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Population Pharmacokinetic Characteristics of Amikacin in Suspected Cases of Neonatal Sepsis in a Low-Resource African Setting: A Prospective Nonrandomized Single-Site Study

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ABSTRACT

Background: Amikacin exhibits marked pharmacokinetic (PK) variability and is commonly used in combination with other drugs in the treatment of neonatal sepsis. There is a paucity of amikacin PK information in neonates from low-resource settings.
Objectives: To determine the PK parameters of amikacin, and explore the influence of selected covariates, including coadministration with aminophylline, on amikacin disposition in neonates of African origin.
Methods: Neonates with suspected sepsis admitted to an intensive care unit in Accra, Ghana, and treated with amikacin (15 mg/kg loading followed by 7.5 mg/kg every 12 hours), were recruited. Serum amikacin concentration was measured at specified times after treatment initiation and analyzed using a population PK modeling approach.
Results: A total of 419 serum concentrations were available for 247 neonates. Mean (SD) trough amikacin concentration (from samples collected 30 minutes before the fourth dose) among term (n = 25), and preterm (< 37 weeks' gestation n = 36) neonates were 6.2 (3.4) and 9.2 (5.7) μg/mL, respectively ($P = 0.02$). A 1-compartment model best fitted amikacin disposition, and birth weight was the most important predictor of amikacin clearance (CL) and distribution (V). The population CL and V of amikacin were related as CL (L/h) = 0.153 (birth weight/2.5)$^{1.31}$, V (L) = 2.94 (birth weight/2.5)$^{1.18}$. There was a high between-subject variability (58.9% and 50.7%) in CL and V, respectively. CL and V were 0.058 L/h/kg and 1.15 L/kg, respectively, for a mean birth weight of 2.1 kg, and the mean half-life (based on 1-compartment model), was 13.7 hours.
Conclusions: The V and half-life of amikacin in this cohort varied from that reported in non-African populations, and the high trough and low peak amikacin concentrations in both term and preterm neonates suggest strategies to optimize amikacin dosing are required in this population.

Introduction

Aminoglycosides in combination with other antibiotics such as beta-lactams, are frequently used to extend the spectrum of antimicrobial activity for neonatal infection treatment.[1] However, near-ubiquitous resistance of common pathogenic organisms to gentamicin has necessitated the increasing use of amikacin as first-line treatment.[2] Amikacin exhibits wide interindividual variability in pharmacokinetic (PK) parameters during the neonatal period[3–6] and with unique PK characteristics among preterm neonates. The wide interindividual variability in amikacin concentrations in heterogeneous neonatal populations require amikacin therapeutic monitoring; however, such data rarely exist in most

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low-resource settings. There is limited information on amikacin PK parameters in neonates of African origin, and there is no consensus on target amikacin concentration ranges in different neonatal populations. This makes it necessary to conduct setting-specific studies to generate information that would improve understanding of amikacin PK characteristics and optimize amikacin dosing in such populations.

The PK characteristics of amikacin may be altered in conditions such as sepsis[7] and concurrent administration of amikacin with nonsteroidal anti-inflammatory drugs during the first day of life[3] result in increased distribution volume (V) and reduced clearance (CL), respectively. Other commonly used drugs in neonatal intensive care settings may also alter aminoglycoside PK characteristics. For example, methylxanthines increase urine output and filtration fraction.[8] Aminophylline is used for management of apnea of prematurity and is often concurrently administered with amikacin in preterm neonates (< 35 weeks' gestation) with suspected sepsis. However, the potential influence of coadministration of aminophylline on the CL of amikacin, which is excreted largely via the renal route (but also with some amount of nonrenal CL), is not known in this population. The aim of this study was to describe the PK characteristics of amikacin in neonates with suspected sepsis in a low-resource sub-Saharan Africa setting where such information is unavailable, and explore the influence of selected clinical and paraclinical parameters as covariates, including aminophylline coadministration, on amikacin PK parameters.

Materials And Methods

Ethical issues

The Ethical and Protocol Review Committee of the University of Ghana School of Medicine and Dentistry approved this study (protocol ID: MS-Et/M.8-P.5.3/2011-2012). Written informed consent was obtained from all parents and/or guardians of recruited neonates.

