# Paracetamol Pharmacokinetics in Term and Preterm Neonates

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## Background & Aim

In neonates processes underlying drug disposition are continuously changing.

Information on the influence of these developmental changes on drug disposition remains largely unidentified, but is essential for the development of rational dosing schemes.

AIM: To describe the influence of the maturational changes on the PK of iv propacetamol in term and preterm neonates.

## Methods

Data:

28 term & 42 preterm neonates (1,2,3)

Postnatal age (median) : 2 days
Postmenstrual age (median) : 37 weeks
PMA at birth (median) : 36.2 weeks
Bodyweight (median) : 2.6 kg

Samples:

457 paracetamol in blood
154 unchanged paracetamol in urine
143 paracetamol glucuronide in urine
154 paracetamol sulphate in urine

No samples of metabolites in blood

Model building:

A population PK model was developed using NONMEM VI, ADVAN6.

Assumptions:

$V_2 = V_3 = 0.18 * V_1$ (4)
$k_{24} = k_{36} = k_{15} * mf$

Covariate analysis:

A systematic covariate analysis was performed to identify the best descriptor for maturational changes.
Tested covariates were:

- Postnatal age (PNA)
- Postmenstrual age (PMA)
- PMA at birth / prematurity
- Bodyweight (BW)
- Sex

Evaluation:

The model was evaluated using:
- Goodness-of-fit plots
- Bootstrap with 250 refits
- NPDE with 1000 simulations

References:
(1) Allegaert *et al.* Eur J Clin Pharmacol 60(3); 191-197 (2004)
(2) Allegaert *et al.* Arch Dis Child Fetal Neonatal Ed 89(1); F25-F28 (2004)
(3) Allegaert *et al.* Acta Paediatr 94(9); 1273-1279 (2004)
(4) Lowenthal *et al.* J Pharmacol Exp Ther 196(3); 570-578 (1976)

## Results – Model Building

**Covariates:**

- BW[1] (linear) on volumes
- BW[1] (linear) on $Cl_1$ and $Cl_4$ ($Cl_3$ and $CL_5$ are related to $Cl_4$)
- $BW^k$ (exponentially) on $Cl_2$

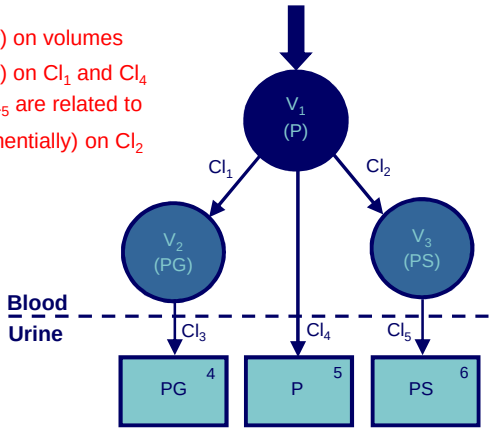



***Figure 1.*** *Schematic representation of the model.*

***Table 1.*** *Parameter Estimates.*

| *Parameter (unit)* | *Model fit (CV%)* | *Bootstrap (CV%)* |
|---|---|---|
| **Fixed Effects** | | |
| $V_1$ (L/kg) | 1.09 (4.0) | 1.09 (4.3) |
| $V_2 = V_3$ (L/kg) (derived) | 0.196 | 0.196 |
| $Cl_1$ (ml/min/kg) | 0.270 (17) | 0.277 (18) |
| $Cl_2$ (ml/min/kg) | 1.68 (14) | 1.71 (15) |
| $Cl_4$ (ml/min/kg$^k$) | 0.286 (7.0) | 0.285 (8.3) |
| k (exponent on BW for $Cl_4$) | 1.29 (21) | 1.28 (10) |
| mf (multiplication factor for $k_{24}$ and $k_{36}$ compared to $k_{15}$) | 11.4 (9.1) | 11.8 (29) |
| $Cl_3 = Cl_5$ (L/kg) (derived) | 0.587 | 0.605 |
| **Inter-Individual Variability** | | |
| $\omega^2$ ($V_1$) | 0.0911 (26) | 0.0889 (27) |
| $\omega^2$ ($Cl_1$) | 0.612 (42) | 0.590 (45) |
| $\omega^2$ ($Cl_2$) | 0.291 (65) | 0.290 (29) |
| $\omega^2$ ($Cl_4$) | 0.0905 (53) | 0.114 (93) |
| **Residual Variability** | | |
| $\sigma^2$ (P blood, additive) | 0.131 (24) | 0.313 (41) |
| $\sigma^2$ (P blood, proportional) | 0.0227 (16) | 0.0227 (26) |
| $\sigma^2$ (PG urine, proportional) | 0.223 (15) | 0.222 (17) |
| $\sigma^2$ (P urine, proportional) | 0.188 (28) | 0.189 (16) |
| $\sigma^2$ (PS urine, proportional) | 0.331 (33) | 0.336 (29) |

