

Pre- and postnatal maturation are important for fentanyl exposure in preterm and term newborns: a pooled population pharmacokinetic study

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INTRODUCTION

- The use of fentanyl in newborn infants is off-label and mostly based on bodyweight.
- Fentanyl PK shows a large variability in newborns. The sources of this variability have not been extensively quantified throughout different gestational and postnatal ages.
- To describe the PK of fentanyl in preterm and term infants from 24-42 weeks of gestation with varying postnatal age.
- To evaluate variability in fentanyl PK upon current weight-based dosing.

METHODS

1. Dataset – pooled from two studies (677 observations)

Table 1 The summary of characteristics of patients included (range)

	Saarenmaa et al.[1] (n=66)	Völler et al.[2] (n=96)
Gestational age	25-42 weeks	24-32 weeks
Birthweight	760-4245 g	390-1905 g
Current weight	760-4245 g	390-2087 g
Postanal age	0.06-7.43 days	0-68 days
Fentanyl Regimens	- All patients received 1 hour infusion of 10.5 mcg/kg, followed by 1.5 mcg/kg/h infusion for a median duration of 58 hours (IQR 37-82). 11 patients received additional boluses of 1.5 mcg/kg	29 patients received continuous infusion of median 1.0 mcg/kg/h (IQR 1.0–2.0) for a median duration of 23 hours (IQR 7-55). 89 patients received boluses of median 2.1 mcg/kg (IQR 1.5–3.7)

2. Population PK analysis

- Software: NONMEM® 7.4
- Model selection criteria: objective function value (OFV) and (split) goodness of fit plots
- Evaluated covariates: birthweight (BW), current weight (CW), gestational age (GA), postnatal age (PNA), postmenstrual age (PMA), sex and being small for gestational age (SGA).

3. Model evaluation

- Normalized prediction distribution errors (NPDEs) based on 1000 simulations.

4. Dosage evaluation

- Using the final model, simulations were performed to generate concentration time profiles in typical patients receiving a continuous infusion of 1 mcg/kg/hour for 7 days.

RESULTS

Table 2. Final model and parameter estimates

Parameter	Final model estimate (RSE %)
$CL\ (L/hour) = TVCL \times (\frac{BW}{1055})^{\theta_{BW}} \times (PNA+0.01)^{\theta_{PNA}}$	
TVCL	0.31 (10 %)
θ_{BW}	1.47 (6 %)
θ_{PNA}	0.505 (10 %)
$V1\ (L) = TVV1 \times (\frac{CW}{1165})^{BDE}$ with $BDE = L1 \times \frac{CW^M}{1165^M}$	
TVV1	10.6 (7 %)
L1	1.56 (10 %)
M	-0.417 (32 %)
Q (L/hour)	0.573 (35 %)
V2 (L)	3.37 (23 %)
Interindividual variability [shrinkage %]	
On CL (%)	44.4 % (9 %) [18 %]
On V1 (%)	45.6 % (13 %) [30 %]

BDE, bodyweight-dependent exponent, L1, the intercept in the scaling exponent; M, the exponent which allows the scaling exponent to change with current bodyweight

