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Different Perspectives - Informing Drug Development Decision Making Through Complementary M&S Approaches

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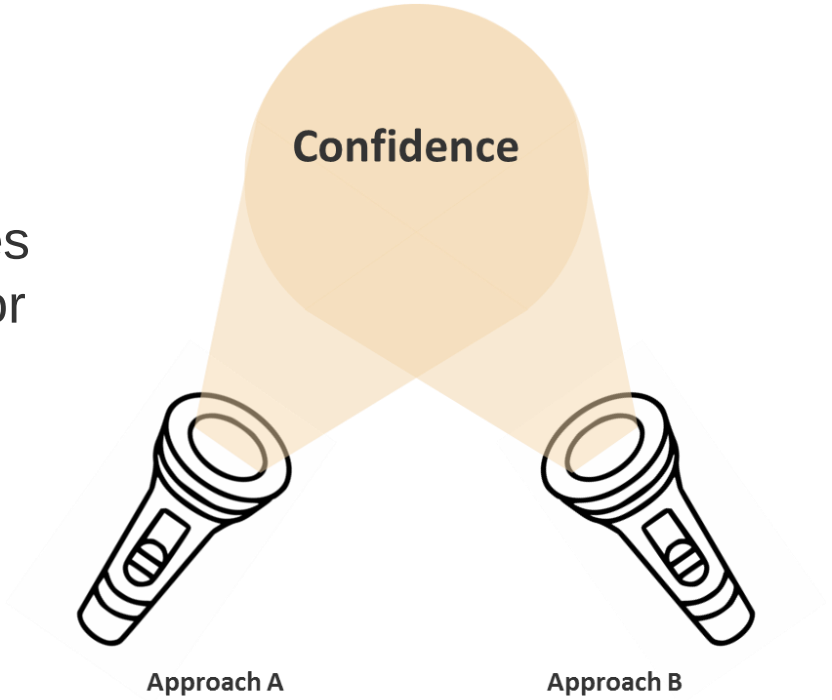
Outline

- Complementary M&S approaches
  - Introduction
- M&S approaches to study drug disposition
  - PBPK vs population PK (PPK) models
  - Factors affecting the choice
- Case study
  - Application of complementary M&S approach for dose determination in younger children (1 - < 24 months)

Complementary M&S Approaches to Predict PK

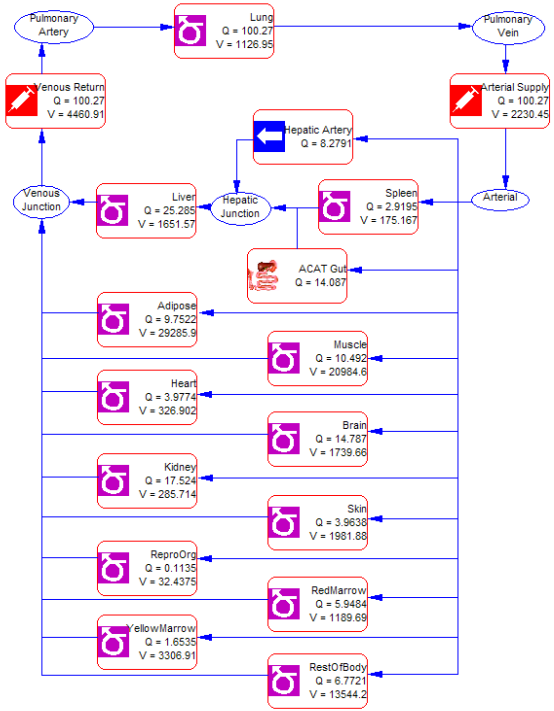
Two independent modeling approaches applied to predict drug PK when little or no supporting data available



PBPK Approach

General concept

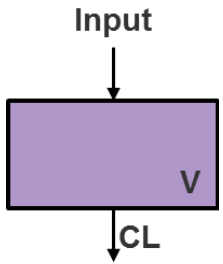
- Each compartment represents a tissue
- Distinction between physiology and drug related parameters
- Physiology related parameters (associated with a population)
  - Specific volumes
  - Blood-perfusion rate
  - Enzyme/transporter expression levels
- Drug related parameters (predicted using in silico methods or measured using in vitro experiments)
  - LogD vs pH
  - pKa
  - Plasma protein binding
  - Blood: plasma concentration ratio
  - Enzyme/transporter kinetic parameters
  - Effective permeability



