POPULATION PHARMACOKINETICS OF TEICOPLANIN IN PRETERM AND TERM NEONATES: IS IT TIME FOR A DIFFERENT DOSING REGIMEN?

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INTRODUCTION

Neonatal late-onset sepsis (LOS) remains a significant cause of morbidity and mortality and requires appropriate empiric antimicrobial therapy. Gram-positive cocci constitute the most frequent causes of LOS. Although glycopeptides are among the most commonly used antimicrobials in neonates with suspected LOS, little is known about the pharmacokinetics (PK) of teicoplanin in term/preterm neonates. We aimed to develop a population PK model in order to evaluate currently recommended dosing regimen and safety.

METHODS

Teicoplanin was used at the discretion of the caring physician & a sparse PK study using D-Optimal design approach in neonates was performed.

- **Inclusion criteria:** neonates with PMA ≤44wks who received TEIC and were likely to survive
- **Exclusion criteria:** serious congenital malformations, perinatal asphyxia, acute kidney injury, liver dysfunction
- **Dosing regimen:** loading dose 16mg/kg , maintenance dose 8mg/kg once daily (30-min iv infusion)
- Duration of treatment: minimum duration of 5 days, until sepsis laboratory exams were definitively negative
- 4 blood samples/neonate
- 3 groups according to different times of specimen collection

A	3 & 20 h after loading dose & 5 th dose
B	0.5 & 5 h after loading dose & 5 th dose
C	0.5 & 16 h after loading dose & 5 th dose

- An UHPLC–MS/MS method was developed and validated for the quantification of TEIC concentration
- Using NONMEM software with FOCEI method, a basic model was determined. Statistically significant covariates were screened. Final PK model was validated using nonparametric bootstrapping and visual predictive check (VPC)

Monte Carlo (MC) simulations were performed using the developed PopPK model in MATLAB that generated a simulated population of 10.000 neonates in each of the following weight (WT) groups: **Group 1:** WT1<1kg, **Group 2:** 1kg≤WT2<2kg, **Group 3:** 2kg≤WT3<3kg, **Group 4:** WT4≥3kg. AUC/MIC>400 (using the standard EUCAST MIC susceptibility breakpoint of 1 mg/l) was used as the PK target. All calculations were performed at steady state between 4th and 5th day of treatment.

RESULTS

Study population: 60 neonates (35 females) at a NICU of a tertiary care level hospital

Demographic characteristics: median (range) values: GA=31wks^{+4d} (25⁺⁴–39⁺⁴), BW=1550 g (580–3620), PNA=10d (3–54), PMA=33wks^{+3d} (26wks–41wks^{+1d}), Cr=0.68 mg/dl (0.36–1.28), SGOT= 26U/ml (8–83), SGPT= 8U/ml (1–51)

A two-compartment model with proportional error, parameterized as clearance (CL), volume of distribution of central compartment (V1), volume of peripheral compartment (V2) and inter-compartmental clearance (Q) described teicoplanin PK. **Weight** was found to be a significant covariate on CL, V1, Q and V2 following an allometric model while **Creatinine Clearance** was also found to be a significant covariate on CL but was removed for the MC simulations. Inter-individual variability on CL, V1, V2 was 37%, 46%, 51.4% The model used for the MC simulation was the following:

$$CL = 0.0234 \left(\frac{WT}{1765} \right)^{0.75} \text{ L/h, } V1 = 0.287 \left(\frac{WT}{1765} \right) \text{ L}$$
$$Q = 0.159 \left(\frac{WT}{1765} \right)^{0.75} \text{ L/h } V2 = 0.515 \left(\frac{WT}{1765} \right) \text{ L}$$

Monte Carlo (MC) simulations revealed that with the current recommended dosing regimen only 68.5% of neonates with WT1<1kg attained the target of AUC/MIC>400 (for MIC=1).

Other weight bands, i.e. groups 2 to 4 had PTA 82.2%, 89.7% and 92.7%, respectively.

For the lower weight band (group1) a dose of 12 mg/kg has acceptable PTA of 93.3%. The following graphics depict the Probability of target attainment (PTA) for each weight group for different doses mg/kg & MIC.

PTA VS MIC FOR WEIGHT GROUPS AND DOSES

CONCLUSIONS

- Teicoplanin population PK is variable in neonates with weight having the most significant impact on pharmacokinetics.
- Based on MC simulation ELBW and VLBW neonates need higher doses up to 12mg/kg, especially for *Staphylococcus* spp. with MIC≥1
- These findings are likely applicable in neonatal sepsis, as a significant proportion of CoNS strains have MIC at least 2mg/l

References

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