Simulation of Midazolam absorption and bioavailability in pediatric patients

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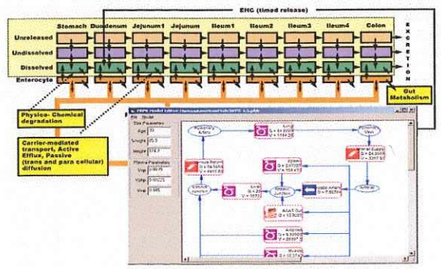
Abstract:

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 of 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 CYP3A4 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-vitro* K_m and V_{max} values were used along with rat tissue:plasma partition coefficients and *in-silico* estimation of remaining biopharmaceutical 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 or *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.



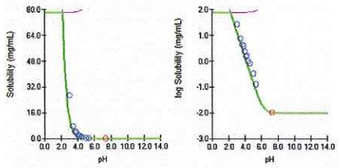
Advanced Compartmental Absorption and Transit Model with PBPK (ACAT + PBPK)

References:

1. Bjorkman, S. et al. J. Pharm. Sci. 90:1226 (2001)
2. Poulin, P. et al. J. Pharm. Sci. 91:129 (2002)
3. Loftsson, T. et al. Int. J. Pharm. 212:29 (2001)
4. Paine, M. J. Pharmacol. Exp. Therap. 283(3):1552 (1997)
5. Johnson, T.N. et al. Br. J. Clin. Pharmacol. 51:451 (2001)
6. Kupferschmidt, H.H. et al. Clin. Pharmacol. Therapeut. 58:20 (1995)
7. Bornemann, L.D. et al. Eur. J. Clin. Pharmacol. 29:91 (1985)
8. Johnson, T.N. et al. Br. J. Anaesth. 83:428 (2002

Data:

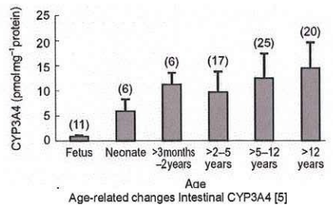
Physico-chemical properties: values predicted by ADMET Predictor™ (Simulations Plus, Inc.); for some properties, experimental values were obtained from literature: fraction unbound in plasma [1,2] =2.5%, blood:plasma concentration ratio [1,2] =0.55, octanol:water partition coefficient=2.7, pKa=6.15; experimental values for solubility vs pH were also found in literature [3], however, these data did not cover the entire pH range of the GI tract but matched the predicted solubility values very well, so the calculated solubility profile was used for all simulations



Solubility profile of Midazolam: Blue – experimental data points, Red – solubility predicted by ADMETPredictor at drug's native pH, Green – solubility profile calculated by pKa-based solubility model built into GastroPlus

***In vitro* metabolism data:** *In vitro* K_m=3.7μM and V_{max}=850pmol/min/mg protein values obtained from literature [4]

Gut and Liver 3A4 expressions: initial estimates for Adult and Children physiologies were obtained from literature [4], expression in adult liver was fitted, 2/3 of the fitted value was used for the pediatric simulations [5]



Age-related changes Intestinal CYP3A4 [5]

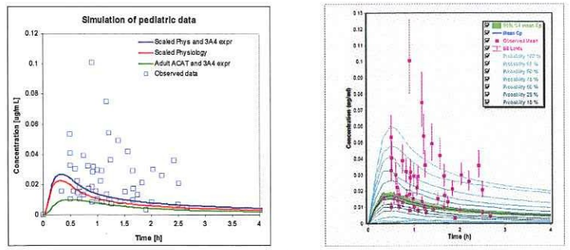
Adult and Pediatric physiology: created using the Population Estimates for Age-Related (PEAR) Physiology™ generator based on the National Health and Nutrition Examination Survey (NHANES - 2002) database. The NHANES database includes extensive physiological parameters for 11,039 people of diverse age, ethnicity, and gender.

Tissue:Plasma partition coefficients (Kp): *in silico* values calculated using published method [2]; values for rat obtained from literature [1]

Experimental data: all experimental Cp-time data after *i.v.* [1] and *p.o.* [6,7] administration in adults as well as *p.o.* administration in children [8] were obtained from literature

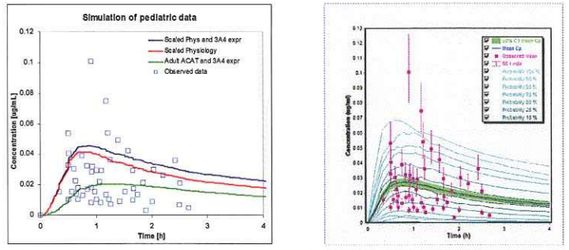
Virtual Trial Settings: CV % for virtual trial were: 3A4 expression in liver 44%, in gut 31%, V_{max} 30%, K_m 20% (estimated based on the variation in literature data); the default values were used for remaining properties.

