Quantification of renal drug clearance in neonates born Small for Gestational Age (SGA) compared to neonates born Appropriate for Gestational Age (AGA)

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INTRODUCTION

- (Pre)term neonates are dosed based on weight, in combination with gestational age (GA) or postnatal age (PNA).
- Currently, no attention is paid to neonates that are born small for gestational age (SGA).
- **SGA neonates:** neonates with a birth bodyweight (bBW) < 10th percentile of the bBW for their GA.

AIM

To determine the influence of being born SGA on the clearance (CL) and volume of distribution (Vd) of gentamicin and amikacin in neonates.

METHODS

- **Datasets:** were already available for both drugs (**Table 1**).

Table 1. *Patient demographics of gentamicin and amikacin dataset*

	Gentamicin [3,4]	Amikacin [5–8]
Number of patients (n)	733	944
Gestational age (weeks)	35 (23-42.1)	32 (24-42)
Postmenstrual age (weeks)	35.29 (23.1-43.3)	33 (24-55)
Postnatal age (days)	3 (1-30)	3 (1-30)
Birth bodyweight (g)	2390 (440-5240)	1780 (420-5420)
Current bodyweight (g)	2385 (440-5420)	1920 (420-5420)
Co-administration of ibuprofen (n(%))	76 (10.4%)	52 (5.5%)
Small for Gestational Age (n(%)) [10]	**84 (11.5%)**	**121 (12.8%)**
Birth bodyweight Z-score	0.11 (-4.1 - 4.8)	-0.17 (-3.4 - 4.0)

Values are expressed as median [range]

- **Software:** NONMEM 7.4, PsN 5.2.6 , Pirana 3.0
- **Previous published gentamicin and amikacin model** [1,9]**:**
  - Two compartment model
  - bBW and PNA as covariates for CL
  - cBW as covariate for Vd
- **Covariate analysis:**
  - To study SGA on CL and Vd
  - To study SGA together with GA or bBW (as antenatal predictor) and PNA (as postnatal predictor) for CL
  - To study SGA together with cBW for Vd
- **Model validation:** NPDE and bootstrap.

CONCLUSIONS

- SGA neonates are different from AGA neonates and as a result, SGA needs to be studied as part of a full covariate analysis with covariates like bBW and PNA, thereby accounting for the large interindividual variability in neonates.
- Gentamicin and amikacin CL is **higher** in SGA neonates, with only small differences in the first 5 days of life, and with **faster** postnatal maturation in SGA vs AGA neonates.
- SGA should be considered when designing dosing guidelines for renally cleared drugs in (pre)term neonates.

RESULTS

- **Figure 1a:** large variability in SGA and AGA neonates with no difference in median CL between SGA and AGA neonates.
- **Figure 1b:** for CL vs bBW; trend towards higher CL in SGA vs AGA neonates.
- **Figure 1c:** for CL vs GA; lower CL values in SGA vs AGA neonates.

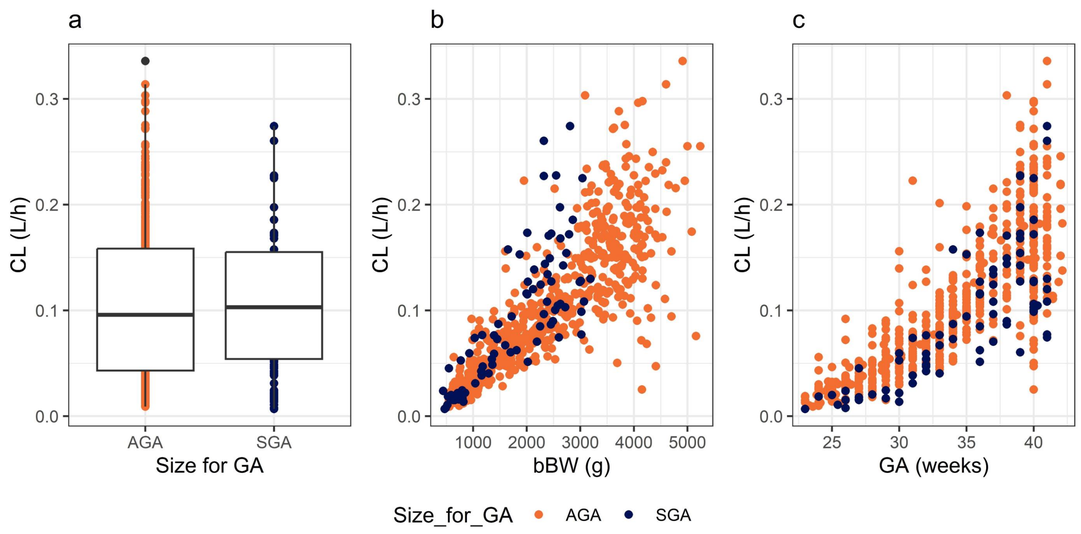

Figure 1: Gentamicin clearance versus size for gestational age (a), birth bodyweight (bBW) (b), and gestational age (GA) (c) of the simple model.

