Bridging Physiologically Based Pharmacokinetic (PBPK) & Population Pharmacokinetic (PopPK) Analyses in Paediatric Drug Development

A case study based on intravenous esomeprazole

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Objectives

- To adopt the two well established modelling methods PBPK and PopPK for scaling the pharmacokinetic (PK) characteristics from adults to paediatric populations
- To establish complementary and synergistic modelling approaches for selection of optimal dosage regimens in children

Background

Model-based approaches are implemented in obligatory steps of pediatric drug development. PBPK and PopPK are modelling methods often proposed to characterize PK and to support clinical trial design in children. It has been suggested to estimate the dosing using both of these approaches, and then select the most conservative dose.

Methods

Software: PBPK models were built in PK-Sim (v. 7.1).
PopPK models were built using NONMEM (v. 7.3, FOCE+I).

Target populations: Children 0 ≤12 years

PBPK adult model

Model Development
Drug-specific parameters [1]
Clinical observation [2]
- IV esomeprazole 20 + 40 mg in adults
- PK profiles and parameters

PopPK adult model

Structural and statistical model [3]

BWT as covariate on CL and Vd

Adult model verification [4]

PBPK paediatric model
Age dependent physiology and ontogeny

PopPK paediatric model
Allometric scaling

Paediatric Dose Investigation
Paediatric models
Virtual paediatric populations (VPP)

Dose in drug label

Simulation according to drug label (Tab 1) using VPPs (n=1000) generated in PK-Sim®.

Table 1. *Doses in drug label*

Population	Dose
< 1 month	0.5 mg/kg
1 - < 6 months	0.5 mg/kg
6 months - < 1 year	0.5 mg/kg
1 - < 6 years	10 mg
6 - < 12 years (BW < 55 kg)	10 mg

Dose optimization

Exposure matching to 20 mg IV dose in adults (2.67 μmol h/L)

Estimation of the optimal doses for the age groups in Table 1

Optimal doses estimated in NONMEM [5] based on output from suggested **PBPK** and **PopPK model** using VPPs (n=1000) generated in PK-Sim®

Dose regimen

Estimation of optimal dose regimens according to Table 2

Table 2. *Dosing schemes*

Weight	Dose regimen
< 18 kg	BWT-based dose (mg/kg)
≥ 18 kg	Fixed dose (mg) 0, 1, 2, or 3 BWT cut-offs

Optimal doses estimated in NONMEM [5] based on output from suggested **PBPK** and **PopPK model** using a VPP of 4000 children, 0 ≤12 years

Figure 1. *Project workflow*

Conclusions

This study demonstrates how dose-optimization algorithms can be applied to both PopPK and PBPK derived models. In line with regulatory recommendations, these complementary results can be used as support in selection of dosing regimen in children.

Results

- The PBPK and PopPK models provided adequate descriptions of the esomeprazole's PK characteristics in adults (Fig 2).
- With the dosing regimen in the label both models resulted in higher exposures in children than target (Fig 3) and lower optimal doses for specified paediatric populations were consequently estimated (Tab 3, Fig 4).
- In general, the PopPK model resulted in higher doses in young children compared to the PBPK model.
- The deviation from the target exposure decreased dramatically with optimal dosing regimens compared to the labelled dose. The between subject variability decreased for dosing regimens with one body weight (BWT) based dose switch. However, additional dose switches did not result in meaningful improvements of the exposure matching (Tab 4, Fig 4).

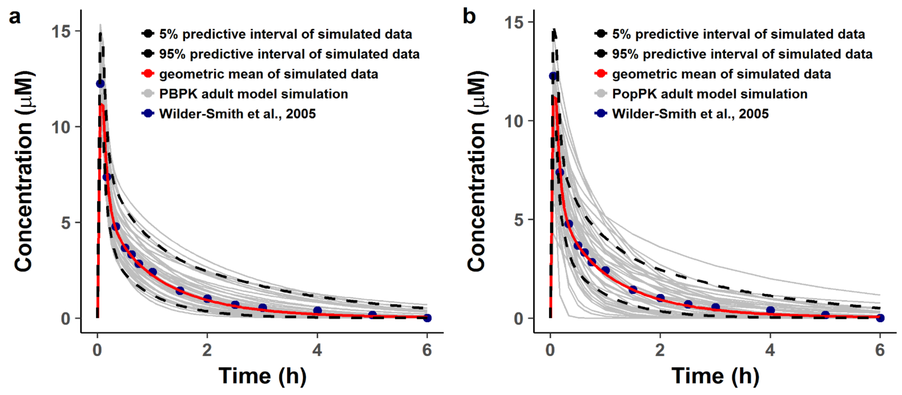

Figure 2. *Plasma concentration time profiles of adult model verification by using PBPK adult model (a), PopPK adult model (b)*

Table 3. *Estimated optimal dose for all the groups by PBPK and PopPK based methods*

Group	Labelled dose	PBPK based optimal dose	PopPK based optimal dose
< 1 month	0.5 mg/kg	0.23 mg/kg	0.38 mg/kg
1 - < 6 months	0.5 mg/kg	0.27 mg/kg	0.36 mg/kg
6 months - < 1 year	0.5 mg/kg	0.30 mg/kg	0.34 mg/kg
1 - < 6 years	10 mg	4.71 mg	4.90 mg
6 - < 12 years (BW < 55 kg)	10 mg	9.59 mg	8.79 mg

