Adult and Pediatric GastroPlus-PBPK Simulations of Gabapentin using *in silico* Population Estimates for Age-Related (PEAR) Physiology.

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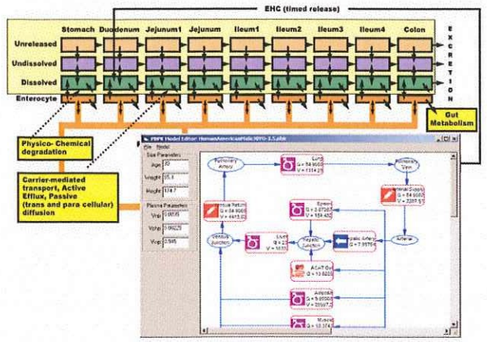
Abstract:

Purpose. The purpose was to validate the application of the advanced compartmental absorption and transit (ACAT)-PBPK model for simulations of Gabapentin absorption and distribution and to test the performance of *in silico* calculation of PBPK parameters including tissue:plasma partition coefficient (Kp) and fraction unbound in tissue (fut) for adult and pediatric populations.

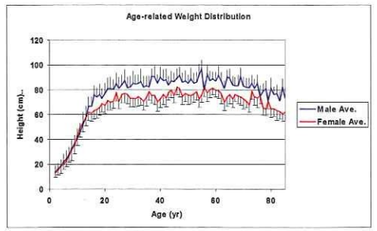
Methods. GastroPlus®-PBPK (Simulations Plus, Inc., Lancaster, CA) was used to simulate adult human plasma concentration time profiles (Cp vs. time) observed for Gabapentin when administered in solution at a dose of 400 mg. Renal CL was estimated from creatinine clearance. Subsequent simulations of solid dosage forms between 400 mg and 1600 mg were compared to corresponding literature data in order to validate the non-linear dose dependence and bioavailability due to saturable amino acid transporter mediated absorption. PEAR-Physiology™ was used to calculate organ weights, volumes, perfusions, and tissue-plasma partition coefficients for a 41 yo female and a 5 yo male. Intrinsic clearance optimized for the adult was used for simulation of the pediatric Cp vs. time profiles. The resulting data was compared to clinical data for pediatric populations from the literature.

Results. GastroPlus-PBPK simulations accurately reproduced the non-linear dose dependence for Gabapentin bioavailability and Cp vs. time profiles for administration of Gabapentin from 400 mg to 1600 mg doses. Using a purely *in silico* calculation of pediatric physiology and tissue:plasma partition coefficients and an estimate of the pediatric Gabapentin renal clearance, the pediatric Cmax, and Tmax were accurately simulated.

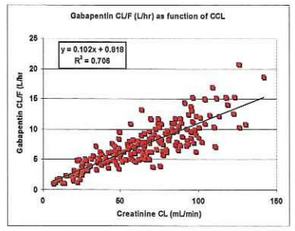
Conclusions. Following calibration of a physiologically-based gastrointestinal simulation for adult physiology, a purely *in silico* estimation of pediatric physiology and tissue:plasma partition coefficient could be used to predict the pediatric Cp vs. time profile for Gabapentin following oral liquid or capsule administration.



Advanced Compartmental Absorption and Transit (ACAT-PBPK)



