

EVALUATION OF GENTAMICIN AND TOBRAMYCIN DOSING GUIDELINES FOR NEONATES; TOWARDS MODEL-BASED DOSING

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Introduction

Recently, the existing amikacin dosing guidelines were found to lead to suboptimal concentrations in neonates upon which a novel model-based dosing regimen was proposed[1]. Because aminoglycosides are all cleared through the same mechanism, i.e. glomerular filtration, the covariate model of amikacin was successfully extended to include gentamicin and tobramycin[2]. A simulation study was undertaken to evaluate existing gentamicin and tobramycin dosing guidelines and, if necessary, to propose a new dosing guideline.

Methods

The previously published model for gentamicin and tobramycin in neonates [2] was used with

$$CL = \theta_{CL} \times \left(\frac{bBW_i}{1.75kg} \right)^{1.34} \times \left(1 + \left(\frac{PNA_i}{2d} \right) \times 0.213 \right) \times 0.838^{ibu}$$
$$V_c = \theta_{Vc} \times \left(\frac{cBW_i}{1.76kg} \right)^{0.919} \quad | Q = CL, V_p = V_c$$

in which PNA is postnatal age, birth bodyweight is bBW and current bodyweight is cBW. Monte Carlo simulations with a representative patient population were undertaken to evaluate how well the dosing guidelines (Dutch Kinderformularium, British National Formulary for Children, Neofax and Red Book) reach target peak (5-12 mg/L) and trough (<0.5 mg/L) concentrations. Simulations were conducted with 5000 patients resampled from the original model-building datasets. Peak and trough concentrations were simulated for one week of treatment, with inter- and intraindividual variability included.

Results

- The existing dosing guidelines generally resulted in acceptable peak concentrations but also trough concentrations above 0.5 mg/L, which are associated with increased toxicity (Figure 1A). The Red Book was an exception in this regard; it resulted in acceptable trough concentrations and too low peak concentrations.
- A dosing guideline on the basis of a uniform mg/kg dose was proposed with dosing intervals being modified using postnatal age and birth bodyweight (Table 1). The proposed dosing guideline results in >80% of the peak concentrations and about two thirds of the trough concentrations to reside in target range (Figure 1 A and B).

Discussion and conclusions

Most of the existing gentamicin and tobramycin dosing guidelines result in trough concentrations that are associated with increased renal toxicity. A new dosing guideline is therefore proposed for neonates (Table 1).

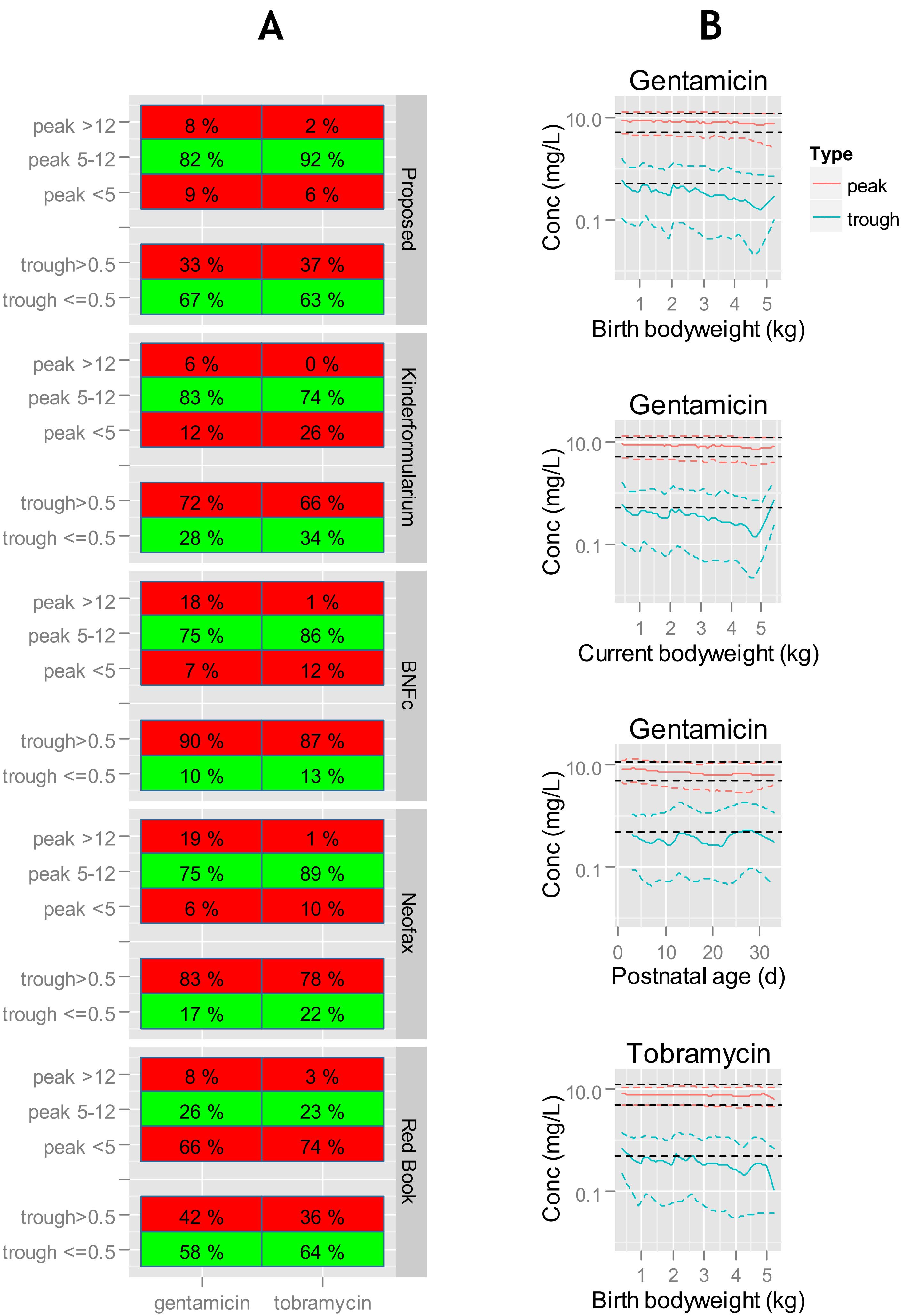


Figure 1.
A) Performance of the evaluated dosing regimens and the proposed dosing regimen in Monte Carlo simulations. Most of the currently used dosing regimens result in elevated trough concentrations. Colours: Red means outside target range, green means inside target range.
B) Performance of the proposed dosing regimen versus continuous covariates: Birth bodyweight, current bodyweight and postnatal age. Dashed lines represent 5 % and 95 % quantiles of predictions, and solid lines represent median predictions. Black dashed lines represent the limits of target range (<0.5mg/L for trough concentrations and 5-12mg/L for peak concentrations).

References

1. de Cock RFW et al. Clin Pharmacokinet. 2012; 51:105-17.
2. de Cock RFW et al. Pharm Res. 2014;31(3):754-67.

Table 1. Proposed dosing intervals after a uniform dose of gentamicin (4.5 mg/kg) or tobramycin (5.5 mg/kg).

	bBW less than 1kg	bBW between 1 and 2kg	bBW more than 2kg
PNA less than 5d	72 h	60 h	48 h
PNA between 5d and 10d	60 h	48 h	36 h
PNA between 10d and 20d	48 h	36 h	24 h
PNA more than 20d	36 h	24 h	24 h

Abbreviations: PNA is postnatal age and bBW is birth bodyweight. Additionally, ibuprofen coadministration leads to 12 h increase in dosing interval.