

Pharmacometric approach to characterize key metabolites of acetaminophen in preterm and term neonates

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Objectives

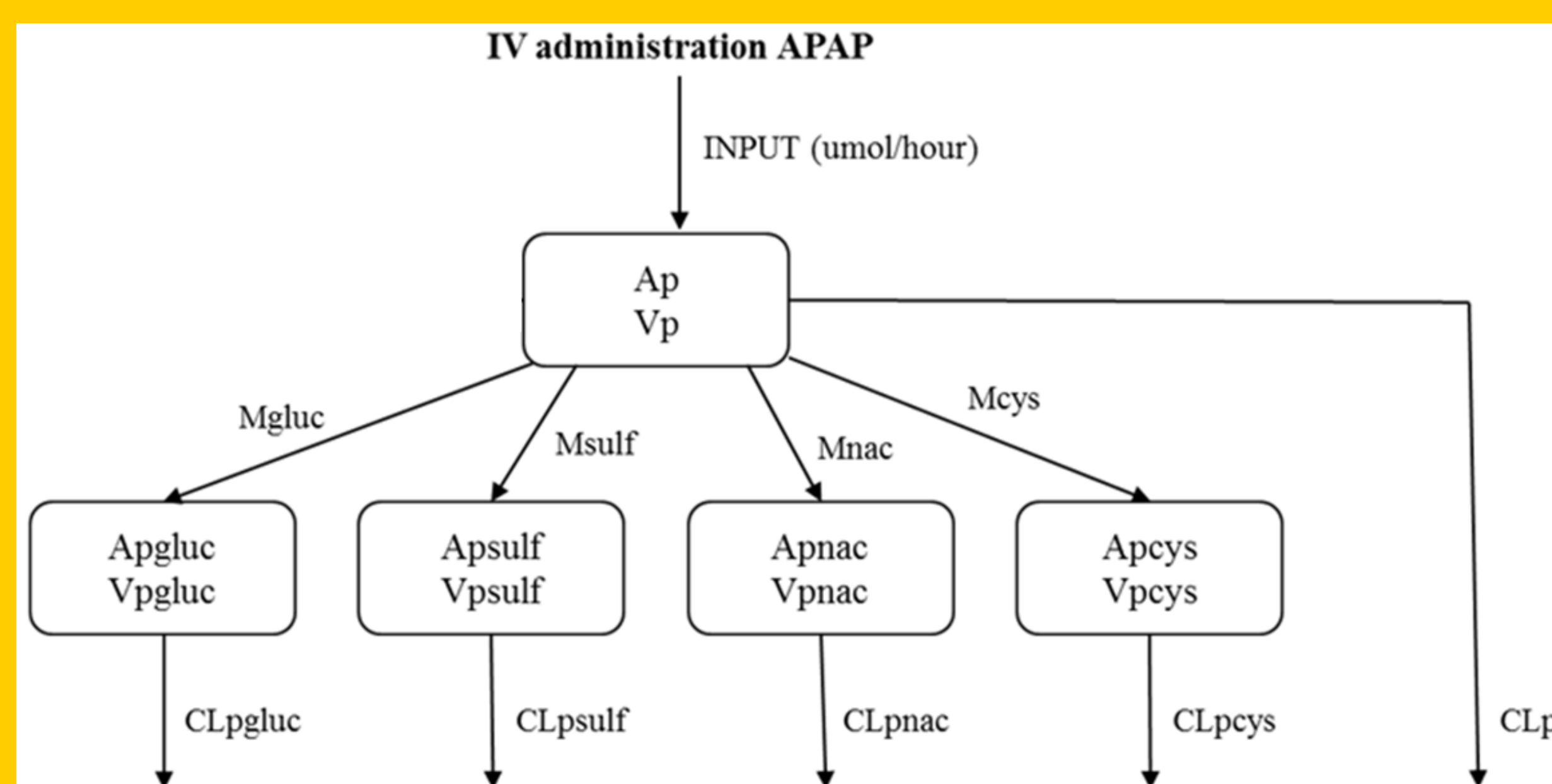
Neonates of all gestational ages perceive pain [1]. Due to undesired side effects of opioids, acetaminophen (APAP) is used as an alternative [2]. Risk for hepatotoxicity associated with APAP [3,4] depends on its metabolism, which changes during the first weeks of life [5]. Preterm neonates (gestational age (GA)<37 weeks) may have less drug metabolism/elimination capacity than term neonates (GA≥37). Characterizing population pharmacokinetics (PK) of APAP and its key metabolites is critical for establishing safe and effective IV dosing regimens for use of APAP in neonates.