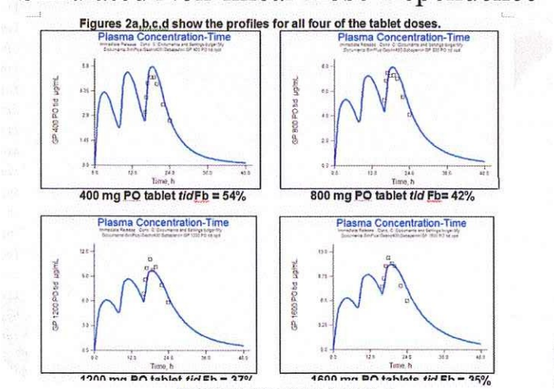
NHANES Body Weight vs. age



Gabapentin Clearance vs. Creatininie CL

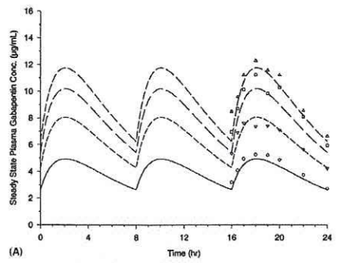
The Population Estimates for Age-Related (PEAR) Physiology™ program is based on the National Health and Nutrition Examination Survey (NHANES - 2002) database. The NHANES database includes extensive physiological parameters for 11,039 people of diverse age, ethnicity, and gender.

Simulated Non-linear Dose Dependence



B.E. Gildal et al. Epilepsy Research 31 (1998) 91–99

Predicted and Observed Steady-state Plasma Gabapentin Concentrations



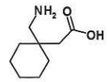
Predicted Steady-state Plasma Gabapentin Concentrations Following q6h Administration

PEAR-Physiology Method

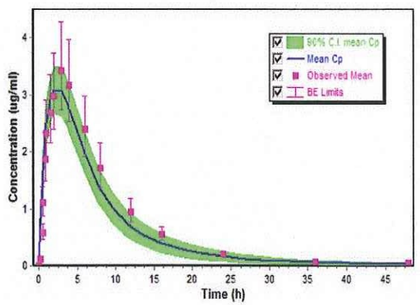
Input parameters for PEAR-Physiology are species, age, gender, and venous hematocrit. The output is a complete set of tissue physiology parameters.

1. Lookup average weight, height, bioimpedance.
2. Calculate BMI and Fat Free Mass (FFM)
3. Set the constant perfusion rates per mL tissue Price, P.S. Crit. Rev. Toxicol. 33(5):469 (2003), Table 13
4. Calculate blood volumes (Haddad S., et al., J. Tox. Envir. Health 64:453 (2001))
5. Calculate weight, volume, density, perfusion for each tissue.

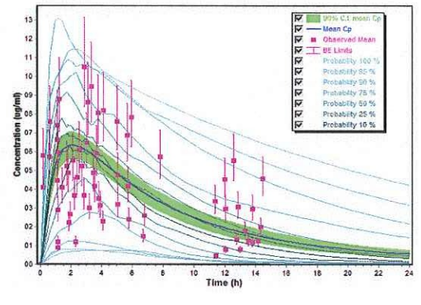
Gabapentin Virtual Trial Population Parameters



- Substrate for L-type amino acid transporter (LAT-1 IC_{50} = 340 µM)
- High solubility and Low passive permeability.
- Log P = -1.1 (exp.) , fup = 0.064 (estimated by ADMET Predictor)
- Renal Clearance estimated from Creatinine CL (CCL):
  - Adult and Child Gabapentin Cl (GCL) = 0.102 x CCL + 0.818
  - Adult GCL average of Schwartz and Cockroft Gault = 10.3 L/hr
  - 7 yo Child Gabapentin CL = 5.21 L/hr.
- Virtual Trial log Normal distributions CV% assumptions:
  - Influx Vmax = 200%, Influx Km = 50%, SITT = 20%, ColonTT = 20%
  - Peff = 60%, Kidney CL = 40%, Other Phys. Params = 10%



400 mg Solution – 41 yo Female



400 mg Tablet to 7 yo Child

References:
Ouellet D., Epilepsy Research 47:229 (2001), "Population pharmacokinetics of gabapentin in infants and Children".
Gildal B.E., Epilepsy Res. 40:123 (2000) "Inter- and intra-subject variability in gabapentin absorption and absolute bioavailability".
Gidal B.E., Epilepsy Res. 31:91 (1998) "Gabapentin bioavailability: effect of dose and frequency of administration in adult patients with epilepsy".