PPK Approach

General concept

- Empirical model structure:
  - [No. of CMTs] ~ [No. of EXP phases]
- Fixed-effect parameters
  - PK parameters for a typical subject
  - Sources of variability
  - Covariate-parameter relationships
- Random-effect parameters
  - Within-subject, Between-subject, and inter-occasion variability
  - Assumption of normality/symmetry
  - Statistical models (i.e. exponential, proportional, additive etc.)



$$TVCL_i = \theta_1 \times \left(\frac{WTKG_i}{70\ kg}\right)^{0.75}$$

$$CL_i = TVCL_i \times EXP(\eta_{CL,i})$$

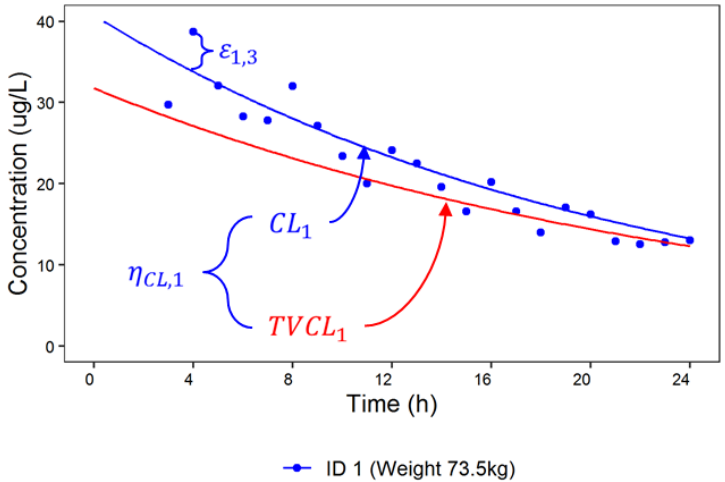
$$TVV_i = \theta_2 \times \left(\frac{WTKG_i}{70\ kg}\right)$$

$$V_i = TVV_i \times EXP(\eta_{V,i})$$

$$C_{i,j} = \frac{Dose}{V_i} \times EXP\left(-\frac{CL_i}{V_i} \times t_j\right) \times (1 + \varepsilon_{i,j})$$

$$\eta = N(0, \Omega^2)$$

$$\varepsilon = N(0, \sigma^2)$$



PK M&S Approaches Used in Drug Development

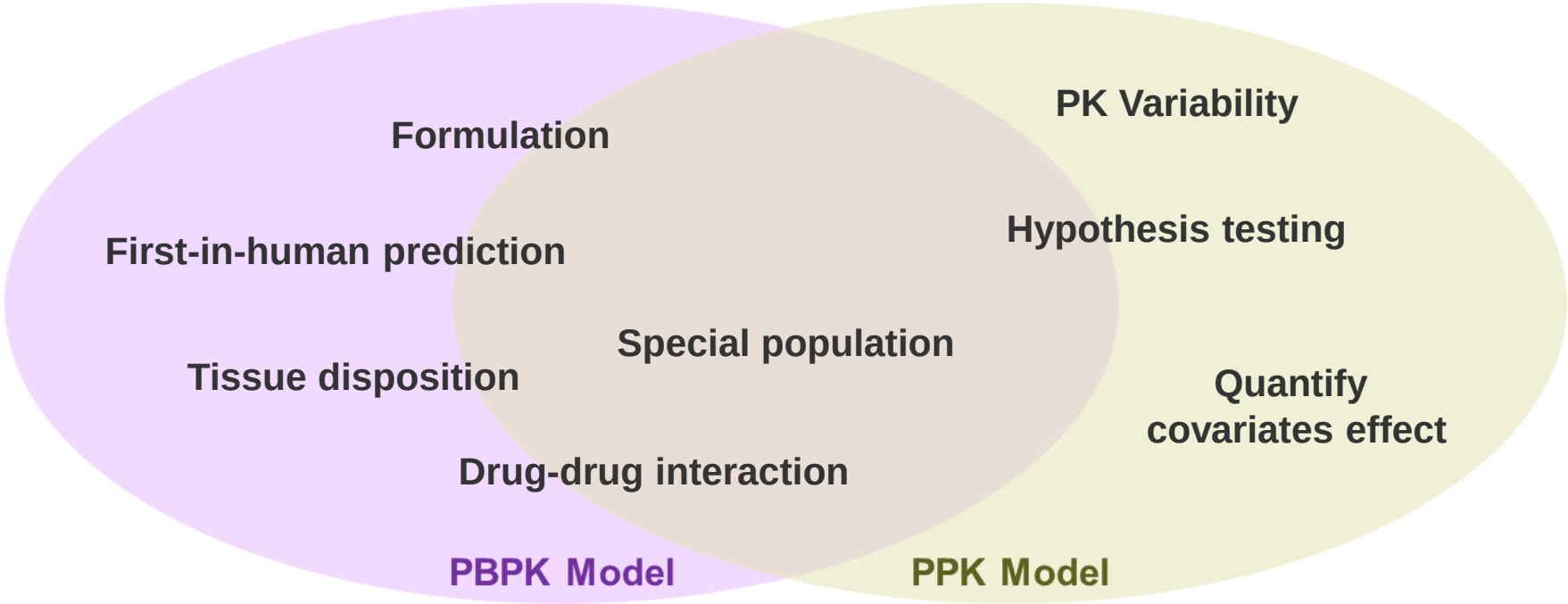
PBPK Model (Bottom-up Approach)