- SGA (as fold change) to **bBW and PNA:** CL **19% higher** in SGA vs AGA neonates for gentamicin (ΔOFV -16.0, OFV 2258.4) and amikacin (ΔOFV -25.4 OFV 4684.4).
- SGA (as fold change) to **GA and PNA:** CL **30-32% lower** in SGA neonates for gentamicin (ΔOFV -64.6, OFV 2316.4) and amikacin (ΔOFV -90.1, OFV 4750.4).
- The **bBW and PNA + SGA model** proved to be the best model and was taken as a basis to explore the influence of postnatal maturation in SGA vs AGA neonates.
- **Final model:** in the bBW and PNA + SGA model, postnatal maturation in CL was faster in SGA neonates for gentamicin and amikacin (ΔOFV -18.3, -4.5), **Figure 2**.

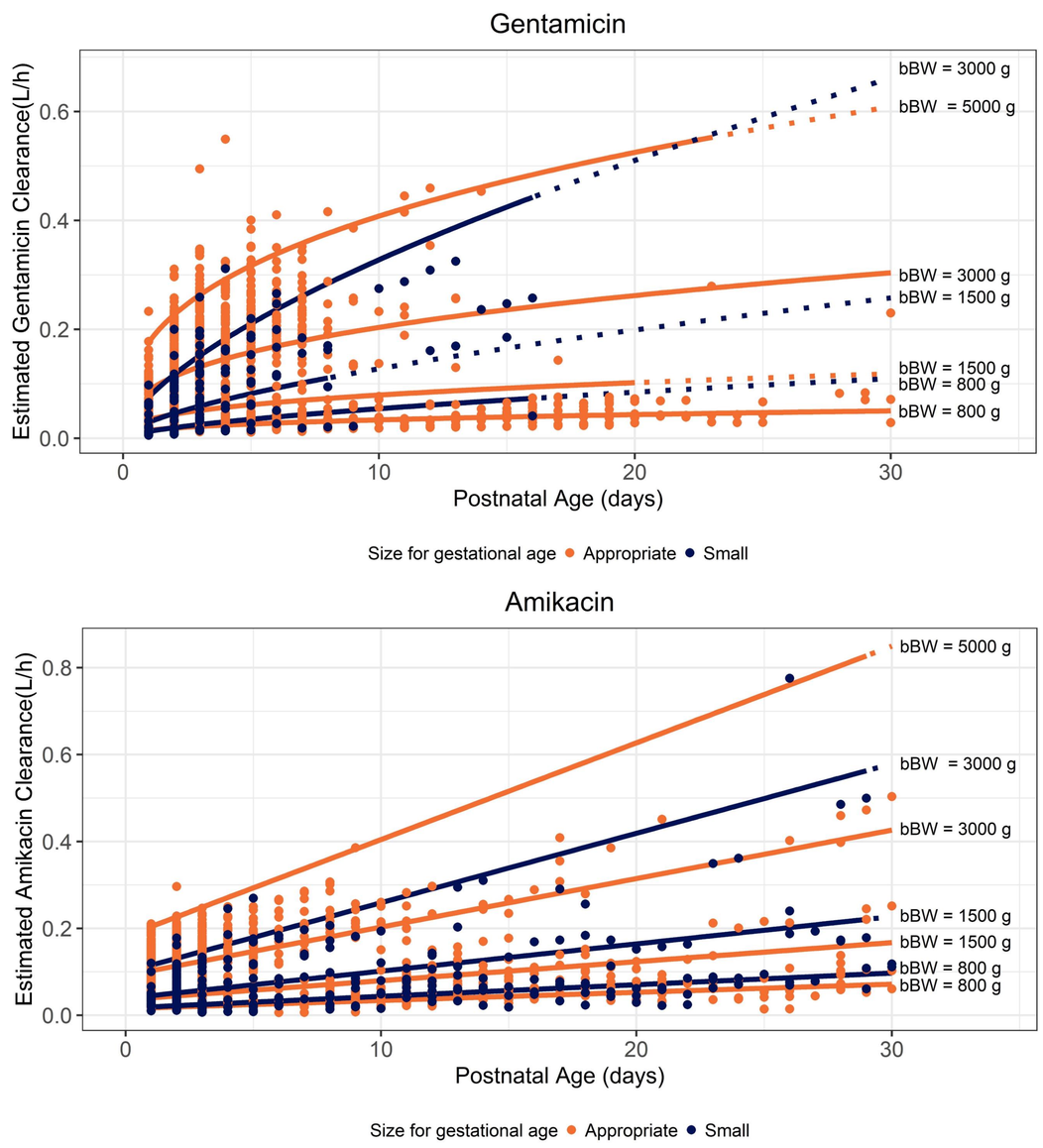

Figure 2: Gentamicin and amikacin clearance vs PNA for bBW of 800, 1500, 3000 and 5000 (AGA only) grams for SGA and AGA neonates of the final postnatal maturation model with a different exponent (power function) for PNA for SGA neonates. Solid lines = estimated function for CL, dotted lines = predicted function for CL

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