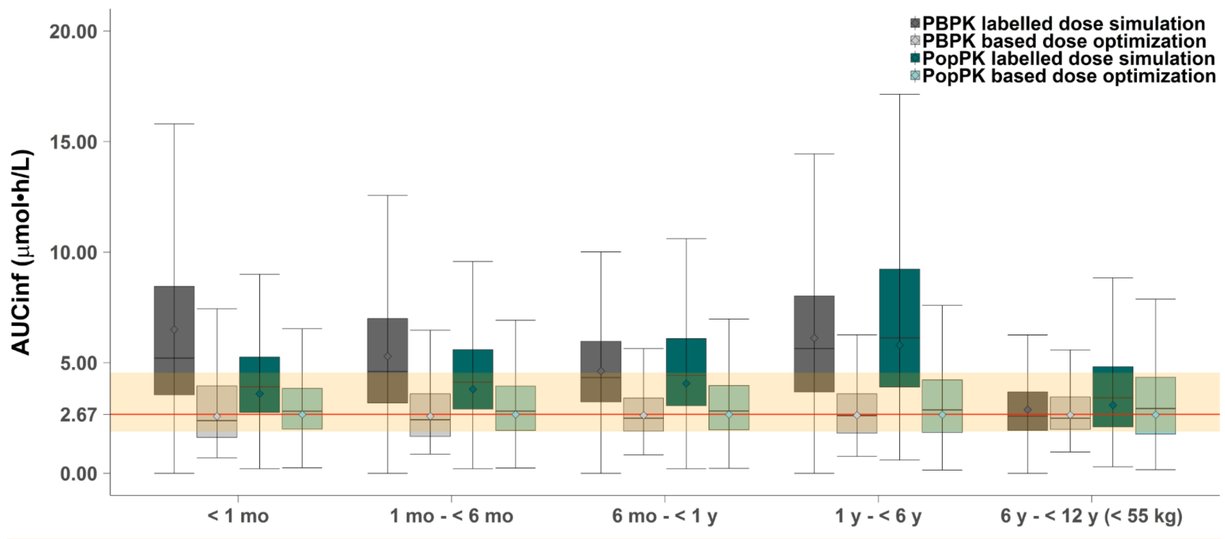

Figure 3. *Box plots of individual predicted AUCinf values, simulated with labelled and estimated optimal doses, by PBPK and PopPK paediatric model. The diamond points represent the predicted geometric mean AUCinf values. The red line and orange shade are the target AUCinf value and the target exposure range, respectively.*

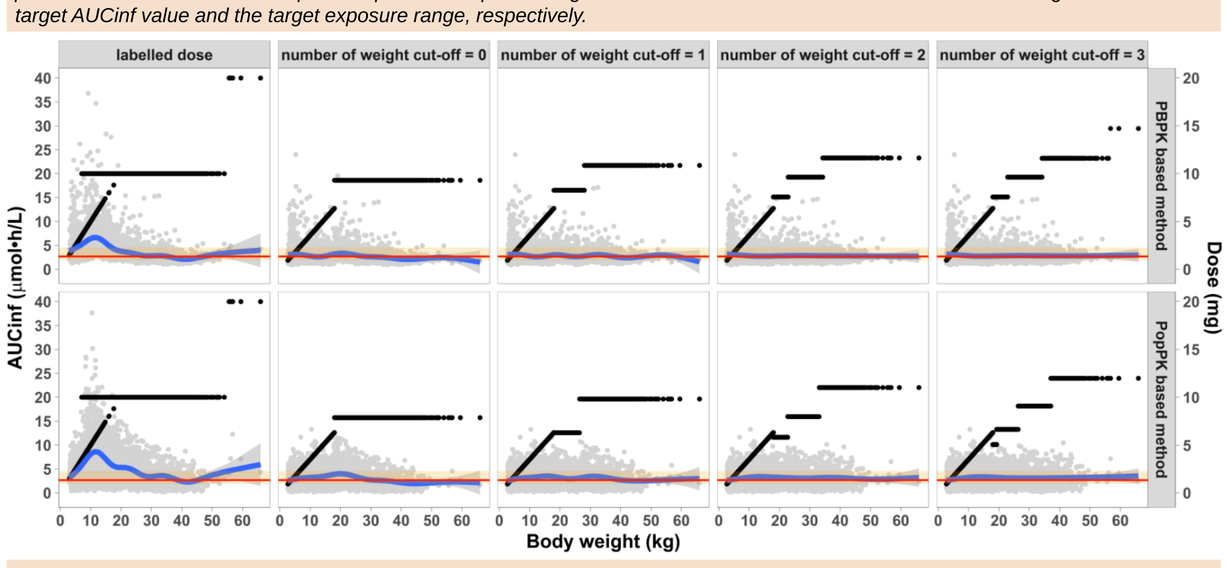

Figure 4. *The dosing regimens are presented with estimated doses (black circles) and body weight cut-off points (body weights which the estimated doses are switched to the other dose). The gray circles and blue lines represent the individual predicted AUCinf values and their trend lines.*

Table 4. *Statistical analysis of predicted AUCinf values and percent bias from the determined weight-based cut-off regimens*

Dosage regimens	PBPK based method				PopPK based method			
	Gmean	sd	%CV	Percent bias	Gmean	sd	%CV	Percent bias
labelled dose	3.845	2.95	76.72	44.02	4.374	3.75	85.73	63.84
number of weight cut-off = 0	2.626	1.63	62.07	-1.65	2.656	1.74	65.51	-0.52
number of weight cut-off = 1	2.626	1.60	60.93	-1.66	2.656	1.67	62.88	-0.52
number of weight cut-off = 2	2.626	1.59	60.55	-1.64	2.655	1.66	62.52	-0.55
number of weight cut-off = 3	2.626	1.59	60.55	-1.64	2.656	1.65	62.12	-0.54

References

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