- Mechanism-driven
- Theoretical
- Predictive
- Simulation-based
- Physchem properties
- Physiological variability

Population PK model (Top-down Approach)

- Data-driven
- Empirical
- Descriptive
- Estimation-based
- Real-world data
- Random variability

Applications of PBPK and PPK Approaches in Drug Development

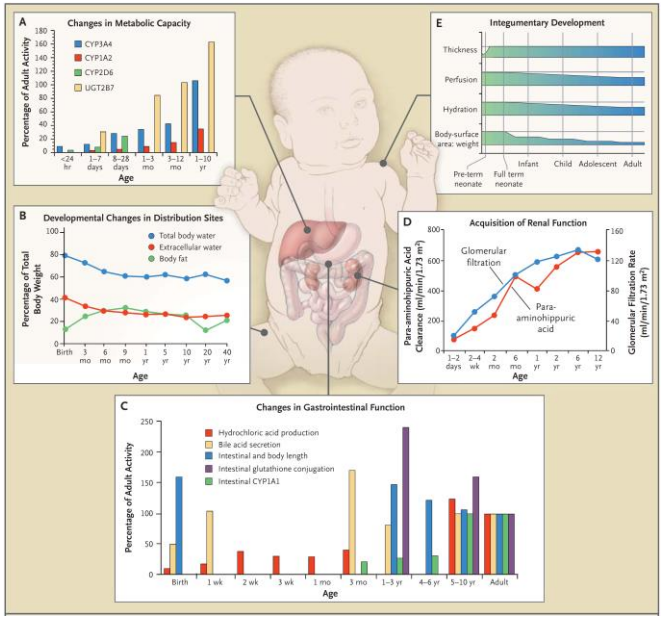


Factors to Consider to Choose Two Complementary Approaches

- Degree of confidence needed
- Availability of ADME information
  - In vitro and in vivo metabolism studies
  - Excretion mechanism of drug
  - Plasma protein binding
- Physiological parameters
  - Extent of enzyme/transporter expression in a tissue
- Nature of clinical PK data available
  - Sparse versus rich sampling scheme
  - Number of subjects and covariate information
- Subjective factors
  - Knowledge and expertise

