Determination of Gentamicin Pharmacokinetics in Neonates to Develop Practical Initial Dosing Recommendations

Monique Potrykus, BS,Phm, Sandra An Walker, BSc,Phm, ACPR, PharmD, FCSHP, Marion Elligson, BScPhm, ACPR, Dolores C Laban, BS,Phm, Carla Findlater, PharmD, Scott E Walker, BSc,Phm, MScPhm, FCSHP, Winneko Seto, BSc,Phm, PharmD; Lesley Palmer, BSc, Phm, ACPR, MSC, Phm; Andrew Simor, MD, FRCPC, Eugenie N, MD, FRCP, FAAP

Sunbird Health Sciences Centre (SHSC), Department of Pharmacy, Sunnybrook Health Sciences Centre (SHSC), Division of Infectious Diseases, SHSC, Women and Babies Program, Neonatal Intensive Care Unit; Hospital for Sick Children (HSC), Department of Pharmacy, University of Toronto, Faculty of Medicine, Undergrad Author: Pharmacy Resident working under supervision of Sandra Walker at time of study; Senior Author; sequence determines credit approach to authorship

ABSTRACT

Background: Although antimicrobials are routinely used in neonatology, controversy exists regarding optimal dosing in infants. Despite side effects and efficacy differences across formulations of the same antimicrobial agent, there is no consensus regarding ideal recommendations for neonates.

Objective: The objective of this study was to determine gentamicin pharmacokinetics in neonates, and develop initial mg/kg dosing recommendations that optimize peak and trough concentrations for both conventional and non-dosing regimens

Methods: Population demographics and steady-state gentamicin concentration data were retrospectively collected for 60 neonates. Mean pharmacokinetic values were determined using non-compartmental pharmacokinetics and multiple linear regression was performed to determine significant covariates of dose (Ct) to allow for a mathematical model of gentamicin disposition and steady state concentrations.

RESULTS

- Gentamicin levels were significantly associated with weight at gentamicin initiation. CART identified breakpoints for weight at gentamicin initiation at 700g, 1200g, 3600g and 8000g. These weight breakpoints were associated with increased association from dose to drug concentration. CART identified that >3mg/kg were administered every 48 hours for neonates weighing <850g, and every 24 hours for neonates weighing ≥850g. The best probability of attaining conventional targets (peak:5mg/L and trough:0.5mg/L) was identified for neonates weighing >1200g.

- The objective of this study was to determine gentamicin pharmacokinetics in neonates, and develop initial mg/kg dosing recommendations that optimize peak and trough concentrations for both conventional and non-dosing regimens.

- Conclusions: In conclusion, this study provides recommendations for conventional dosing and extended interval dosing for neonates. Further studies are needed to prospectively evaluate these dosing recommendations and identify dosing recommendations for neonates weighing ≥1200g.

OBJECTIVES

- To determine the pharmacokinetics of gentamicin in neonates admitted to Level 3 ICU
- To identify significant covariates of gentamicin pharmacokinetic parameters in neonates
- To develop initial mg/kg dosing recommendations with the highest probability of attaining target peak and trough serum concentrations for both conventional dosing and extended interval dosing (EID).

METHODS

- A query of the SPIRIT database identified neonates admitted to the ICU at Sunnybrook between March 12, 2010 and November 24, 2010 who received gentamicin for <24h and had results for >4 gentamicin levels.
- To be included, patients were required to have recording of the time of gentamicin administration, and at the time of which the background information was collected the infants were on stable therapy.
- Patients were included if their baseline urine output was ≥1 mL/kg/hr, baseline serum creatinine (sCr) was ≤110umol/L, and ≥90% for 24h prior to gentamicin initiation.

- A retrospective chart review was conducted to collect additional patient information.

Data Analysis

- Univariate linear regression (p<0.05) was performed for all pharmacokinetic parameters. Parameter estimates were calculated using HLM software for a given gentamicin level obtained in the first order elimination phase.

- A linear regression (p<0.05) followed by multiple linear backward elimination (MLES) was performed to identify significant covariates of dose (Ct) to allow for a mathematical model of gentamicin disposition and steady state concentrations.

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LIMITATIONS

- Dosing recommendations for gentamicin from this study are limited to neonates weighing ≤850g at gentamicin initiation. However, this is also a strength, because this category of patient has not been extensively studied in the literature and our study provides robust data for these neonates.

- As per the administration protocol of gentamicin at SHSC, the majority of patients included in this study were administered gentamicin as a 1-hour intravenous infusion divided into multiple doses. However, as we determined the time at which the peak concentration should be drawn within a given drug dosage, routine practice at our institution is to draw the peak concentration at 48h. This study is unique in determining if a 48h peak concentration of gentamicin in the neonate is a sufficient measure in determining the best probability of attaining serum gentamicin levels that may not be fully distributed at the time of sampling, which would result in underestimation of anemia and an overestimation of the half-life of gentamicin.

- There may be potential confounders due to the retrospective design. However, we attempted to reduce the impact of the brown inter-individual pharmacokinetic variability on the models by use of a large sample size and 1 million iterations Monte Carlo simulations in the above.

CONCLUSION

- Our study evaluated the population pharmacokinetics of hospitalized neonates and developed initial mg/kg dosing recommendations to target peak and trough concentrations for both conventional and EID regimens.

- Multiple linear regression and CART analysis identified weight at gentamicin initiation to be significantly associated with both peak and trough serum concentrations in neonates.

- Using MLES, it was determined that a dose of 3.5mg/Kg given to ≤850g neonates weighing ≤750g and ≤450mg in neonates weighing >750g provided the best probability of achieving conventional targets (peak:5mg/L and trough:0.5mg/L).

- Similarly, a dose of 6mg/kg given every 72 hours in neonates weighing ≤754g and every 48 hours in neonates between 851-1200g were found to provide the best probability of achieving 10mg/L (peak:2-10mg/L) and trough:0.5mg/L.

- Few pharmacokinetic studies include neonates born at ≤4 weeks gestation; those with a BSA of less than 150cm².

- In total, 52% of neonates (55/109) weighed less than 1500g at birth, and 75% (82/109) were born at ≤28 weeks gestation. The results of our study therefore help to define the pharmacokinetics of a unique population of preterm and low-birth weight neonates for whom data is lacking.

- Conclusions: In conclusion, this study provides recommendations for conventional dosing and extended interval dosing for neonates. Further studies are needed to prospectively evaluate these dosing recommendations and identify dosing recommendations for neonates weighing ≥1200g.

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