  were accurately simulated.

**Conclusions:** *In vitro* data or *in vivo* Cp vs. time profiles from adult populations can be successfully used to predict the midazolam Cp vs. time profiles in pediatric patients if the organ physiology for given age is accompanied by scaling of the gastrointestinal tract parameters and the enterocyte metabolism to the same age.

#### **References:**

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