Methods

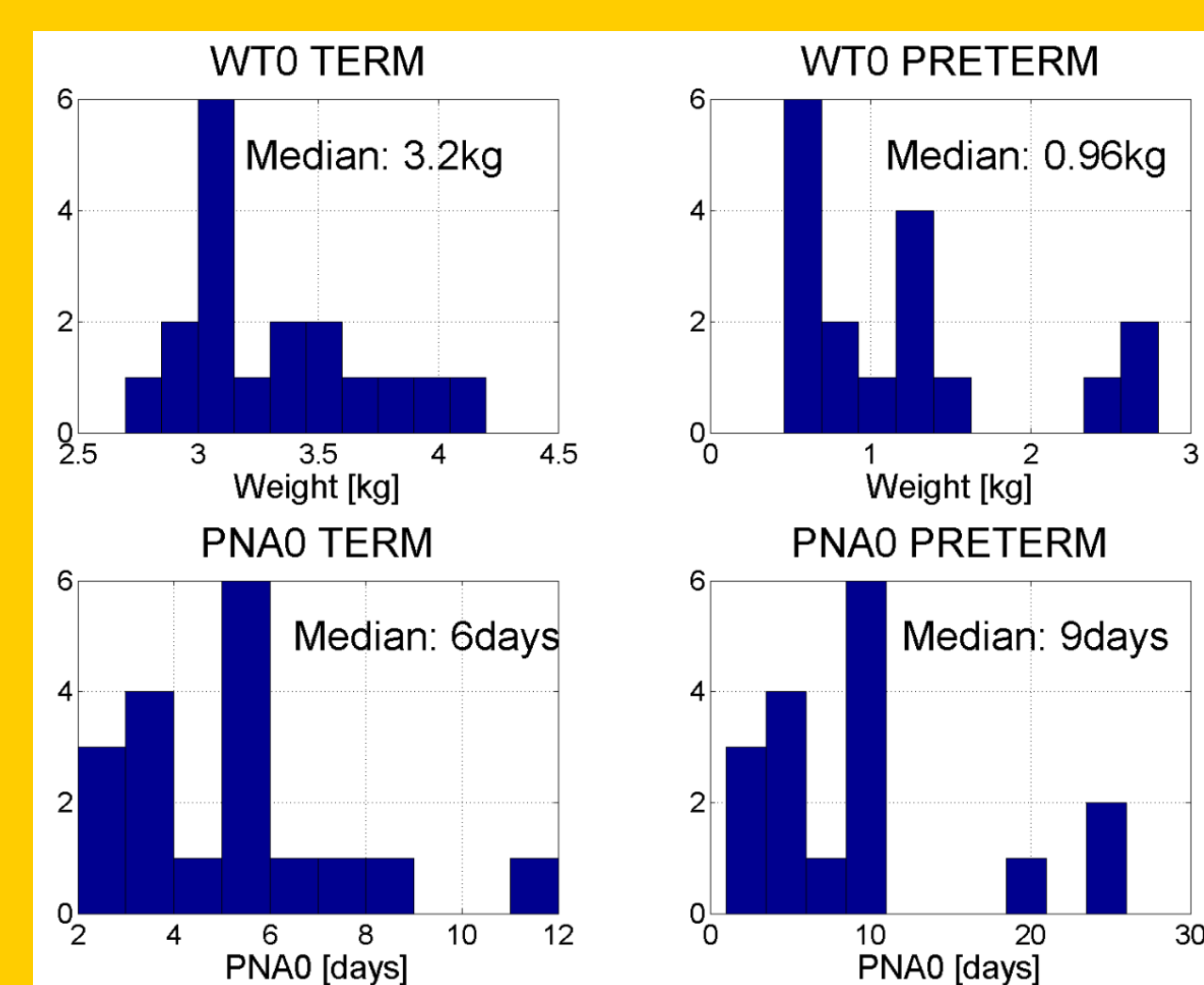
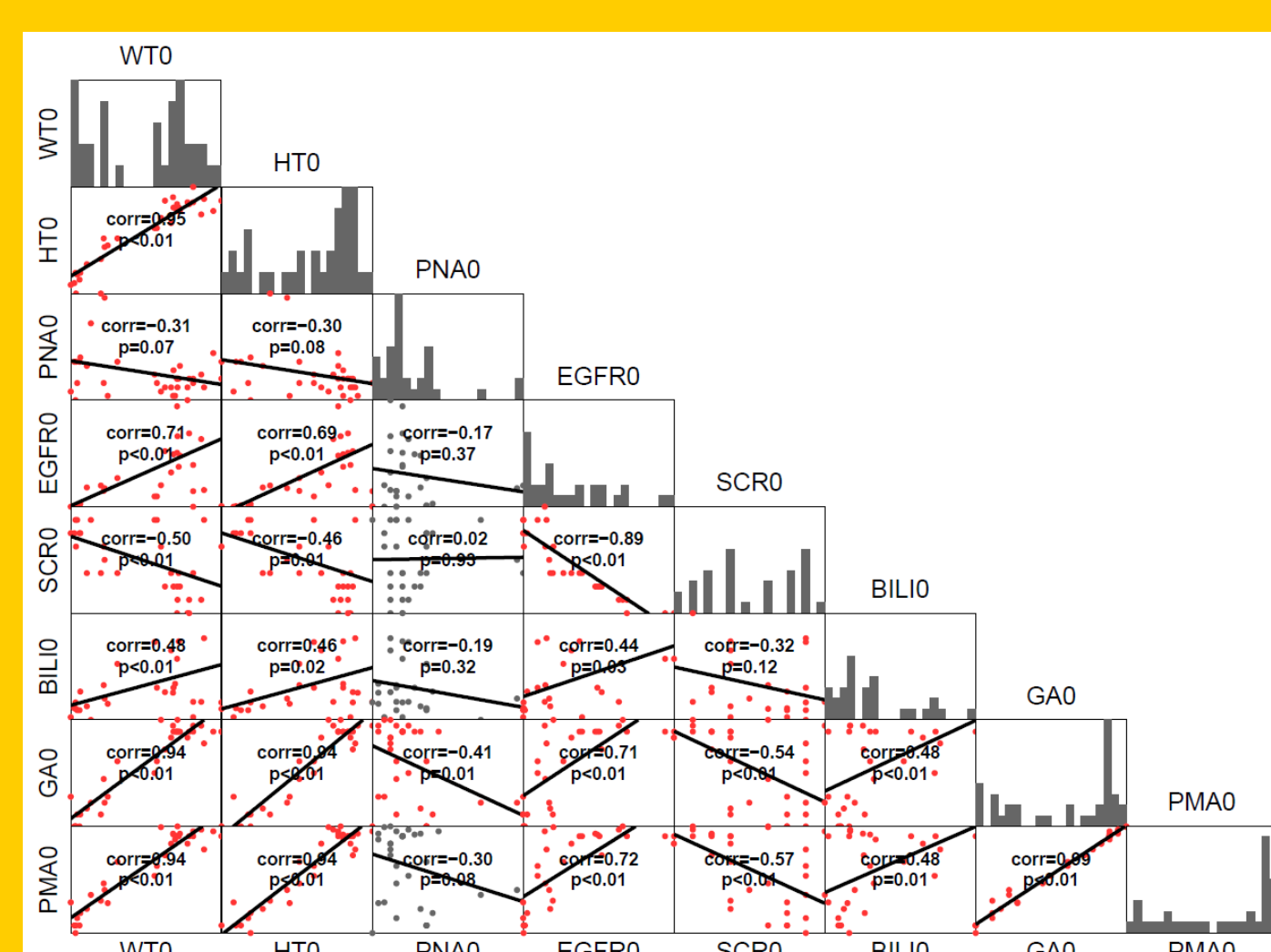
A total of 1361 evaluable observations of APAP and its metabolites were available from 35 neonates with gestational ages between 23 and 41 weeks. The major metabolites, APAP-glucuronide (Mgluc) and APAP-sulfate (Msulf) were quantitated in serum, as well as two surrogate markers of APAP-induced toxicity, APAP-cysteine (Mcys) and APAP-mercapturate (Mnac). Neonates with GA≤28 weeks were dosed 5x 15 mg/kg every 12h (N=23), whereas neonates with GA>28 weeks were dosed 7x 15 mg/kg every 8h (N=12). Non-linear mixed effect modeling was used to characterize population PK of APAP and its key metabolites.