1) Assuming that only *in vitro* V_{max} and K_m values are available (PBPK model) – all other inputs are *in silico* predictions



Left: Simulations using *in silico* properties (including K_p values) and in vitro metabolism values: green – adult Gut parameters, adult 3A4 expression, *in vivo* V_{max} as would be obtained by conversion from *in vitro* V_{max} value using adult liver size; red – pediatric physiology (Gut parameters and liver size for V_{max} conversion) with adult 3A4 liver expression; blue – pediatric physiology and 3A4 expression in liver. **Right:** virtual trial using the baseline values with scaled pediatric physiology and 3A4 expression in Liver

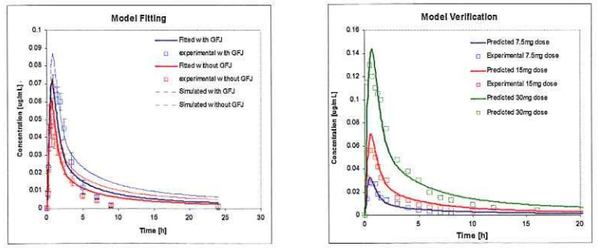
2) Experimental Values for some properties and rat tissue:plasma partition coefficients (Kp)



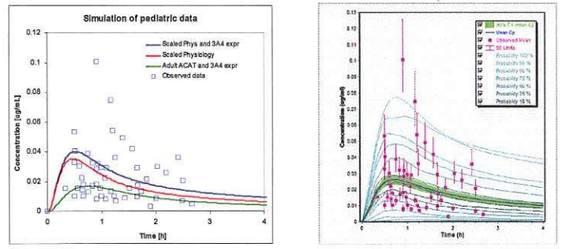
Left: Simulation using experimental and *in silico* properties, *in vitro* metabolism values, and rat K_p values: green – adult Gut parameters, adult 3A4 expression, *in vivo* V_{max} as would be obtained by conversion from *in vitro* V_{max} value using adult liver size; red – pediatric physiology (Gut parameters and Liver size for V_{max} conversion) with adult 3A4 liver expression; blue – pediatric physiology and 3A4 expression in Liver. **Right:** virtual trial using the baseline values with scaled pediatric physiology and 3A4 expression in Liver

3) Adult Cp-time data available after *p.o.* administration (PBPK model)

Adult Cp-time profiles after p.o administration were available from two different sources: data from one source were used to fit the 3A4 expression in liver, data from the second source were used to verify the fitted model before applying it to pediatric physiologies. Experimental values were used where available, remaining properties were from ADMET Predictor. Rat tissue:plasma partition coefficients were used.



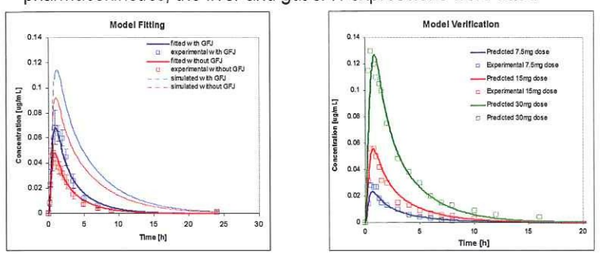
Left: Model fitting to experimental data from one literature source: dashed lines – simulations before the Liver 3A4 expression was optimized, solid lines – simulations with optimized Liver 3A4 expression, Squares – experimental data, blue – drug was taken with Grapefruit juice, red –drug was taken without grapefruit juice (Grapefruit juice was shown to inhibit the 3A4 activity in gut which was simulated by 62% decrease in gut V_{max}) **Right:** Fitted model was verified by comparing with the experimental data for three different doses from another literature source



Left: Simulation using experimental and *in silico* properties, *in vitro* metabolism values, and rat Kp values: green – adult Gut parameters, optimized adult 3A4 expression, *in vivo* V_{max} as would be obtained by conversion from *in vitro* V_{max} value using adult liver size; red – pediatric physiology (Gut parameters and Liver size for V_{max} conversion) with adult 3A4 liver expression; blue – pediatric physiology and 3A4 expression in Liver. **Right:** virtual trial using the baseline values with scaled pediatric physiology and 3A4 expression in Liver

4) Adult Cp-time data available after *i.v* and *p.o.* administration (Compartmental model)

Cp-time profile after *i.v.* administration was used to fit 2-compartment pharmacokinetics, the liver and gut 3A4 expressions were fitted the same way as in the PBPK model above, experimental values were used where available, remaining properties from ADMET Predictor



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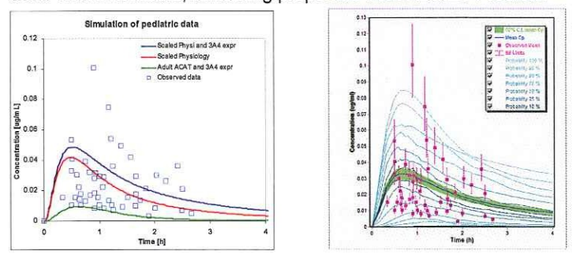

Left: Simulation using experimental and *in silico* properties, and *in vitro* metabolism values: green – adult Gut parameters, adult 3A4 expression, *in vivo* V_{max} as would be obtained by conversion from *in vitro* V_{max} value using adult liver size; red – pediatric physiology (Gut parameters and Liver size for V_{max} conversion) with adult liver 3A4 expression; blue – pediatric physiology and 3A4 expression in Liver. **Right:** virtual trial using the baseline values with scaled pediatric physiology and 3A4 expression in Liver