Pediatric Drug Development

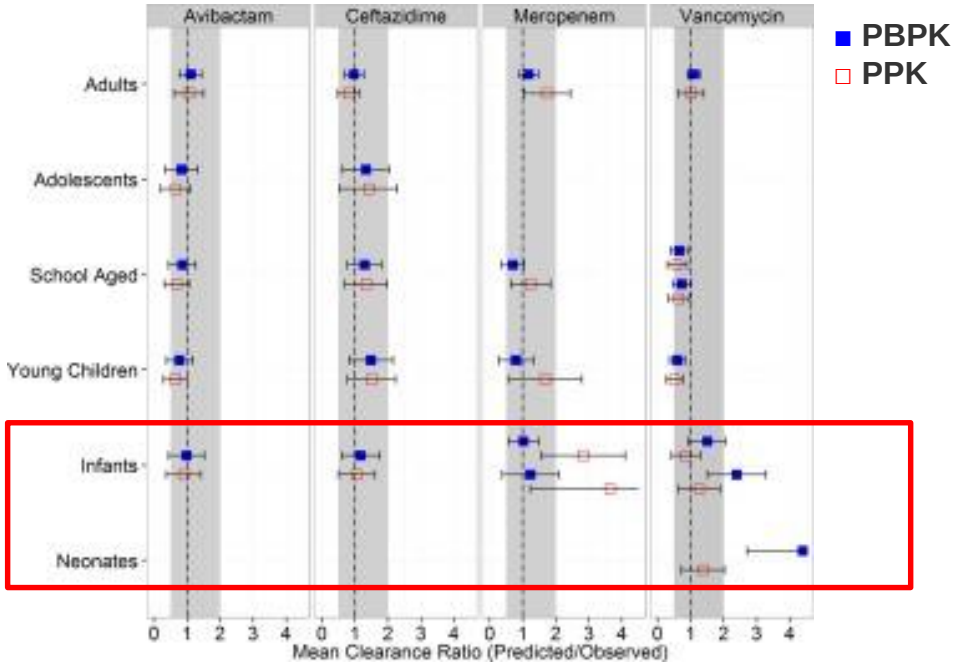
- Relevant regulations and guidance
  - FDA and EMEA guidance
  - Visibility of safety and efficacy evaluation in pediatric population
- Pediatric development challenge
  - Developmental changes in the physiological factors
  - Limited sample size
- Known developmental changes in physiology
  - Enzyme/transporter ontogeny
  - Renal function maturation
- Uncertainty remains in very young children (<2years)



Kearns, N Engl J Med, 2003

Relatively Higher Uncertainty in Predicting Clearance in Very Young children

Drugs eliminated via renal clearance only



Predictive performance of PBPK and PPK models

Zhou et al, CPT-PSP, 2016

Relatively Higher Uncertainty in Predicting Clearance in Very Young children

Drugs eliminated via renal and/or metabolic clearances

		Clearance ratio						
		Pediatric < 2 years				Pediatric > 2 years		
Performance criteria	Clinical studies	PBPK	Allometry exponent: 0.75	Allometry: age-dependent exponent	Population PK	PBPK	Allometry exponent: 0.75	Population PK
0.8–1.25	All (< 2 years, 30; > 2 years, 29)	37%	17%	30%		52%	69%	
0.5–2.0	All (< 2 years, 30; > 2 years, 29)	67%	47%	67%		93%	90%	
0.8–1.25	Subset of studies with popPK interpolation, extrapolation (< 2 years, 18; > 2 years, 13)	33%	11%	38%	28%	62%	77%	62%
0.5–2.0	Subset of studies with popPK interpolation, extrapolation (< 2 years, 18; > 2 years, 13)	67%	33%	72%	44%	100%	85%	85%

Predictive performance of PBPK and PPK models

Wu and Peters, CPT-PSP, 2019

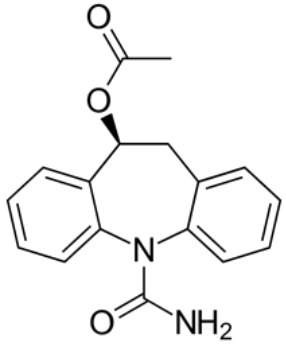
CASE STUDY

To select eslicarbazepine acetate (ESL) dose that matches exposure observed in adult patients for evaluation as adjunctive therapy in children (aged 1 - <24 months)