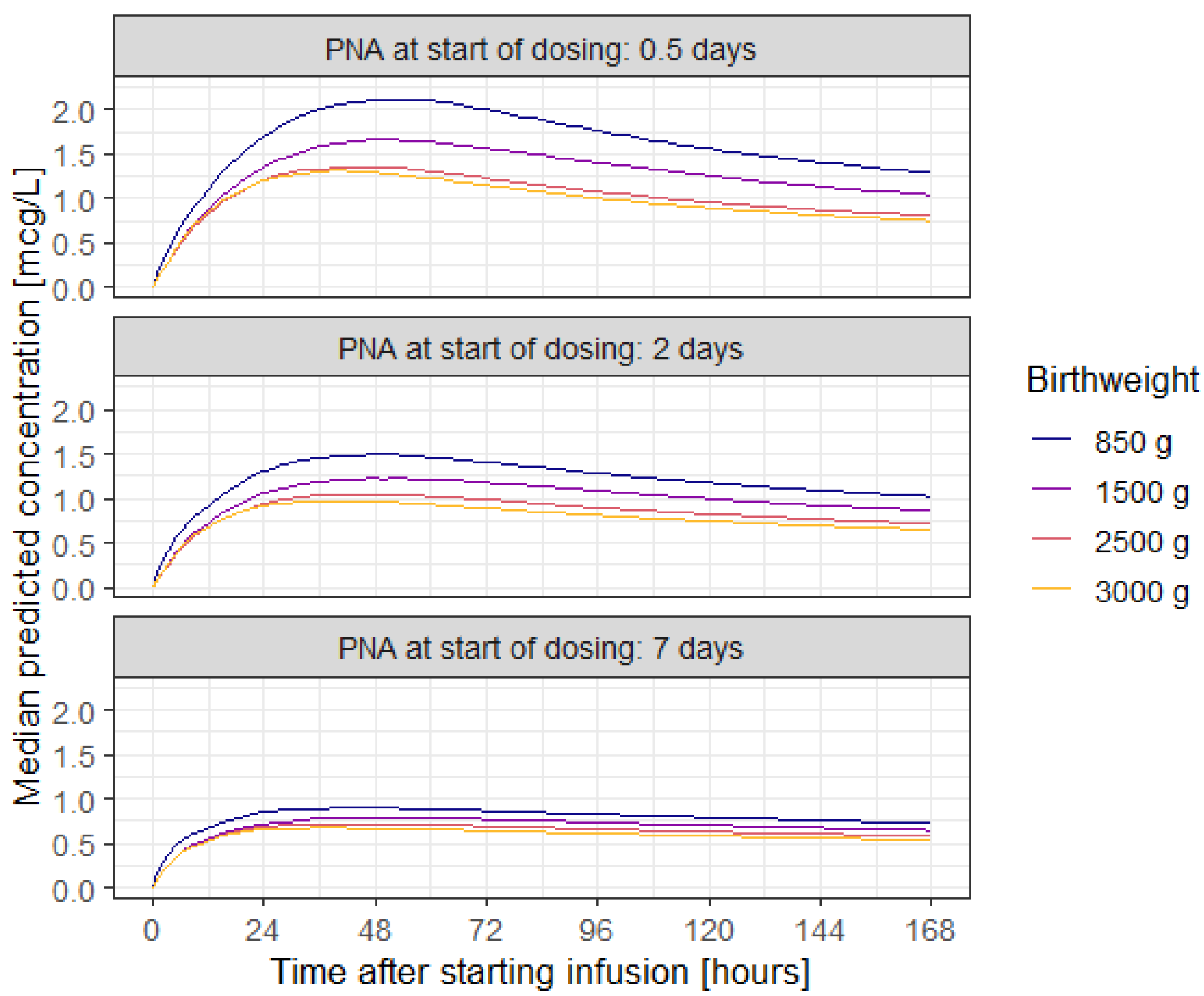


Fig. 3 Fentanyl concentration time profiles with each line representing the median concentration (n=1000) of typical neonates receiving a continuous infusion of 1 mcg/kg/hour for 7 days.

