Maturation of Glucuronidation; a System Specific Property

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Hypothesis

We hypothesize that the maturation rate of a metabolic pathway is a system specific rather than a drug specific property.

This would imply that a covariate model describing maturation of glucuronidation for one drug can be extrapolated to another drug that is metabolized through the same route.

As morphine and zidovudine are both glucuronidated by UGT2B7, it is tested whether a previously published covariate model for the maturation of morphine glucuronidation can also be used to describe maturation in zidovudine glucuronidation.

Methods

Zidovudine data:
473 zidovudine (ZDV) and173 zidovudine-glucuronide (G-ZDV) concentrations in blood were available from 29 individuals varying from term neonates to infants of 5 months [*Boucher et al. J.Pediatr. (1993); 122(1):137-144 (PACTG 049)].*

Two PK models were developed using this zidovudine dataset with different covariate models and each with optimized structural and error models.

1) System specific covariate model: this model used the covariate model previously obtained for the maturation of morphine glucuronidation (*Knibbe et al. Clin. Pharmackinet(2009); 48(6):371-385*). This model is based on sparse data in 248 patients ranging from preterm neonates up to infants 3 years of age and is thoroughly validated (*Krekels et al. Clin. Pharmacokinet.(2011); 50(1):51-63*)

2) Reference model: for this model a systematic covariate analysis of the zidovudine dataset was performed. Covariates were tested for their significance and only included in the model when they improved the model. This provides the best possible description of the data.

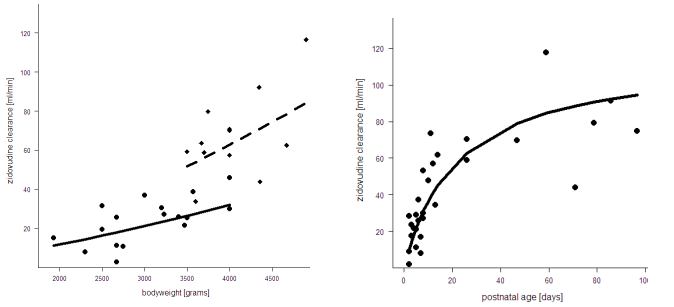
For both PK models, the descriptive and predictive model performance was evaluated using basic goodness-of-fit plots and NPDE with 1000 simulations.

Results – Covariate Models

In the system specific covariate model the maturation of glucuronidation is described by a bodyweight-based exponential equation with an exponent of 1.44 and reduced clearance in individuals younger than 10 days.

In the reference model the maturation of zidovudine glucuronidation in the dataset was best described by an age-based sigmoidal equation.

System Specific Covariate Model | *Reference Model*



$$CL_{pna<10d} = 4.35 * BW^{1.44}$$
$$CL_{pna>10d} = 8.53 * BW^{1.44}$$

$$CL = \frac{116 * (PNA/medianPNA)}{1.63 + (PNA/median\ PNA)}$$

Figure 1. *Population (line) and individual post hoc (symbols) parameter estimates of the ZDV glucuronidation clearance versus the most predictive covariate in each model.*

Results – Descriptive Properties of Models

System Specific Covariate Model | *Reference Model*

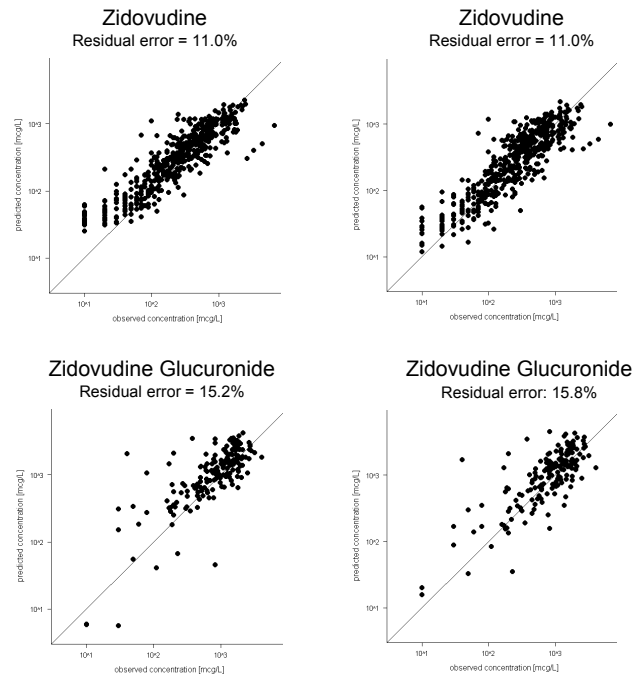


Figure 2. *Observed vs population predicted concentrations of ZDV (top) and G-ZDV (bottom) – Accuracy and precision of the data description by both models is equally well*

Results – Predictive Properties of Models

System Specific Covariate Model | *Reference Model*

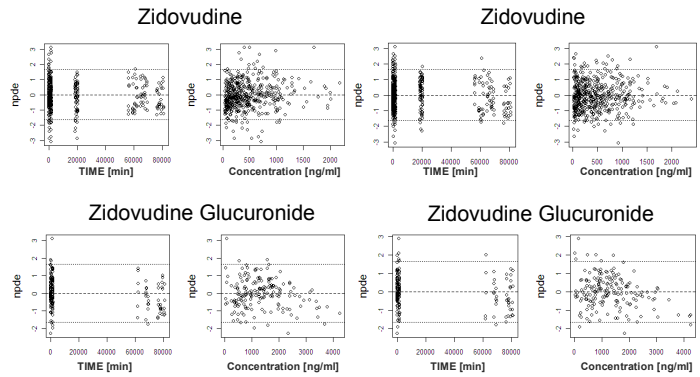


Figure 3. *NPDE distribution of ZDV (top) and G-ZDV (bottom) versus time and versus predicted concentration – Concentration predictions by both models show limited bias.*

Conclusion

Validated covariate models describing maturation of metabolic pathways can be used for extrapolation between different drugs that are metabolized through the same route to develop models with descriptive and predictive properties that cannot be discerned from models based on a thorough systematic covariate analysis in a time-efficient manner.

This study supports our hypothesis that maturation of metabolic pathways is a system specific rather than drug specific property.

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