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Serum levels of vancomycin: is there a prediction using doses in mg/kg/day or m^2/day for neonates?

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ABSTRACT

Coagulase-negative Staphylococcus has been identified as the main nosocomial agent of neonatal late-onset sepsis. However, based on the pharmacokinetics and erratic distribution of vancomycin, recommended empirical dose is not ideal, due to the inappropriate serum levels that have been measured in neonates. The aim of this study was to evaluate serum levels of vancomycin used in newborns and compare the prediction of adequate serum levels based on doses calculated according to mg/kg/day and m^2/day. This is an observational reprospective cohort at a referral neonatal unit, from 2011 to 2013. Newborns treated with vancomycin for the first episode of late-onset sepsis were included. Total dose in mg/kg/day, dose/m^2/day, age, weight, body surface and gestational age were identified as independent variables. For predictive analysis of adequate serum levels, multiple linear regressions were performed. The Receiver Operating Characteristic curve for proper serum vancomycin levels was also obtained. A total of 98 patients received 169 serum dosages of the drug, 41 (24.3%) of the doses had serum levels that were defined as appropriate. Doses prescribed in mg/kg/day and dose/m^2/day predicted serum levels in only 9% and 4% of cases, respectively. Statistical significance was observed with higher doses when the serum levels were considered as appropriate ($p < 0.001$). A dose of 27 mg/kg/day had a sensitivity of 82.9% to achieve correct serum levels of vancomycin. Although vancomycin has erratic serum levels and empirical doses cannot properly predict the target levels, highest doses in mg/kg/day were associated with adequate serum levels.

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Introduction

The introduction of new technologies in neonatal units has caused high nosocomial infection rates with subsequent complications among newborns. Coagulase-negative *Staphylococcus* has been identified as the main nosocomial agent, affecting more than 50% of all cases of late-onset neonatal sepsis.[1–3]

Vancomycin is widely used for confirmed or suspected neonatal sepsis as around 90% of coagulase negative Staphylococci strains are oxacillin and penicillin-resistant.[4,5] However, toxicity, pharmacokinetic variability and empirical doses used for newborns are important topics related to vancomycin use in this population.[6–11] Measurement of area under the curve to achieve minimum inhibitory concentration (MIC) against *Staphylococci* is an important parameter to therapeutics with this drug.[6,7]

The usual empirical dose for the neonatal population ranges from 10 to 15 mg/kg/dose, administered one to four doses a day.[1,3,5,8] However, studies in pediatric population have reported on the need for higher doses of vancomycin, up to 60 mg/kg/day, in order to achieve the desired serum level.[6,7] A minimum recommended through serum level of at least 5–10 mcg/mL is required for effective therapy and fewer side effects, including nephrotoxicity.[8–10] Higher concentration targets ranging from 15 to 20 mcg/mL are recommended even for children with more severe infections such as osteomyelitis and meningitis.[6,11]

However, empirical dose of vancomycin is not ideal according to inappropriate serum levels of the drug that have been reported in neonates in several studies.[5,9,10,12,13] Although there have been previous descriptions of dose calculations based on nomograms and adjustments according to drug clearance and the patient's renal function,[5,14–17] no study has analyzed doses that were prescribed according to body surface (m^2/day) and the resulting serum vancomycin levels. We hypothesized that higher serum levels could be achieved based on doses calculated according to body surface.

The present study was conducted in order to evaluate serum levels of vancomycin that were used to treat late-onset sepsis in newborns and compare the prediction of adequate serum levels based on doses calculated according to mg/kg/day and m^2/day.

Material and methods

Design

This is an observational retrospective cohort, real life study, held at the Neonatal Progressive Care Unit (NPCU) of the Hospital das Clinicas, Federal University of Minas Gerais, from January 2011 to June 2013.

Inclusion criteria

Newborns who were admitted to the NPCU, diagnosed with Healthcare Associated Infections (HAI), and treated with vancomycin for the first episode of late-onset sepsis (defined as sepsis after 48 h of age), were included in this study if they had vancomycin level tested as recommended.

Data collection

Information was collected through prospective and active surveillance of infants at risk by trained professionals of the Hospital Infection Control Commission (HICC). Standardized information about gestational age at delivery, birth weight, gender, data and criteria for diagnosis and treatment of bloodstream infection are routinely registered.

Clinical or laboratory-confirmed bloodstream infection followed the criteria of the Agência Nacional de Vigilância (ANVISA) based on National Healthcare Safety Network of the Centers for Diseases Control and Prevention recommendations.

a) Clinical Bloodstream Infection – at least one of clinical signs (thermal instability, apnea, bradycardia, food intolerance, worsening respiratory distress, glucose intolerance, hemodynamic instability, and hypoactivity or lethargy) AND all of following criteria: hemogram with three altered parameters or increased C-Reactive protein; not performed or negative blood culture; no evidence of infection at another site; antimicrobial therapy initiated or sustained by the attending physician.
b) Laboratory-confirmed bloodstream infection – at least one of clinical signs (thermal instability, apnea, bradycardia, food intolerance, worsening respiratory distress, glucose intolerance, hemodynamic instability and hypoactivity or lethargy) not related to an infection at another site AND at least one of the following:
   - common skin contaminant cultured from two or more blood cultures drawn on separate occasions;
   - common skin contaminant (e.g., diphtheroids, *Bacillus* sp., *Propionibacterium* sp., coagulase-negative staphylococci, or micrococci) cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes appropriate antimicrobial therapy.

Information were collected daily and systematically included in the HICC internal program for further analysis.

Main outcome

Vancomycin levels were always collected before next dose, corresponding to through levels. Adequate serum levels of vancomycin were considered as those between 10 and 20 mg/dL. According to recent studies and considering that neonatal sepsis is a severe event, levels below 10 mg/dL were considered as decreased and inappropriate while those above 20 mg/dL were defined as increased and inappropriate.[6,9,10]

Statistical analysis

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS Inc., USA), version 19.0.

Total dose in mg/kg/day, dose/m^2/day, age, weight, body surface and gestational age at delivery were independent variables in the predictive model of adequate serum levels in