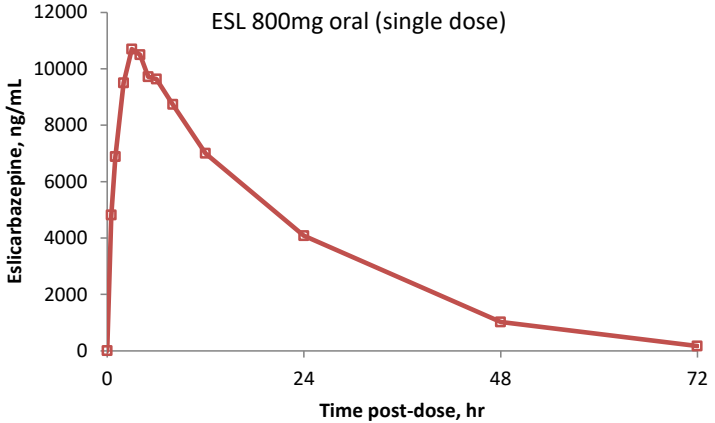
S Sunkaraneni, S Bihorel, E Ludwig, J Fiedler-Kelly, D Morris, S Hopkins, G Galluppi, D Blum, American Academy of Neurology, April, 2017

Eslicarbazepine Acetate

- Approved as adjunctive treatment and monotherapy for partial onset seizure (POS) in adults
- Administered orally and has high bioavailability
- Rapidly metabolized to eslicarbazepine, the primary active metabolite representing about 95% of total systemic drug exposure
- Steady-state is attained after 4 to 5 days
- More than 90% dose excreted in urine as eslicarbazepine or glucuronide conjugate forms



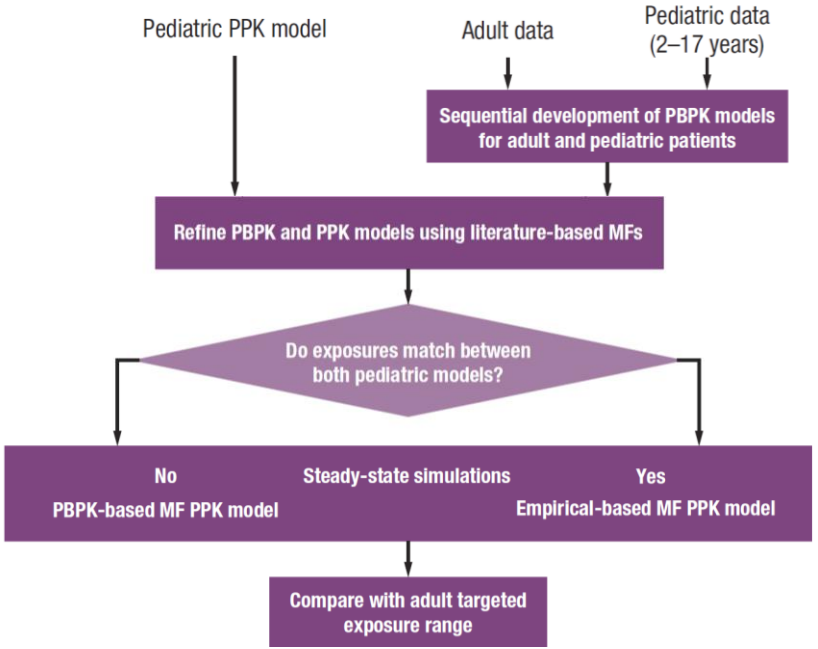
Eslicarbazepine Acetate



Almeida et al, J Clin Pharmacol, 2005

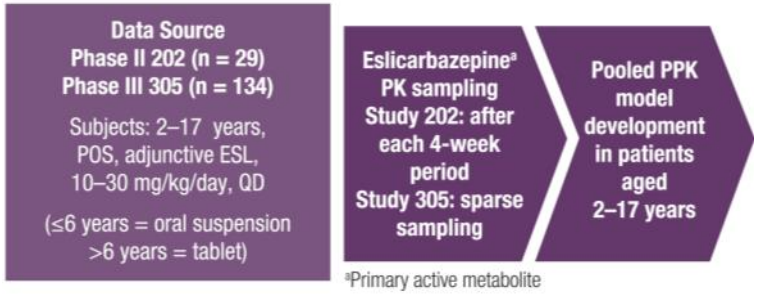
M&S Strategy to Inform Dose Selection in Pediatric Patients (Aged 1 - <24 Months)

