Predicting Pharmacokinetics in Children using PK-Sim®

Andrea N. Edginton [1], Stefan Willmann [1], Walter Schmitt [1]

[1] Bayer Technology Services GmbH, Process Technology, Competence Centre Biophysics, D-51368 Leverkusen, Germany

INTRODUCTION

- The prediction of pharmacokinetic (PK) differences in children compared to adults is important for dosage adjustment, therapeutic response analysis and risk assessment
- Physiology-based pharmacokinetic (PBPK) modeling is a tool for simulation of concentration-time profiles based on physiology (body and organ weights, blood flows, partition coefficients, etc)
- **Objective:** determine the appropriateness of the PBPK software, PK-Sim®, to predict plasma concentration-time curves in children

METHODS

Physiological Scaling

- PK-Sim® includes the age-dependent scaling of body & organ weights, organ composition and blood flows. The age-dependence of physiological parameters were summed and compared with literature values for:
  - Blood Volume
  - Cardiac Output
  - Total Body Water
  - Extracellular Water
  - Body Fat

Clearance Scaling

- Clearance was predicted using a 'Combined Physiology-based and Enzyme Ontogeny Approach' (see other poster) as described in Edginton *et al* (2005). The age-dependence of unbound fraction was predicted using the method of McNamara and Alcorn (2002).

Simulations

- **Box 1** describes the PK-Sim® inputs required to simulate plasma concentration-time curves
- Adult simulations were compared to literature values. Adjustments in partition coefficients were made if necessary. The altered model was used for simulations with children. Mean age & weight of studied group was used as input.
- Observed children values superimposed over simulated curve.

Box 1: PK-Sim® Input Information

★ Physiochemical Data of Compound

[Lipophilicity, Molecular Weight]

★ Plasma Protein Binding

[Age-dependence predicted - McNamara & Alcorn (2002)]

★ Age & Weight of Simulated Individual(s)

★ Administration Regime

★ Renal and Hepatic Clearance Value

[Age-dependence predicted - Edginton *et al* (2005)]

RESULTS

Table 1. Observed (Obs) cardiac output, blood volume, total body water [% of body weight (BW)], total extracellular water (% BW) and total body lipid (% BW) and the corresponding values as predicted in PK-Sim (Pred). Values are for males aged birth to adult. References available on the reverse side of the handout. NA = not available.

	Newborn		1 yr		5 yrs		10 yrs		15 yrs		30 yrs	
	Pred	Obs	Pred	Obs	Pred	Obs	Pred	Obs	Pred	Obs	Pred	Obs
Cardiac Output (L/min)	0.59	0.5, 0.7	1.5	1.4	3.2	3.4, 3.9	4.4	4.0	5.9	4.4, 6.6	6.1	5.8
Blood Volume (L)	0.27	0.27	0.63	0.50	1.3	1.4	2.2	2.4	3.3	3.3	3.8	3.9
Total Body Water (%)	66	60, 75	56	60	59	56	57	59, 57	60	NA	58	61, 59
Extracellular Water (%)	36	37, 40	28	25	26	22	22	20	20	NA	18	21, 17
Total Lipid (%)	17	NA	29	25	23	NA	23	13	19	NA	22	NA

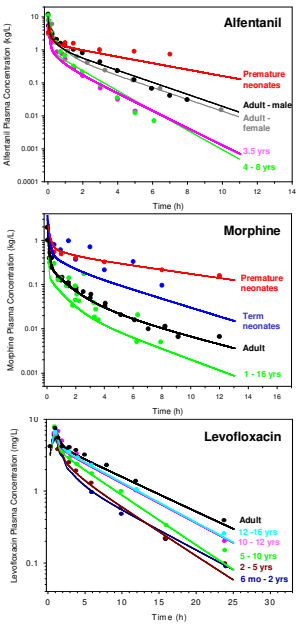

Figure 1. Observed (•) and predicted (-) plasma concentration vs. time curve following intravenous administration of alfentanil (Top), morphine (Middle) and levofloxacin (Bottom), to adults (black/gray) and children of various age. Input clearance for all children plots was that predicted by Edginton *et al* (2005).

Physiological Scaling

- All anatomical and physiological parameters were age-dependent and well-represented by PK-Sim (See **Table 1** for an example).
- Differences in body water & lipid primarily due to the age-dependence of interstitial space in adipose and muscle tissue (Baker, 1969; Boulton *et al*, 1978; Dickerson & Widdowson, 1960)

Simulations in Children

- The distribution phase was well-predicted. Both simulated and experimental data suggested that distribution was more rapid in premature & term neonates compared to older children and adults.
- Trends associated with differing age groups were well-represented by PK-Sim (**Figure 1**) where,
  - premature & term neonates had higher plasma concentrations compared to adults
  - children over 6 months had lower plasma concentrations compared to adults

CONCLUSIONS

- **The PBPK modeling tool, PK-Sim®, accurately predicted plasma concentration time curves for all ages, based on physio-chemical & physiological principles.**
- **In conjunction with appropriate clearance predicition, pediatric clinical trial development could highly benefit from the use of PK-Sim®. Possible uses of this technology inlude the guidance of dosing regimes and sampling time, and ultimately reduce the number of subjects required.**

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