AMIKACIN IN NEONATES: DOSING RECOMMENDATIONS SHOULD BE BASED ON BOTH PHARMACOKINETICS AND DYNAMICS

Dear Sir,

We read with great interest the paper of Siddiqi et al on amikacin therapeutic drug monitoring (TDM) observations in 104 preterm neonates at gestational age 29–40 weeks.[1] Following a uniform dose (15 mg/kg), the authors documented extensive interindividual variability in amikacin disposition, only in part explained by age. Secondly, both in term (31%) and preterm (85%) neonates, a significant portion of TDM observations was out of the target range. It is thereby intriguing that clinical pharmacologists and neonatologists all over the world are still in search of the optimal dosing regimen for aminoglycosides, including amikacin. Although there is no evidence in support of this statement, we agree that TDM can help to reduce the interindividual variability in pharmacokinetics (PK) based on target concentration intervention. At least, TDM helped both groups to further individualise the administration and to improve our clinical knowledge of the appropriate administration of aminoglycosides this specific population. We therefore felt it appropriate to share some of the clinical experiences collected and published by both groups.[2-10] Based on these experiences, we would like to challenge the dosing recommendations made by Siddiqi et al.[1]

Aminoglycoside PK in early life displays an extensive interindividual variability and mainly reflects the interindividual variability in the glomerular filtration rate (GFR).[6,11] This explains why gestational age is of relevance, but other covariates, such as ibuprofen/indomethacin, asphyxia, dopamine or growth restrictions, further contribute to it.[2-10] The limited predictability at birth improves with postnatal age, most likely because creatinaemia becomes a more reliable marker of GFR after the first week of life.[11] Age, sepsis and patent ductus arteriosus are covariates of the interindividual variability in distribution volume.[4-6] Both parameters of drug disposition (clearance and distribution volume) are of relevance when dosing recommendations are made and should be based on the pharmacodynamics (PD) of aminoglycosides. High peak concentrations are aimed for to facilitate the killing of aminoglycoside concentration-dependent bacterial, while nephro- and ototoxicity relate more to the average aminoglycoside serum concentration due to the saturation of the intracellular transport processes. Finally, there is a poorly defined post-antibiotic effect on bacterial killing, especially when penicillins are co-administered.

Table I: Amikacin dose recommendations for preterm and term neonates at birth.

Study	Postmenstrual age (weeks)	Dose (mg/kg)	Interval (hours)
Neofax[12]	< 30	18	48
	30–34	18	36
	> 34	15	24
Sherwin et al[3]	< 29	15	36
	29–36	14	24
	> 36	15	24
Allegaert et al[10]	< 28	20	42
	28–30	20	36
	31–33	18.5	30
	34–37	17	30
	> 37	15.5	24

For all ages: + 6 h additional time interval with ibuprofen is co-administered.

Taking both the extensive interindividual variability in PK and its covariates and the aminoglycoside-specific PD into account, we disagree with the dosing protocol suggested by Siddiqi et al.[1] The incremental dose of 7.5 mg/kg/day for preterms weighing less than 1,200 g, 10 mg/kg/day for preterms weighing between 1 and 2 kg, and 15 mg/kg/day for preterms weighing above 2 kg mainly aims to reduce the number of toxic through levels. However, assuming a distribution volume of 0.65 L/kg, a dose of 7.5 or 10 mg/kg will, respectively, result in a peak concentration of 11.5 (7.5/0.65) or 15 (10/0.65) mg/L, while Sherwin et al documented that the amikacin peak concentrations should be in the range of 24–35 mg/L.[3] To achieve both an effective and safe administration of aminoglycosides, an extention of the time intervals between consecutive administrations is needed, instead of a reduction of the consecutive doses, although it still needs to be proven that extended intervals beyond 36 hours remain covered by the post-antibiotic

bacterial killing phenomenon. In order to illustrate this approach, the doses as mentioned in the Neofax (2007 version), suggested by Sherwin et al[3] and published by Allegaert et al,[10] are provided in Table I. Although there are minor differences in the dosing and intervals used, they all have a relatively higher dose (mg/kg) and a more extended time interval (h) between consecutive administrations in more preterm neonates.

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Yours sincerely,

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