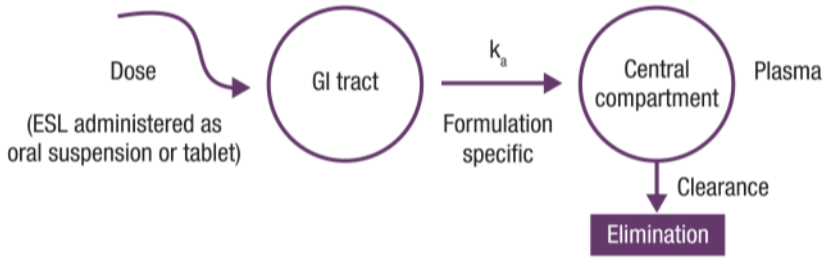
- Targeted exposures based on adults
  - Low dose 600 mg QD
  - High dose 1200 mg QD



Sunkaraneni et al, AAN, 2017

Eslicarbazepine Pediatric PPK Model was a 1-CMT Model with First-order Absorption and First-order Elimination





$$\widetilde{CL}_i = 1.69 \times \left(\frac{WTKG_i}{33}\right)^{0.75} \times \left(\begin{array}{c}0.824 \text{ for} \\ \text{Levetiracetam} \\ \text{ConMed}\end{array}\right) \times \left(\begin{array}{c}1.626 \text{ for} \\ \text{Phenobarbital-like} \\ \text{ConMed}\end{array}\right)$$

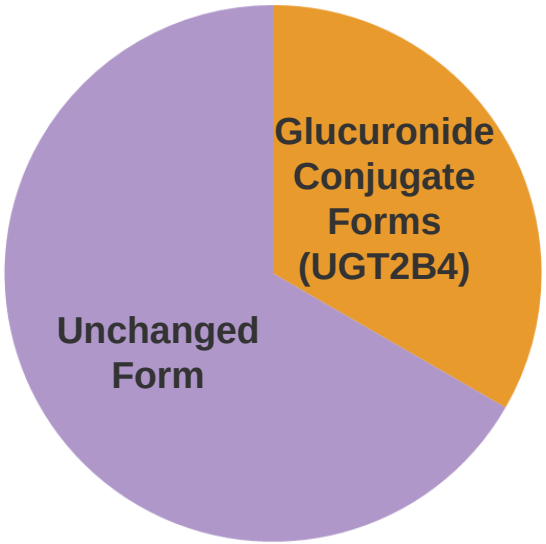
$$\tilde{V}_i = 32.8 \times \frac{WTKG_i}{33}$$

Sunkaraneni et al, J Pharmacokinet Pharmacodyn, 2018

Eslicarbazepine Systemic Clearance in Pediatric PPK Model (Age 2-17 years) as a Function of Body Weight and ConMed

$$\widetilde{CL}_i = 1.69 \times \left(\frac{WTKG_i}{33}\right)^{0.75} \times \begin{pmatrix} 0.824 \text{ for} \\ \text{Levetiracetam} \\ \text{ConMed} \end{pmatrix} \times \begin{pmatrix} 1.626 \text{ for} \\ \text{Phenobarbital-like} \\ \text{ConMed} \end{pmatrix}$$

- > 90% dose excreted in urine
- Metabolism primarily by UGT2B4
- Levetiracetam elimination exclusively by renal clearance
- Phenobarbital-like effect associated with metabolic induction



Renal Elimination of Eslicarbazepine

Sunkaraneni s et al, AAN, 2017; Maia J et al, Int J Clin Pharmacol Ther, 2008; Loureiro A et al, Drug Metab Dispos, 2011; Radtke R, Epilepsia, 2001

Eslicarbazepine Systemic Clearance in Pediatric PPK Model (Age 2-17 years) as Renal and Non-renal Elimination

$$\widetilde{CL}_i = \frac{2}{3} \times 1.69 \times \left(\frac{WTKG_i}{33}\right)^{0.75} \times \begin{pmatrix} 0.728 \text{ for} \\ \text{Levetiracetam} \\ \text{ConMed} \end{pmatrix}$$

$$+ \frac{1}{3} \times 1.69 \times \left(\frac{WTKG_i}{33}\right)^{0.75} \times \begin{pmatrix} 2.86 \text{ for} \\ \text{Phenobarbital}-\text{like} \\ \text{ConMed} \end{pmatrix}$$

