Top-Down Modeling Meets Bottom-Up Modeling

The Physiological and Physicochemical Basis for the Ontogeny of UGT2B7-Mediated Drug Glucuronidation

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Background & Objective

Paediatric PopPK models described ontogeny of drug CL with a limited number of descriptive covariate relationships.

Paediatric covariate models for CL have be successfully extrapolated between drugs that share a common elimination pathway[1,2], suggesting they constitute system-specific rather than drug-specific information.

Using a PBPK modeling approach, the current study examines the physiological (system-specific) and physicochemical (drug-specific) basis of a paediatric population covariate model for UGT2B7-mediated CL in children <3 years[1,3]:

$$CL_{ind} = CL_{pop} * f_{<10d} * BW^{1.44} \qquad \textit{equation 1.}$$

According to covariate relationship UGT2B7-mediated CL increases exponentially with bodyweight ($BW^{1.44}$) and is reduced in neonates <10 days ($f_{<10d}$).

Methods

Simcyp v.11 was used to simulate morphine and zidovudine CL in 1000 children aged 0 – 3 years, split into 5 age-groups:

I) 0 – 3 mo, II) 3 – 6 mo, III) 6 – 12 mo, IV) 1 – 2 yrs, V) 2 – 3 yrs

Assumptions:
- Only drug elimination through UGT2B7-mediated glucuronidation.
- No active drug transport into or out of hepatocytes.

System-specific parameters
- Hepatic blood flow
- Liver volume
- Milligram protein per gram of liver
- UGT2B7 ontogeny (fractional expression and function compared to adults)
- Unbound drug fraction (driven by presence of drug binding plasma proteins)

The contribution of each parameter to the ontogeny of UGT2B7-mediated glucuronidation was determined as follows:
- The percentage change in each system-specific parameter value was calculated for each age-group.
- The system-specific parameter values were changed by a physiologically relevant value (the average percentage change of all age-groups) and used to simulate *in vivo* morphine and zidovudine CL.
- For each system-specific parameter in each age-group the mean sensitivity ratio (SR) was calculated:

$$SR = \frac{\%Change\_in\_CL_{Predicted\_InVivo}}{\%Change\_in\_ParameterValue}$$

- The percentage change in overall *in vivo* CL as a result of changes in the system-specific parameters was calculated for each age-group:

$$\%Change\_CL_{Overall\_InVivo} = \%Change\_in\_ParameterValue * SR$$

Drug-specific parameters
- Parameter values for morphine and zidovudine were obtained from literature.

The influence of physicochemical drug parameters on paediatric UGT2B7-mediated glucuronidation was determined as follows:
- Hypothetical drugs with different physicochemical properties were simulated:
  MW range: 100 – 1000 g/mol
  logP range: 0.01 – 5.5
  pKa range: 2 – 12
  Blood binding parameters were derived with the Simcyp toolbox from logP and pKa.
  Enzyme kinetic parameters of morphine were used.
- The *in vivo* CL in each age-category was assessed for each hypothetical drug.

Results: System-Specific Parameters

Table 1. *Percentage parameter change, mean sensitivity ratio, and resulting percentage change in* in vivo *UGT2B7-mediated clearance per age-group, for the system-specific parameters that caused >5% change in* in vivo *clearance.*

Parameter	Age-related change in parameter value	Mean sensitivity ratio		Percentage change in *in vivo* CL as a result of changes in parameter	
		morphine	zidovudine	morphine	zidovudine
Liver volume	I: 38% II: 18% III: 19% IV: 17% V: 21%	I: 0.82 II: 0.81 III: 0.79 IV: 0.76 V: 0.72	I: 0.58 II: 0.56 III: 0.50 IV: 0.43 V: 0.35	I: 31% II: 15% III: 15% IV: 13% V: 15%	I: 22% II: 10% III: 9.5% IV: 7.3% V: 7.4%
UGT2B7 ontogeny	I: 12.7% II: 11.4% III: 20.2% IV: 33.8% V: 25.2%	I: 0.90 II: 0.90 III: 0.88 IV: 0.85 V: 0.81	I: 0.66 II: 0.65 III: 0.60 IV: 0.52 V: 0.45	I: 11% II: 10% III: 18% IV: 29% V: 20%	I: 8.4% II: 7.4% III: 12% IV: 18% V: 11%
Hepatic blood flow	I: 33% II: 17% III: 19% IV: 22% V: 24%	I: 0.059 II: 0.061 III: 0.081 IV: 0.103 V: 0.127	I: 0.24 II: 0.22 III: 0.29 IV: 0.22 V: 0.29	I: 1.9% II: 1.0% III: 1.5% IV: 2.3% V: 3.0%	I: 7.9% II: 3.7% III: 5.5% IV: 4.8% V: 7.0%

