Simulation of Gabapentin Absorption and Bioavailability in Pediatric Patients

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Abstract

Purpose: To fit an absorption-pharmacokinetic model for simulation of Gabapentin in adult and pediatric populations. The model will be able to describe the nonlinear dose dependence of absorption mediated by an amino acid transporter as well as age-dependent renal clearance of Gabapentin.

Methods: GastroPlus™ 5.3 with the PBPKPlus™ Module (Simulations Plus, Inc., Lancaster, CA) was used to simulate adult human plasma concentration time (Cp-time) profiles after oral administration of Gabapentin in adults (doses ranging from 400mg to 1600mg) and children (400mg dose). A physiologically-based pharmacokinetic model (PBPK) was used in all simulations. Tissue/plasma partition coefficients were calculated using *in silico* physicochemical properties (ADMET Predictor™, Simulations Plus, Lancaster, CA) and the Rodgers (2005, 2007) algorithm. The renal clearance of Gabapentin was estimated to be equal to glomerular filtration rate (GFR) times fraction unbound in plasma (Fup) in both populations. Experimental GFR values from literature were used for both populations. The nonlinear dose dependent absorption of Gabapentin was simulated by incorporating an intestinal influx transporter and *in vitro* affinity measurements of Gabapentin interaction with LAT1.

Results: The fitted absorption-pharmacokinetic model was able to simulate the nonlinear dose-dependent pharmacokinetics in an adult population. The adult model was successfully scaled to pediatric physiologies to estimate Gabapentin absorption and pharmacokinetics in children. For both populations the renal clearance estimated as GFR × Fup provided an accurate estimate of the clearance for the drug which is not extensively metabolized in humans and the urinary secretion is governed only by glomerular filtration.

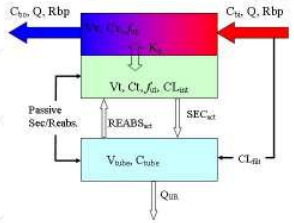
Conclusion: *In vitro* data and/or *in vivo* Cp-time profiles from adult populations can be successfully used to predict the Gabapentin Cp-time profiles in pediatric patients if the organ physiology for a given age is accompanied by scaling of the gastrointestinal tract parameters and glomerular filtration rate to the same age.

Cp-time profiles in pediatric population [3] and in adults [4-5] were obtained from literature. Default Human-Physiological gut model with added expression of influx intestinal transporter was used to simulate the absorption of Gabapentin in adults. The gut physiology was scaled to proper age for simulation of pediatric population. Km value for Gabapentin interaction with influx transporter was used as measured *in vitro* [8], Vmax was optimized against Cp-time profiles from adults after PO doses in range 400-1600mg which exhibited non-linear dose dependency.

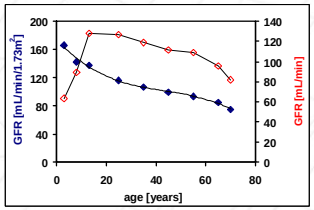
Physiologically-based pharmacokinetic models for a typical 41 year old adult (body weight 76.5kg) and a 7 year old child (body weight 27.7kg) were used to describe the pharmacokinetics of Gabapentin. Tissue distribution was modeled based on tissue:plasma partition coefficients calculated using modified Rodgers & Rowland equation [1-2]. The renal clearance of Gabapentin was estimated by glomerular filtration. The filtration rate was calculated as:

$$CL_{filt} = F_{up} \times GFR$$

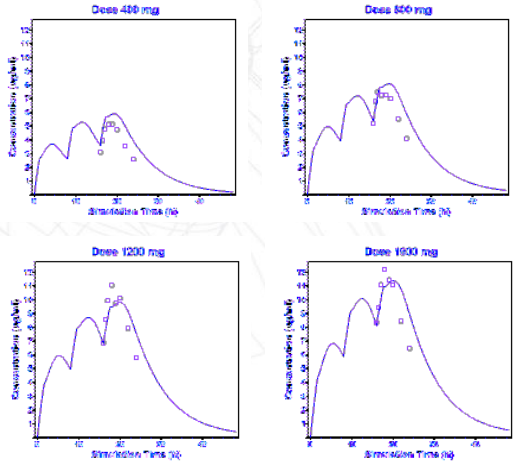
where Fup is fraction unbound in plasma and GFR is glomerular filtration rate.
The age dependency of GFR in range of ages 3 to 75 years was based on data from literature [6-7].



Physiological model of Kidney tissue as implemented in PBPK model in GastroPlus.

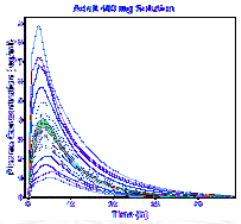


Glomerular filtration rate vs. age [6-7].

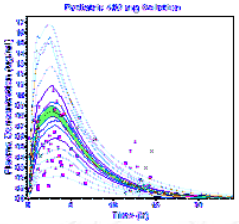


Dose [mg]	Fa [%]		Cmax [ug/mL]		Tmax [hrs]	
	simulated	observed	simulated	observed	simulated	observed
400	54	51	5.9	5.1	19.4	18.0
800	39	42	8.1	7.5	19.7	17.0
1200	32	36	9.8	11.0	20.0	18.0
1600	29	36	11.4	12.2	20.0	18.0

The final model consisting of physiological gut model with fitted Vmax value for influx transporter and physiologically based PK model with renal clearance of Gabapentin closely reproduced nonlinear dose dependency of fraction absorbed and Cp-time profiles after three times a day PO dosing of Gabapentin in adults.



Virtual Trial simulation for 400mg PO dose in adult population (30 to 50 year old). The mean and 90% confidence intervals from virtual population of 125 subjects closely reproduced the observed mean Cp-time profile. The error bars on experimental points represent bioequivalence limits (80-125% of observed value)



Virtual Trial simulation for 400mg PO dose in pediatric population (3 to 12 year old). The simulated variability in population of 125 subjects reproduced the observed variability.

References

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