

POPULATION PHARMACOKINETICS OF PARACETAMOL ACROSS THE HUMAN AGE-RANGE FROM (PRE)TERM NEONATES, INFANTS, CHILDREN TO ADULTS

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Objectives

- To characterize the variation in pharmacokinetics of paracetamol in neonates, infants, children and adults with a population pharmacokinetic model with specific focus on clearance.
- To demonstrate the model based dose adaption for guiding treatment in neonates, infants and children from pharmacokinetic perspective by simulation

Methods

- 220 subjects from 8 published studies [1-8] on pharmacokinetics of (intravenously or rectally administered) paracetamol or propacetamol were included (Table 1).
- Population pharmacokinetics model was developed with NONMEM 7.2
- The Bodyweight-Dependent-Exponent (BDE) model [9] was applied as the covariate model for paracetamol clearance
- The model was internally validated with criteria proposed by Krekels et., al [10]
- Model based simulation was performed for intravenous paracetamol in children with two scenarios: a standard-of-care dosing regimens and a model optimized regimen (with a hypothetical target concentration of 9mg/L) (Table 2)

Table 1. Summary of studies included.

Population	N	PNA	Weight	Administration
Preterm/term neonates [1]	30	1 day	0.5-4 kg	Propacetamol i.v. bolus
Preterm/term neonates [2]	18	1-76 days	0.8-4 kg	Propacetamol i.v.
Preterm/term neonates [3]	60	1-28 days	0.6-4.3 kg	Paracetamol i.v.
Infants [4]	26	0.11-1.33 yrs	7.5-12.2 kg	Paracetamol rectal or propacetamol i.v.
Infants [5]	19	0.67-1.25 yrs	7.9-12.2 kg	Paracetamol rectal
Children [6]	29	2-7 yrs	14-33 kg	Paracetamol rectal
Adults (male) [7]	12	21-25 yrs	63-83 kg	Propacetamol i.v.
Adults [8]	26	19-34 yrs	49.2-94 kg	Paracetamol i.v.

Table 2. Standard of care and model suggested dosing regimen (partly).

Weight	Standard of care regimen	Model suggested regimen
0.5 kg	5mg/kg 4times daily	11.2 mg/kg loading dose + 5.1mg/kg 4 times daily maintenance dose
2 kg	5mg/kg 4times daily	13.3 mg/kg loading dose + 7.4 mg/kg 4 times daily maintenance dose
5 kg	7.5mg/kg 4times daily	13.5 mg/kg loading dose + 10.4 mg/kg 4 times daily maintenance dose
9 kg	7.5mg/kg 4times daily	16.8 mg/kg loading dose + 12.9 mg/kg 4 times daily maintenance dose
15 kg	15 mg/kg 4times daily	19.2 mg/kg loading dose + 14.8 mg/kg 4 times daily maintenance dose

Figure 1. Four goodness-of-fit diagnostic plots of the final model with trend line (blue): Observed vs Individual Predicted, Observed vs Population Predicted, Conditional Weighted Residual Error vs Time, Conditional Weighted Residual Error vs Population Predicted

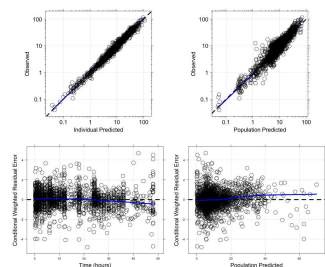
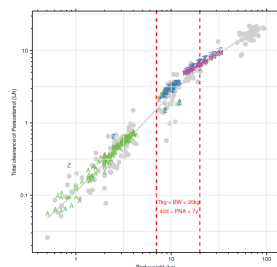


Figure 2. Paracetamol clearance (post-hoc individual grey circles, BDE model predicted grey line, Anderson model predicted letter "A", Zuppa model predicted letter "Z", Mohammed model predicted letter "M") against bodyweight.



Results

- A three-compartment distribution model can well describe concentration profile of intravenously administered paracetamol/propacetamol (Figure 1).
- A extra deposit rectal compartment with bioavailability (F) was added to describe the concentration profile of rectally administered paracetamol (Figure 1).
- The BDE model can well describe changes in paracetamol clearance across different age groups (Figure 2) and age (PNA, PMA or GA) did not correlate with clearance after BDE model was applied (Figure 3).
- The prediction of paracetamol clearances in all age groups by the BDE model was non-inferior to the prediction by other models (Table 3, Figure 2)
- Simulation showed that the model based dosing regimen is better than the standard-of-care regimen (Table 2) in reaching a given hypothetical target concentration of 9mg/L (Figure 4).

Figure 3. Plot of interindividual variability (ETA) in paracetamol clearance of the BDE model versus candidate covariates, including bodyweight (a), postnatal age (b), postmenstrual age (c) (only for neonates) and gestational age (d) (only for neonates).

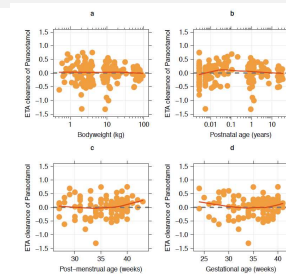


Figure 4. Simulated paracetamol concentration profiles of intravenously administered paracetamol 4 times daily based on standard of care regimen (a) and a final model optimized regimen (b) for neonates (0.5-3kg), neonates and infants (3-10 kg), and children (10-50 kg). Red dotted line: the hypothetical target concentration (9mg/L); Blue line: simulated paracetamol concentration; LD: Loading Dose; MD: Maintenance Dose

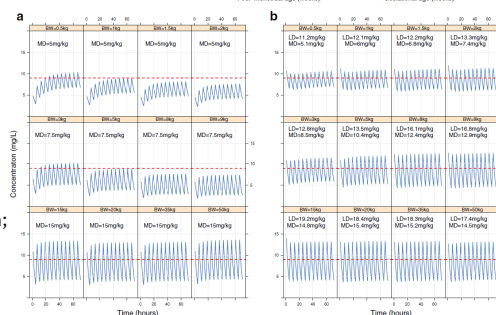


Table 3. The BDE and other covariate models for paracetamol clearance.

Model	Weight	Age-span	Function of covariate model for clearance
Anderson et al [11]	0.5-55 kg	PCA 27 weeks- 14 years	$CL = 16.3 \times (BW/70)^{0.75} \times (1-0.885 \times \exp(-PCA \text{ in weeks} \times \ln(2)/26.6))$
Zuppa et al [12]	not reported	PNA 29 days - less than 18 years	$CL = 18.4 \times (BW/70)^{0.75} \times (1-0.678 \times \exp(-PNA \text{ in weeks} \times \ln(2)/41))$
Mohammed et al [13]	13.7-56 kg	1.8-15 years	$CL = 16.51 \times (BW/70)^{0.75}$
This model	0.5-94 kg	PCA 27 weeks-34 years	$CL = 17.6 \times (BW/70)^k \times (1.204 - 0.454 \times BW^{1.4} / (12.2^{1.4} + BW^{1.4}))$

Conclusions

- The BDE model can characterise changes in paracetamol clearance across neonates, infants, children and adults.
- The model can be easily used for deriving appropriate doses of paracetamol for pediatric population once the therapeutic target concentration is known.

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