EXTRAPOLATION POTENTIAL OF SEMI-PHYSIOLOGICAL COVARIATE MODELS TO NEWBORNS: A SIMULATION-BASED STUDY

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Background and Objective

Background: Semi-physiological covariate models (SPCMs) describe the maturation of plasma clearance (CLp) for specific elimination pathways [1,2]. These models are obtained in PK studies of model drugs that are mainly eliminated through one specific pathway. It has been suggested that SPCMs can be extrapolated between drugs sharing an elimination pathway [1,2].

Objective: To investigate the extrapolation potential of SPCMs between drugs undergoing hepatic metabolism but with different drug properties, when predicting CLp in newborns based on CLp information in adults.

Conclusion

- **The extrapolation potential of an SPCM depends on the properties of the model drug, on the differences in properties between the model drug and the drugs the SPCM is extrapolated to, and on enzyme maturation.**
- **SPCMs have a better overall extrapolation potential when developed on model drugs with low ER. They reflect not only physiological and enzymatic maturation processes, but also drug specific properties.**
- **When investigating the extrapolation potential of an SPCM, CLp predictions for drugs with different drug properties should always be included.**

Methods

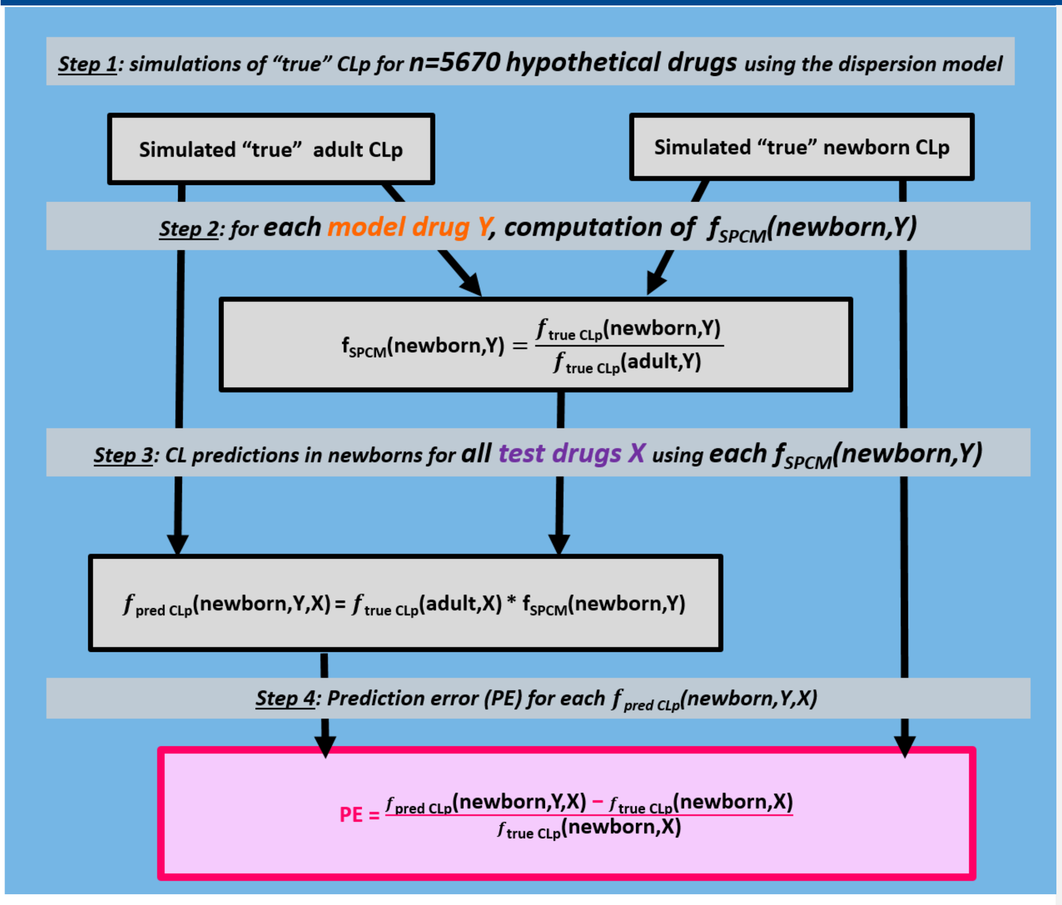

Figure 1. Workflow for SPCM-based CLp predictions in newborns and their prediction error

5670 hypothetical drugs with different combinations of:

- **Unbound fraction between 5 and 95%.**
- **Unbound microsomal intrinsic clearance ($Cl_{int,mic}$) between $0.56*10^{-3}$ and 0.209 L/min/mg microsomal protein in adults [3].**
- **Plasma to red blood cells partition coefficient from 0 to 4.**

Hypothetical drugs were used as model drugs (SPCM building) AND as test drugs (drugs for which CLp predictions were performed).

Simulations in R software followed the workflow in Fig.1, and two extreme maturation scenarios were investigated:

- **Scenario 1: enzyme maturation completed at birth, with $Cl_{int,mic}$ identical between adults and newborns.**
- **Scenario2: enzyme maturation not completed at birth, with changes in $Cl_{int,mic}$ derived from a published SPCM [4] using retrograde calculation.**

Physiological parameters (without variability) for scaling between adults and newborns were compiled from literature [5-9].

The extrapolation potential of SPCMs and their dependence on drug properties was assessed by comparison of the prediction errors (PE).

Results

- **Patterns in PE were best summarized using Extraction Ratio (ER)**
- **For both scenarios: SPCMs tended to over-predict CLp in newborns for test drugs with a lower ER than the model drug, and the opposite for test drugs with higher ER than the model drug.**
- **The SPCMs' prediction errors (PEs) were higher in scenario 2 compared to scenario 1 (Tab.1).**
- **Extrapolation potential increased with decreased ER of the model drug (Tab.1).**

		Extraction ratio of the model drugs			All model drugs
		low	intermediate	high	
Extraction ratio of the test drugs	Low ER	-30% to 43% -39% to 64%	-23% to 66% -25% to 138%	-10% to 89% 12% to 475%	-30% to 89% -39% to 475%
	Intermediate ER	-39% to 30% -58% to 34%	-34% to 50% -49% to 94%	-22% to 72% -23% to 370%	-39% to 72% -58% to 370%
	High ER	-47% to 11% -83% to -11%	-42% to 28% -79% to 29%	-32% to 46% -68% to 213%	-47% to 46% -83% to 213%
All test drugs		-47% to 43% -83% to 64%	-42% to 66% -79% to 138%	-32% to 89% -68% to 475%	-47% to 89% -83% to 475%

Table 1. PE intervals of SPCM-based CLp predictions in newborns for scenario 1 (green) and scenario 2 (brown)

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