Results

Population PK of APAP and its metabolites were described by linear metabolic formation rate constants (Mgluc, Msulf, Mcys, Mnac) and one-compartment models with linear elimination. Analysis was done both in NONMEM (SAEM and FOCEI) and MONOLIX, giving the same clinically relevant conclusions.



Since no urine samples were available at the time of analysis, the formation rate constants and the volumes of distribution of the metabolites are non-identifiable. This was handled by fixing the volumes of distribution to small arbitrary values, not impacting the estimation of the half-live times. Most considered candidate covariates were highly correlated at baseline, suggesting to mainly consider postnatal age (median: 6 days) and bodyweight (median: 2.8kg).



In order to assess PNA0 different for preterm and term neonates, the covariates were introduced to the model as follows:

$$\text{PARAM_PRETERM} = \text{TPARAM} * (\text{WT0}/2.8)^{T1} * (\text{PNA0}_{\text{PRETERM}}/6)^{T2}$$

$$\text{PARAM_TERM} = \text{TPARAM} * (\text{WT0}/2.8)^{T1} * (\text{PNA0}_{\text{TERM}}/6)^{T3}$$

Log-normally distributed random effects on all estimated parameters and additive-proportional error models were used.

Pre-first dose body weight (WT0) was found to be a clinically relevant covariate on all estimated model parameters (except Mnac) in both term and preterm neonates. On the other hand, pre-first dose postnatal age (PNA0) was identified as a clinically relevant covariate mainly in preterm neonates, on parameters CLp, CLpgluc, CLpnac, CLpcys, Mgluc, and Msulf.

Results for total APAP clearance and APAP volume of distribution and half-live times in both term and preterm neonates are given in the tables below (population average values).