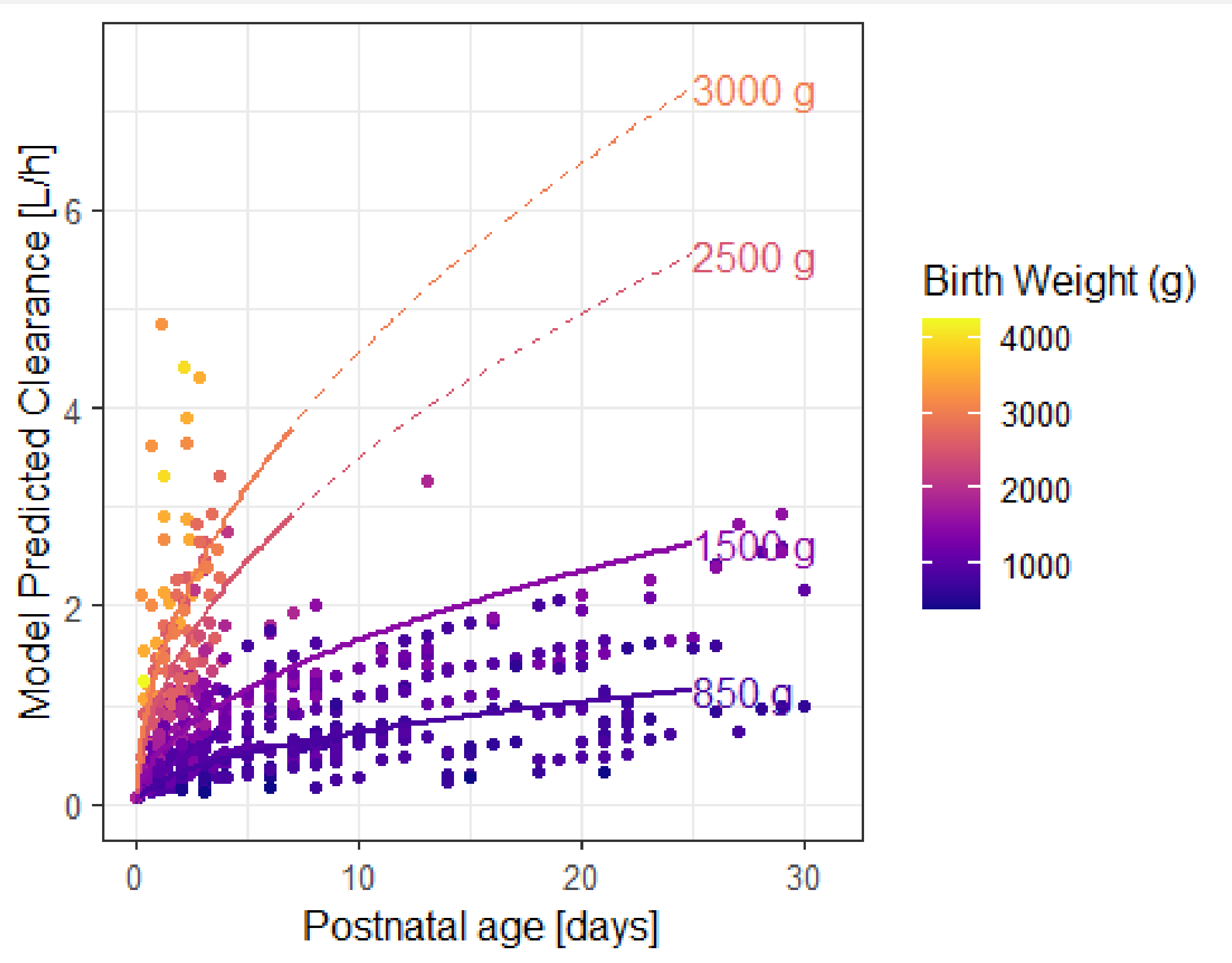


Fig.1 Clearance (L/hour) versus postnatal age (days) for first 30 days of life, depicted as individual post hoc clearance values (dots) and population values (lines) for typical neonates. The dotted lines represent the extrapolated clearance due to a lack of data for neonates beyond 2100g BW with a PNA beyond one week

- For all neonates, concentrations first increase until a ‘peak concentration’ is reached, which then decrease over time as a result of increasing CW and PNA affecting the disposition.
- In neonates with the same PNA, fentanyl concentrations are lower when birth weight is higher
- Within the same neonate, fentanyl concentrations decrease with increasing PNA

CONCLUSIONS

- We quantified the influence of prenatal and postnatal maturation on fentanyl exposure in term and preterm newborns.
- Given the relevance of these covariates for clearance, birthweight and PNA should be considered for neonatal dosing.