Results: Physicochemical Parameters

MW did not influence *in vivo* UGT2B7-mediated CL.

logP and **pKa** influenced the absolute CL value, not the ontogeny pattern (i.e. vertical shift of the profile).

For equation 1 this means that only CL_{pop} is affected by physicochemical drug properties → parameter is hypothesized to be drug-specific.

The paediatric covariate relationship for UGT2B7-mediated CL is not affected by physicochemical drug properties.

Results: Top-Down *Versus* Bottom-Up

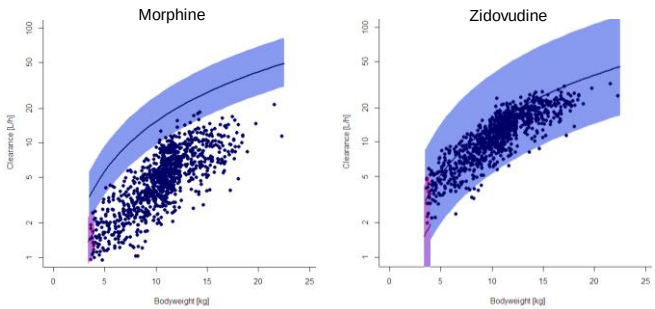

Figure 1. *Morphine and zidovudine CL values according to the PopPK model[1,3] (line and shaded area PopPred and 95% prediction interval respectively) and the PBPK model in Simcyp (symbols)* versus *bodyweight (purple for neonates <10 days of age, blue for older children).*

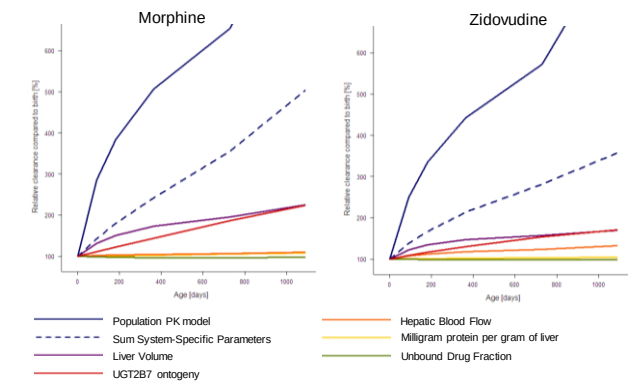

Figure 2. *Morphine and zidovudine* in vivo *CL relative to birth* versus *age, according to the PopPK models[1,3] and the contribution of the 5 system-specific parameters from the Simcyp model, including the sum of all five parameter contributions.*

→ Based on enzyme kinetic parameters from literature, the PBPK model under-predicts *in vivo* CL of morphine and zidovudine (fig1).

→ Except for the first days of life, the ontogeny profile of i*n vivo* CL predicted by the PBPK model is similar to the observed profile quantified by the PopPK model in children <3 years (fig 1 & 2).

→ The 5 system-specific parameters explain 79% and 41% of the observed increase in morphine and zidovudine CL between 10 days and 3 years.

Conclusion

For drugs with intermediate extraction ratio's, key physiological drivers of ontogeny of UGT2B7-mediated drug glucuronidation are liver volume and UGT2B7 ontogeny.

Physicochemical drug parameters do not influence the ontogeny pattern of UGT2B7-mediated glucuronidation of drugs with similar extraction ratios, logP and pKa only influence the absolute *in vivo* CL value.

Scenario's with non-linear or blood flow dependent CL need further investigation.

[1] Krekels EHJ *et al*. PAGE 20 (2011) Abstr 2062
[2] De Cock RFW *et al*. PAGE 20 (2011) Abstr 2096
[3] Knibbe CA *et al*. Clin. Pharmacokinet. 2009;48(6):371-85