Redefine and estimate clearance in pediatric PPK model (Age 2 – 17 years)

Sunkaraneni s et al, AAN, 2017; Maia J et al, Int J Clin Pharmacol Ther, 2008; Loureiro A et al, Drug Metab Dispos, 2011; Radtke R, Epilepsia, 2001

Refinement of Pediatric PPK Model to Account for Maturation of Renal and Non-renal CL in Children Aged 1 – <24 Months

$$\widetilde{CL}_i = \frac{2}{3} \times 1.69 \times \left(\frac{WTKG_i}{10}\right)^{0.75} \times \begin{pmatrix} 0.728 \text{ for} \\ \text{Levetiracetam} \\ \text{ConMed} \end{pmatrix} \times \frac{PMA_i{}^{3.4}}{47.7^{3.4} + PMA_i{}^{3.4}}$$

$$+ \frac{1}{3} \times 1.69 \times \left(\frac{WTKG_i}{10}\right)^{0.75} \times \begin{pmatrix} 2.86 \text{ for} \\ \text{Phenobarbital-like} \\ \text{ConMed} \end{pmatrix} \times \frac{Peds_{mRNA}}{Adult_{mRNA}}$$

- Renal elimination maturation by maturation of glomerular filtration rate
- Non-renal elimination maturation by relative expression of UGT2B4 mRNA in pediatric versus adult subjects

Rhodin M et al, Pediatric Nephrology, 2009; Strassburg C et al, Gut, 2002

Development of PBPK Model for Eslicarbazepine in Pediatric Subjects Aged 1 - <24 Months

Adult PBPK Model	• Described mechanistic absorption and elimination process of eslicarbazepine • Validated using mean and individual data for adult subjects
Pediatric PBPK Model	• Adult model was extended to describe the mean and individual data for pediatric subjects • Physiological parameters were generated in PBPK module of GastroPlus • Maturation of UGT2B4 enzyme expression was estimated
Refined Pediatric PBPK Model	• Custom built ontogeny function of UGT2B4 based on estimated individual UGT2B4 expression and literature

Sunkaraneni et al, AAN, 2017

Exposure Simulation in Virtual Subjects (Aged 1 - <24 months) Using Refined PPK and PBPK Models

Deterministic Simulation using Refined PBPK Model

- Virtual subjects:
  - physiological parameters from PEAR™ physiology module in GastroPlus™
- Dosing regimen:
  - 5 - 25 mg/kg/day QD in increments of 5 mg/kg/day (Max daily dose of 1200 mg)

Stochastic Simulation using Refined PPK Model

- Virtual subjects
  - Age: Uniform distribution between 1-24 months
  - Body weight: Based on CDC growth table
  - ConMed: Based previous distribution on peds
- Dosing regimen:
  - 5 - 60 mg/kg/day QD in increments of 5 mg/kg/day (Max daily dose of 1200 mg)

Sunkaraneni et al, AAN, 2017

Exposure Comparison Between PPK and PBPK Model and Proposed ESL Dosing Regimen

- Comparable exposures between PPK model and PBPK model
- Pediatric doses were selected for evaluation based on PPK and PBPK models to target exposures that are known to be safe and effective in adults

ESL group	Age category	ESL titration Week 1 (dose level 1)	ESL titration Week 2 (dose level 2)	ESL maintenance dose Week 3 (dose level 3)
1 (low dose)	1–<6 months	2.5	5	7.5
	6–<12 months	5	7.5	10
	12–<24 months	5	10	12.5
	24 months–<4 years	5	10	15
2 (high dose)	1–<6 months	5	10	15
	6–<12 months	10	15	20
	12–<24 months	10	20	25
	24 months–<4 years	10	20	30

Sunkaraneni et al, AAN, 2017

Summary

- Although fundamental principles are different between PBPK and population PK approaches, both techniques have been used to study drug disposition during drug development
- Predictive performance of individual PBPK and population PK models remained poor in young children (< 2 years), which creates an opportunity to use complementary M&S approaches
- Complementary approaches consisting of PBPK and population PK models was successfully used to derive an eslicarbazepine dosing regimen for further evaluation in young children (1 - <24 months)

References

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Questions