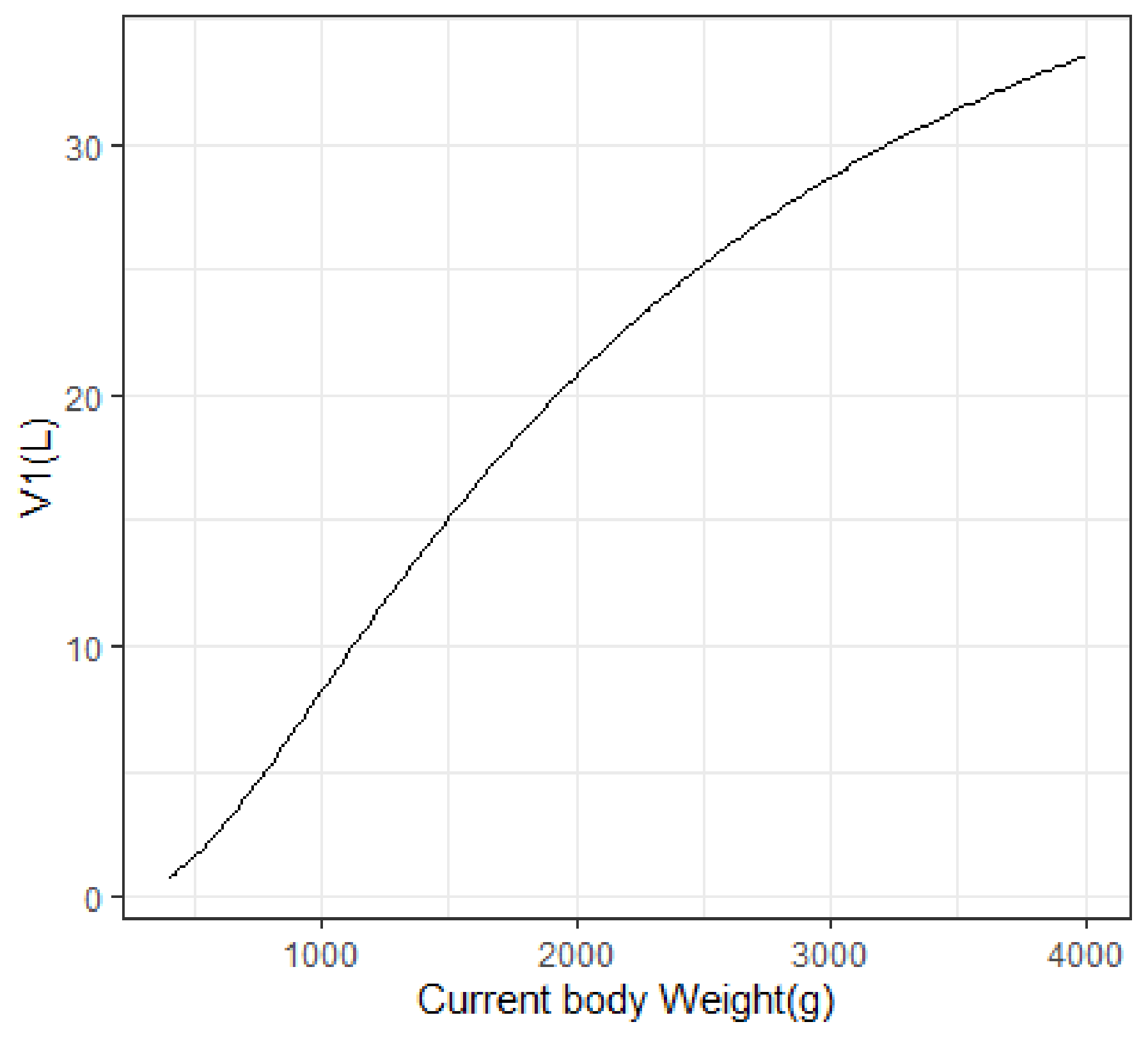


Fig.2 The relationship between current body weight and central volume of distribution (V1) for the bodyweight-dependent function on V1

REFERENCES

- Voller S et al. Arch Dis Child Fetal Neonatal Ed. 2019 Nov;104(6):F598-F603.
- Saarenmaa E et al. | Pediatr. 2000 Jun;136(6):767-70.