1-1-2017

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AMJ Australasian Medical Journal [AMJ 2017;10(2):140–144]

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BRIEF REPORT

Please cite this paper as: Caceres Guido P, Travaglianti M, Castro G, Licciardone N, Ferreyra O, Bramuglia G, Garcia-Bournissen F, Schaiquevich P. Population pharmacokinetics of amikacin in neonatal intensive care unit patients. AMJ 2017;10(2):140–144.
https://doi.org/10.21767/AMJ.2017.2833

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ABSTRACT

Background
Amikacin treatment requires close monitoring of blood concentrations to increase the probability that levels achieved are both effective and safe.

Aims
We described population pharmacokinetics parameters of amikacin in newborns from a Neonatal Intensive Care Unit with suspected or documented sepsis.

Methods
A nonlinear mixed-effect model approach was used to analyse the data.

Results
Twenty seven neonates were enrolled. Final parameter estimates were: Ke(h-1)=0.232x(CR) Exp-0.85; V(mL/kg)=497.

Conclusion
Weight and serum creatinine are associated with neonatal amikacin volume of distribution and elimination constant rate, respectively. The presence of sepsis may decrease amikacin elimination, although this observation should be further explored. These results could help to individualize amikacin dosage for neonates.

Key Words
Amikacin, population pharmacokinetics, neonates

Implications for Practice:

1. What is known about this subject?
Adjusting amikacin doses in neonates, based on population pharmacokinetics studies, are aimed at increasing the probability that levels achieved are both effective and safe.

2. What new information is offered in this report?
There are very few population pharmacokinetics studies on amikacin in neonates. Thus, we estimated amikacin pharmacokinetic parameters in a new neonate cohort.

3. What are the implications for research, policy, or practice?
These results can help to individualize amikacin dosage in neonates and, potentially, to reduce neonatal mortality and morbidity and to improve treatment of sepsis.

Background

Amikacin (AMK) treatment requires close monitoring of blood concentrations to increase probability that levels achieved are both effective and safe.[1,2] Dosing can be

improved by the availability of accurate AMK population pharmacokinetics (PopPK) parameters in neonates. There are very few relevant studies on AMK PopPK in neonates.[3-6] The objective of this study was to describe AMK PopPK parameters in new-borns suffering from neonatal suspected or documented gram negative sepsis. We evaluated correlations among AMK PK parameters and patient covariates, and established a model taking into account relevant covariates.

Case details

A cohort of patients was prospectively recruited from the Neonatal Intensive Care Unit of the Garrahan Paediatric Hospital. Patients were eligible for inclusion if they were prescribed AMK as per institutional guidelines for the management of known or suspected gram negative bacterial infections.

Written informed consent was obtained from the parents or guardians of 27 newborns to collect and store AMK plasma concentration information. No extra blood samples were obtained for the purpose of this report, nor were any drug doses administered that were not included in the routine clinical care of patients. Results were processed in an anonymized manner.

Blood samples (1ml each) were obtained at peak (i.e., half an hour after finishing a 30 minute AMK infusion), and at trough (i.e., immediately prior to the next AMK dose), as per AMK TDM institutional protocol (AMK ampoules, Fada Pharma Lab, LIA - Argentina) after fourth dose (at steady state).[7] AMK was measured by fluorescence polarization immunoassay (Abbott Laboratories, Diagnostics Division, USA). The lower limit of AMK quantitation (LOQ) was 0.8mg/mL. Coefficients of variation were below 5 per cent over the entire calibration range (0.8–50µg/mL).

A nonlinear mixed-effect modeling approach was used for PopPK analysis using a Stochastic Approximation of Expectation Maximization (SAEM) algorithm as implemented in MONOLIX software (V 4.2.2). A one-compartment model best fitted the data, and was parameterized in terms of elimination rate constant (Ke) and volume of distribution (V). Proportional error model was used to describe intraindividual variability. AMK plasma concentrations below LOQ were rejected.

Covariates tested for correlation with AMK pharmacokinetic parameters were height, weight, birth weight, post-natal age, gestational age (GA), post-menstrual age (PMA), serum creatinine (CR) and creatinine clearance, sex, concomitant drugs, and sepsis. Sepsis was defined as Systemic Inflammatory Response Syndrome and/or bacteremia confirmed by blood culture (CDC 2015).[8]
Univariate analysis results were used to define the order each covariate would be incorporated into the multivariate model, based on the change of the objective function (ΔOF) and associated P value, with respect to the base model.

Covariate effects on model parameters were initially evaluated using a forward analysis and were retained in the model if the objective function (OF) value was reduced at least 3.84 units (Chi-square test, $p<0.05$), followed by a backwards elimination procedure where each covariate was independently removed from the full model to confirm its relevance. An increase in the OFV of >10.9 units ($p<0.001$) was required for inclusion in the final model.

Likelihood ratio test, Akaike information criteria, Bayesian information criteria, goodness-of-fit plots, estimates of the PK parameters and their clinical relevance were used to select the most appropriate structural model.

A visual predictive check plot (VPC) was constructed based on the parameters and random effects (final model).

RESULTS

A total of 27 newborn patients (18 males) were enrolled in the study between 2003 and 2007, and received AMK doses of 7.5mg/kg once-, twice-, or thrice-daily, or 10mg/kg twice, or thrice-daily. A total of 50 AMK concentrations were obtained (troughs: 56 per cent). One trough was below LOQ.