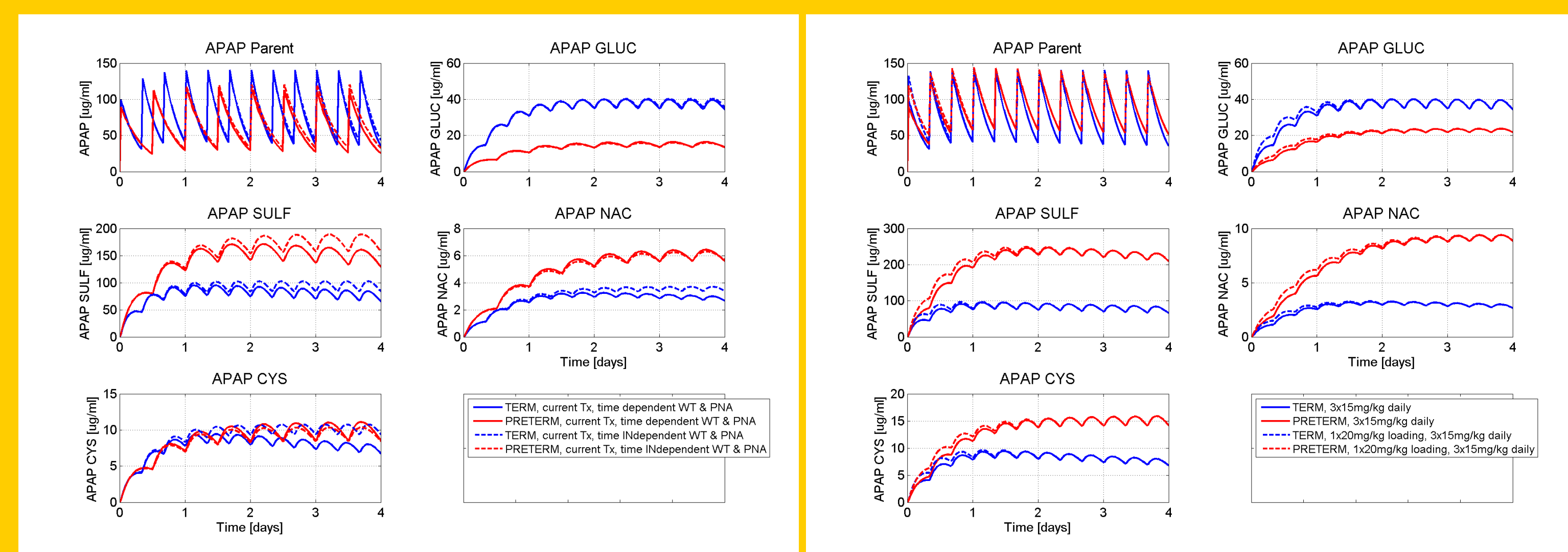
	TERM (90%CI)	PRETERM (90%CI)
Total APAP clearance [L/hour]	0.48 (0.43, 0.53)	0.12 (0.11, 0.13))
APAP volume of distribution [L]	3.1 (2.7, 3.4)	1.04 (0.93, 1.15)

	TERM (90%CI)	PRETERM (90%CI)
APAP half-life time [h]	4.5 (3.9, 5.2)	6.2 (5.4, 6.9)
APAP GLUC half-life time [h]	6.5 (5.6, 7.6)	8.0 (6.9, 9.4)
APAP SULF half-life time [h]	3.8 (3.3, 4.4)	7.2 (6.3, 8.3)
APAP NAC half-life time [h]	8.9 (6.9, 11.6)	12.7 (9.6, 16.5)
APAP CYS half-life time [h]	5.7 (4.9, 6.6)	6.5 (5.6, 7.5)