P = paracetamol, PG = paracetamol-glucuronide, PS = paracetamol-sulphate, BW = bodyweight

## Results – Evaluation

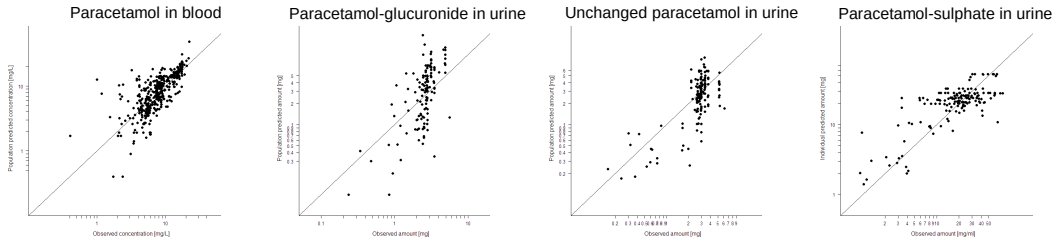



***Figure 2.*** *Population Predicted vs Observed Plots*

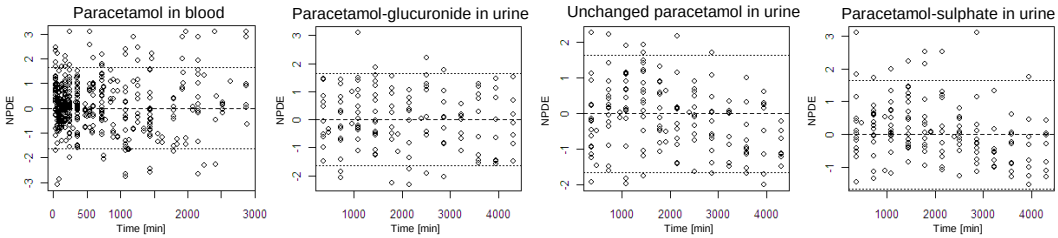
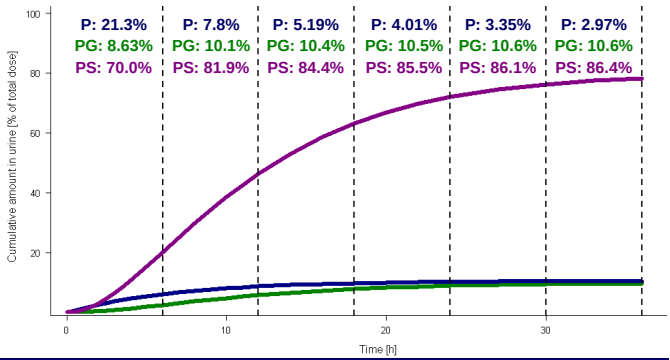



***Figure 3.*** *NPDE distribution in time*

## Model Based Simulations

***Figure 4.*** *Relative cumulative amount of unchanged paracetamol (—, P), paracetamol-glucuronide (—,PG), and paracetamol-sulphate (—,PS) in urine after a single dose in a typical individual. Percentage paracetamol and metabolites in each 6 hrs sampling interval relative to the total amount recovered in each interval are indicated as well.*

**Ratios of paracetamol and metabolites recovered in urine change in time, while clearances remain constant over time.**




## Conclusion & Perspectives

- **In neonates paracetamol excretion and glucuronidation scale linearly with bodyweight, paracetamol sulphation scales exponentially with bodyweight.**
- **Previously reported up-regulation of paracetamol glucuronidation based on increased glucuronide ratio's in urine may be explained by slower elimination through the glucuronidation route compared to the other two elimination routes.**
- **How the observed maturational changes extrapolate beyond the neonatal period is part of future investigations.**

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