Characteristics of patients were (expressed as median and range): weight (kg)=2.65 (1.4-4.0); birth weight (kg)=2.60 (1.5-3.3); height (cm)=48 (37-52); post-natal age (days)=21 (6-58); gestational age (weeks)=37 (28-40); post-menstrual age (weeks)=40.9 (29-43); CR (mg/dL)=0.49 (0.20-1.84) and CR clearance (mL/min/1.73m^2)=38 (12.65-77.59) calculated by Schwartz formula. Fifteen out of the 27 patients were preterm neonates.

Considerable between-subject variability (BSV) in parameter estimates of the base model was observed, with a BSV for AMK V and Ke of 46 per cent and 70 per cent, respectively. Correction of AMK dose by weight explained 48 per cent of the BSV in V and was thus incorporated in the model. Mean population PK parameters after dose normalization by weight were 0.138 h^{-1} and 497ml/kg, respectively.

Covariates with significant impact on AMK BSV for Ke

identified in the univariate analysis included CR, GA, PMA, sepsis, and ibuprofen concomitant administration. The most significant covariate related to Ke was CR.

Covariates such as GA (on Ke, ΔOF=-6.13), PMA (on Ke, ΔOF=-5.49), sepsis (on Ke, ΔOF=-4.88) and concomitant ibuprofen (on V, ΔOF=-5.75), had a statistically significant effect in the univariate analysis, but were not retained in the forward analysis. Analysis of scatterplots and boxplots of the Ke and V with covariates identified those that most likely explain BSV. Final model VPC plot and goodness-of-fit plot showed good predictive performance of the final model (Figures 1 and 2).

Final parameter estimates were:

Ke (h-1) =0.232 x $(CR)^{-0.85}$

V (mL/kg) =497

CR explained 20.1 per cent of the BSV in AMK Ke and the mean population pharmacokinetic parameters were 0.232 h-1 and 497ml/kg for Ke and V, respectively.

Discussion

A reduction in neonatal mortality and morbidity relies heavily on the rapid implementation of an effective treatment of neonatal sepsis, which requires a rational use of antibiotics based on solid scientific evidence.[9,10]

We report the PopPK of AMK for the first time in Latin American neonates. Parameter estimates from our model are similar to previous studies in neonate populations from Europe.[3–6] Bleyzac et al. (2001) showed that AMK Ke and V are dependent on GA, and that differential neonatal renal maturation is responsible for the wide between-subject variability in PK.[9,11] Other researchers identified weight as the best predictor of neonatal AMK V.[4] Similarly, we show the importance of weight on AMK V, and, in univariate analysis, that CR, GA, PMA and sepsis had a statistically significant influence on Ke, and concomitant ibuprofen administration on V. Nonetheless, the only covariate retained in the final model, besides weight, was CR on Ke.[3]

Previous reports in critically ill adult patients showed impaired aminoglycosides clearance.[12] In concordance, we observed in univariate analysis that sepsis seems to decrease AMK elimination by 32 per cent, and that ibuprofen administration was associated to a small decrease on V. Owing to the limited number of patients in our study we could not confirm these observations in the final model. We believe that these observed associations should be explored in larger studies given the importance and high frequency of sepsis, and ibuprofen use, in neonates receiving AMK.

We are aware of the limitations imposed by the small number of patients in our study. It should be noted that such studies in the neonatal population are extremely difficult to carry out, so that even small but very closely monitored studies such as ours can add important information relevant to the clinical management of these patients.

Conclusion

Weight and CR are associated with neonatal AMK V and Ke, respectively, and should be further evaluated for routine use in the clinics to guide AMK dosing in this population. The observed link between sepsis and AMK Ke should be further explored. Our results could help to individualize AMK dosage for neonates.

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PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

FUNDING

Garrahan Paediatric Hospital.

ETHICS COMMITTEE APPROVAL

Department of Bioethics - Garrahan Paediatric Hospital: 1630/F62.

Figure 1: Visual predictive check (VPC). The figure shows the 90 per cent prediction intervals obtained by simulation using the final model. The areas are (a) the 90 per cent confidence intervals for the 5th percentile and the 90th percentile and (b) the median of the simulated data, respectively.

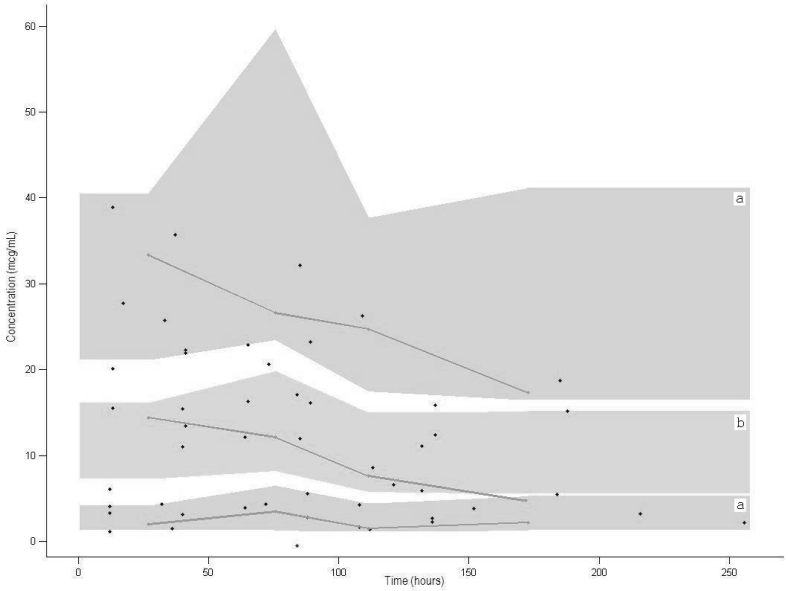

Figure 2: Goodness of fit plots. (A) Observed versus population predicted and (B) observed versus individual predicted values. Concentrations in µg/mL