Study design and site

This was a prospective, nonrandomized single-site study conducted at the neonatal intensive care unit (NICU) of the Department of Child Health, Korle-Bu Teaching Hospital, Accra, Ghana, from November 2013 to June 2014. The NICU is a tertiary referral unit for neonates from health facilities in the southern regions of Ghana. It is a 55-bed unit for preterm and sick neonates and is located in close proximity to the obstetrics and labor wards of Korle-Bu Teaching Hospital. There are about 2000 neonates admitted to the NICU annually, of whom approximately 60% are preterm births. Admission to the NICU is restricted to neonates aged less than 48 hours unless in exceptional circumstances. The unit changed the first-line empirical treatment for neonatal sepsis from gentamicin and ampicillin to amikacin and cloxacillin because of increasing antimicrobial resistance of bloodstream bacterial isolates in recent years.[9]

Study population and inclusion criteria

Hospitalized neonates suspected of having sepsis, and in whom a decision by the attending NICU physician to treat with amikacin, with or without other therapy, were recruited. Neonates who were known to have received any aminoglycoside before admission and those with major congenital anomaly were excluded.

Drug administration

Amikacin (Amikin®- Bristol-Myers Pharmaceuticals, Uxbridge, England) 15 mg/kg body weight was administered as a loading dose, followed by a maintenance dose of 7.5 mg/kg body weight administered every 12 hours. Amikacin was administered in combination with cloxacillin (50 mg/kg body weight every 12 hours) per the NICU dosing guideline at the time of this study. Aminophylline 8 mg/kg body weight was administered as a loading dose followed by a maintenance dose of 3 mg/kg body weight administered every 8 to 12 hours to preterm neonates (< 35 weeks' gestation) who required it for management of apnea. The New Ballard Score (0.95 interrater reliability)[10] was used to determine gestational age. All needed drugs and supportive therapy were given per standard NICU guidelines. Amikacin was administered as an intravenous bolus over 2 to 3 minutes.

Blood sampling

Blood was collected via venipuncture from recruited neonates by a study physician before drug administration for the laboratory investigations described below. Blood samples were collected into pediatric culture vials (BACTEC Peds plus/F, Becton-Dickinson, Gauteng, South Africa) for culture and sensitivity, EDTA tubes for full blood count, and serum separator tubes for C-reactive protein (CRP) and procalcitonin (PCT) levels.

For amikacin levels, 1 or 2 blood samples (500 μL per sample) were collected from each neonate into separator tubes, centrifuged, and serum obtained immediately transferred into Eppendorf tubes. Blood samples collected for the purpose of determining peak amikacin levels were collected 1 hour after the third dose, and samples for trough levels were collected 30 minutes before the fourth dose. Other samples (apart from peak or trough) were collected after 2, 4, 6, or 8 hours (full PK screen) following the third amikacin dose.

Laboratory analysis

Blood culture was done using the BACTEC 9240 blood culture system with subsequent biochemical species identification. Serum amikacin concentration was measured by particle-enhanced turbidimetric immunoassay[11] using an automated method (Indiko; Thermo Fisher Scientific Inc, Waltham, Massachusetts). The lower limit of quantification of serum amikacin concentration was 0.8 μg/mL and coefficient of variation was < 6% over the entire calibration range (1.5–50 μg/mL). CRP assay was performed with a BNII automated system (Dade-Behring Inc, Newark, Delaware). An automated Elecsys (Roche Diagnostics, Rotkreuz, Switzerland) was used to determine serum PCT. All laboratory investigations were done free of charge for all recruited neonates.

PK model building

PK parameters for the study population were estimated by a nonlinear mixed-effects modeling approach using NONMEM version 7.3 (ICON Development Solutions, Dublin, Ireland) and Pirana version 2.8.2 (Pirana Software and Consulting BV). R Software version 3.0.2 and R Package Xpose (R Foundation for Statistical Computing, Vienna, Austria) were used for graphic analysis of model outputs and exploratory covariate analysis. First-order conditional estimation with interaction algorithm was used throughout the model-building process.

The model-building process was done using concentration versus time data after excluding data below the lower limit of quantification. One- and 2-compartment models with linear