Simulations to Evaluate IV Dosing Regimens

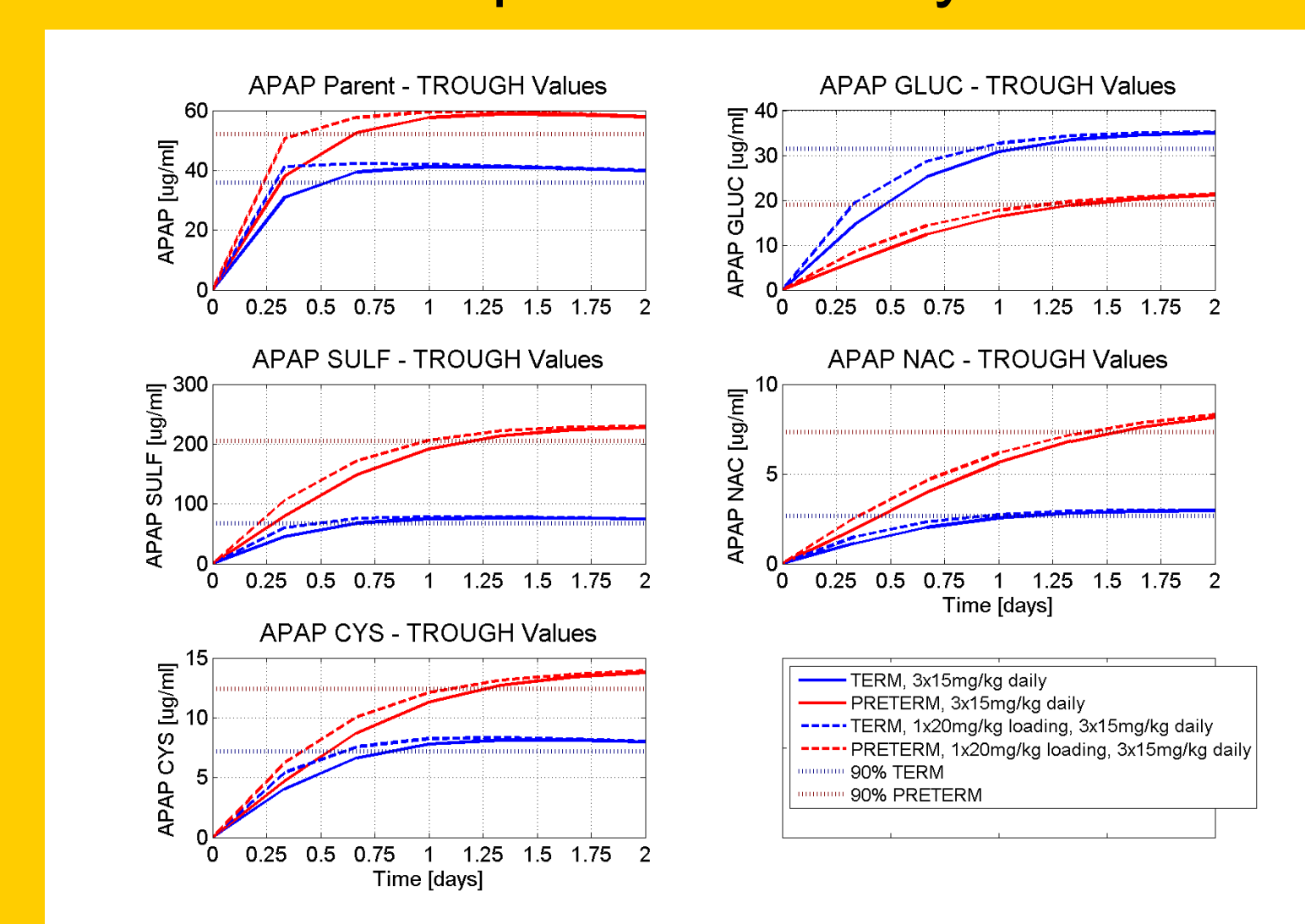
The model has been used to simulate the population mean profiles of APAP and its metabolites for the current regimen and an alternative one. Typical ("population average") term and preterm neonates were simulated assuming bodyweight of 3.2 kg and PNA of 9 days for term neonate (≥ 37 GA), 0.96 kg and 6 days for preterm neonate (< 37 GA), respectively.

- **Left figure:** Current IV dosing regimen – daily dosing of 2 x 15 mg/kg in preterm neonates (< 37 GA) or 3 x 15 mg/kg in term neonates (≥ 37 GA)
- **Right figure:** Alternative IV dosing regimens - same daily dosing 3x15 mg/kg in preterm and term neonates with and without loading dose of 20 mg/kg)



Note: Simulations indicate that time dependent changes in exposure related to maturation (PNA) and development (assumed weight gain of 15 g per kg bodyweight per day) are marginal over an observation period of 4 days.

The plot on the right shows expected trough concentrations over time for evaluated alternative regimens. Simulations reveal that a loading dose of 20 mg/kg reduces time to reach 90% of the steady-state trough concentration (90% C_{ss}). For APAP parent such loading dose reduces time to 90% C_{ss} from almost one day to less than half a day in term and preterm neonates.



Conclusions

For the first time the population PK of APAP and its key metabolites was characterized in preterm and term neonates. Model results suggest that PNA (in addition to body weight) is affecting PK of APAP's metabolites in preterm neonates. This finding is consistent with the hypothesis that preterm neonates have less mature drug metabolism/elimination capacity than term neonates and may benefit most from organ maturation during the first weeks of life. The developed model will be applied to further evaluate and fine-tune APAP dosing strategies in neonates.

References:

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- [3] Anand KJS, Hall RW (2006) *Pediatrics*, 117, 250–253
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- [5] Allegaert K, et al. (2008) *Pediatr Anesth*, 18, 388–392