

Use of semi-physiological covariate model for maturation of glucuronidation to scale from adults to children

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Background

A semi-physiological covariate model describing the glucuronidation clearance (CL_{gluc}) of morphine in young children was successfully applied to model zidovudine paediatric pharmacokinetic data [1]. Both drugs are mainly metabolized by UGT2B7 and have a high unbound drug fraction (fu) and extraction ratio (ER). Physicochemical drug properties were found to not influence the covariate relationship [2]. More recently, this covariate model has been extended to adults [3] and thus could potentially be used to predict paediatric CL_{gluc} based on body weight (BW) only.

Objectives

Assess the predictive value of the recent semi-physiological covariate model (SPC) [3] compared to classical allometric scaling (CAS) for scaling glucuronidation clearance (CL_{gluc}) from adults to different paediatric ages for drugs metabolized by UGT2B7 or UGT2B15 and with different fu and ER.

Method

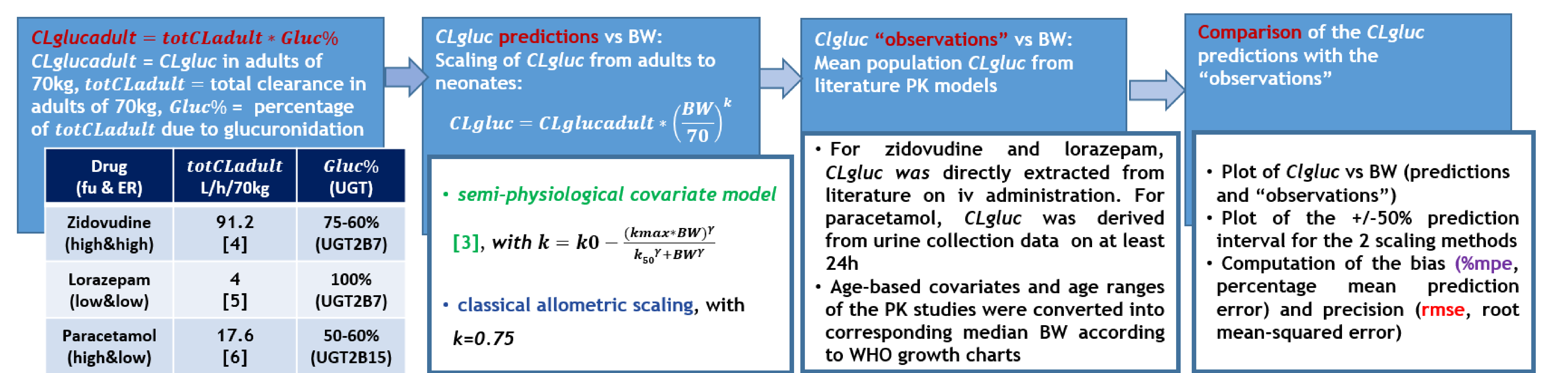


Figure 1. Methodology for the prediction of CL_{gluc} from adults to neonates with the semi-physiological covariate model and classical allometric scaling and their comparison and evaluation

Results

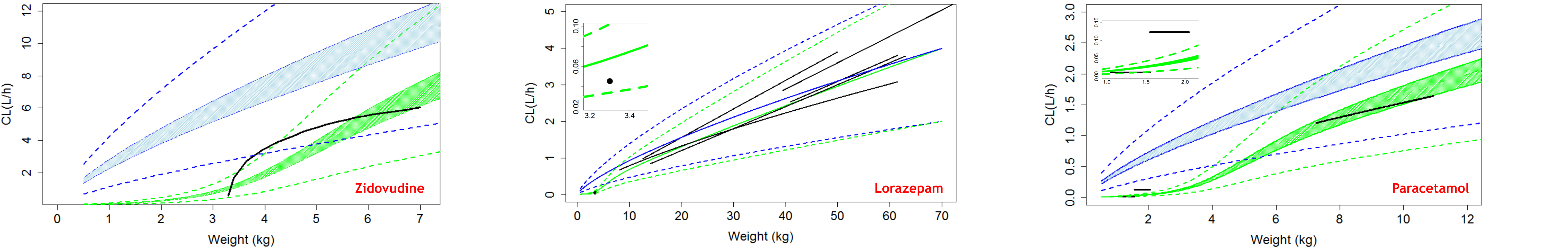


Figure 2. CL_{gluc} vs Weight: for population predictions (—) and the +/-50% prediction interval (---) of the semi-physiological covariate model and classical allometric scaling and mean values from literature (—) [1][5][7][8][9][10] for zidovudine, lorazepam and paracetamol.

Age Categories	Compound	Bias (%mpe) and precision (rmse) for:	
		Semi-physiological covariate model predictions	Classical allometric scaling predictions
Neonates	Zidovudine	-10.221 2.914	125.080 3.249
	Lorazepam	49.386 0.022	786.425 0.358
	Paracetamol	7.854 0.279	2339.617 0.439
Infants	Lorazepam	-13.065 0.104	17.708 0.143
	Paracetamol	0.033 0.002	33.333 0.478
Children	Lorazepam	-3.881 0.271	10.726 0.290
	Lorazepam	-6.168 0.515	-2.050 0.476

Table 1. Comparison of bias and precision for the 2 predictions methods

Conclusion

Scaling drug clearance from adults to children using a semi-physiological covariate model is a rapid and accurate approach that requires less information than whole-body PBPK modelling and should be preferred over the classical allometric scaling approach.

References

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