Population Pharmacokinetics of Vancomycin in Term Neonates with Perinatal Asphyxia treated with Therapeutic Hypothermia

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Background
Little is known about the population pharmacokinetics of vancomycin in neonates with perinatal asphyxia treated with therapeutic hypothermia. We aimed to describe the population pharmacokinetics of vancomycin and propose an initial dosing regimen for the first 48 hours of treatment with pharmacokinetic/pharmacodynamic target attainment

Methods
Neonates with perinatal asphyxia treated with therapeutic hypothermia were included from birth until day 6 in a multicenter prospective cohort-study. A vancomycin population pharmacokinetic model was constructed using non-linear mixed-effects modelling. The model was used to evaluate published dosing-guidelines with regard to pharmacokinetic/pharmacodynamic target attainment. The area under the curve/minimal inhibitory concentration(AUC_{0-24}/MIC) ratio of 400-600 mg*h/L was used as target range.

Results
Sixteen patients received vancomycin (median gestational age: 41 (range: 38-42) weeks, postnatal age: 4.4 (2.5-5.5) days, birth weight: 3.5 (2.3-4.7) kg) and 112 vancomycin plasma concentrations were available. Most samples (79%) were collected during the rewarming- and normothermic phase, as vancomycin was rarely initiated during the hypothermic phase due to its non-empirical use. An allometrically scaled one-compartment model showed the best fit. Vancomycin clearance was 0.17 L/h, lower than literature values for term neonates of 3.5 kg without perinatal asphyxia (range: 0.20-0.32 L/h). Volume of distribution was similar. Published dosing regimens led to overexposure within 24 hours of treatment. A loading dose of 10 mg/kg followed by 24 mg/kg/day in 4 doses resulted in target attainment.

Conclusions
Results of this study suggest vancomycin clearance is reduced in term neonates with perinatal asphyxia treated with therapeutic hypothermia. Lower dosing regimens should be considered followed by model informed precision dosing.

Key Words
antimicrobial therapy, neonates, perinatal asphyxia, pharmacokinetics, therapeutic hypothermia, vancomycin.