

Review on Population Pharmacokinetics of Amikacin in Paediatrics

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Abstract

Amikacin is an aminoglycoside antibiotic with a broad-spectrum bacterial coverage that is frequently utilized both as monotherapy and in combination with other antibiotics for severe bacterial infections in the paediatric population. The narrow therapeutic index of the drug and high inter-individual variabilities in drug exposure results in either drug toxicity or subtherapeutic concentrations. Thus, therapeutic drug monitoring and population pharmacokinetics are pivotal to facilitate the optimal dosage regimens in paediatrics and negate the adverse outcomes. The therapeutic goal is to maintain the target peak and trough concentrations within 30-40mg/l and <5 mg/l respectively. This review aimed to summarize population pharmacokinetic considerations and the pharmacokinetic parameters of amikacin across the paediatric population.

Keywords: Amikacin, Paediatric, Population Pharmacokinetics, Therapeutic Drug Monitoring

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Abbreviations: TDM- Therapeutic Drug Monitoring, GFR- Glomerular Filtration Rate, pop pk- Population pharmacokinetics, ALL- Acute Lymphoblastic Leukemia, NMDA- N-methyl-D-aspartate, Vd- Volume of Distribution, Cl- Clearance, t_{1/2} - elimination half-life.

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INTRODUCTION

Aminoglycosides act synergistically against gram-negative organisms and certain gram-positive organisms. These are used for the treatment of severe infections of the abdomen, urinary tract, and respiratory tract infections and can also be used prophylactically.¹ Gentamicin and Amikacin are the most frequently used aminoglycosides. Toxicities have been reported due to the increased frequency of Aminoglycoside administration. Several studies have concluded that the once-daily dosing of Aminoglycosides is safe and more efficacious than the multiple dosing.²

Amikacin, a narrow therapeutic index drug, is widely used in the paediatric population for various conditions like neonatal sepsis, hospital-acquired infections, acute respiratory tract infections, and urinary tract infections. It acts by disrupting the protein synthesis and inhibits the growth of bacteria. Due to high inter-individual variability, dosage adjustments are required.³ The most reported toxicities include irreversible ototoxicity and nephrotoxicity which is reversible when detected early. Apart from toxicities, a few adverse effects such as tingling, numbness, fever, rash have been reported.²

Pharmacokinetics is the study of movements of drugs through the body enclosing the kinetics of absorption, distribution, metabolism, and excretion (ADME). The application of pharmacokinetic principles to the safe and effective therapeutic management of the drugs in an individual patient is clinical pharmacokinetics. Primary goals of clinical pharmacokinetics include improving efficacy and reducing the toxicity of patient's drug therapy. Drug concentration can be measured in the blood or plasma, urine, saliva, and other easily sampled fluids.⁴⁻⁶

Several studies and practice guidelines recommend a target serum Amikacin peak concentration to be 20 to 35 mg/L, trough concentrations >5-10 mg/L.^{7,14,25} The recommended dosing in neonates and infants is 15mg/kg IV, Once daily (OD) and 7.5mg/kg, twice daily (BD). Comparatively, the OD regimen has reduced toxicity and increased efficacy than the BD regimen.⁸ Amikacin has a mean half-life of 6.0

hours in neonates and 1.9 hours in children aged up to 6 years.¹⁰

Narrow therapeutic drugs tend to cause toxicity. To ensure the safety of the drug a phenomenon called therapeutic drug monitoring (TDM) is performed to optimize the dosage regimen in individual patients.⁹ To perform TDM, 2 blood samples are collected, one peak sample to be collected 30 mins after drug administration and one trough sample should be collected 1 hour before the next dose, and quantification of the drug is performed.¹⁰

High inter-individual variability necessitates the need for Population pharmacokinetic modeling to determine individual Pharmacokinetic parameters and source of variability in a population.¹¹ This review presents the population pharmacokinetics of Amikacin in paediatric population among various age groups and disease conditions.

MATERIALS AND METHODS

Literature Search

A thorough literature survey was conducted for the time period 1990 to 2021, and 50 articles were identified out of which 30 articles were included and 20 excluded depicted in Figure. The search was conducted in PubMed, Google Scholar, ScienceDirect database engine using the following terms (“aminoglycosides” and “indications”) (“amikacin”), (“amikacin” and “pharmacokinetics”) (“amikacin” and “paediatrics”) (“amikacin” and “population pharmacokinetics” and “nonlinear mixed effect model”) (“amikacin” and “neonates”) (“amikacin” and “infants”), (“amikacin” and “disease conditions” and “paediatrics”) (“amikacin” and “dosage optimization”) (“amikacin” and “therapeutic drug monitoring” and “paediatric population”) (“amikacin” and Bayesian modeling”).

Inclusion Criteria

The following studies were included: Studies that conducted therapeutic drug monitoring, Studies that optimized dosage regimens, Studies that determined the population pharmacokinetics in the paediatric population, and Studies that suggested dosage adjustments in different disease conditions.

Table 1. Population Pharmacokinetics among Paediatric Population

Title	Covariates	Equations	Cpeak(mg/mL)	Ctrough(mg/mL)	PK Parameters	Authors
Pharmacokinetic Variability of Amikacin After Once-Daily and Twice-Daily Dosing Regimen in Full-Term Neonates	Gestational age Body weight Proven sepsis	$C_{trough} = C_{peak} \cdot e^{-\beta \cdot (t-t_0)}$ $C_{peak} = \frac{R \cdot D \cdot (1 - e^{-\beta \cdot t})}{\beta \cdot Vd \cdot (1 - e^{-\beta \cdot \tau})}$	BD GROUP= 21.79 OD GROUP= 36.39	BD GROUP=5.67 OD GROUP= 3.99	Vd= 0.78 ± 0.38 L/kg Cl= 86.99 ± 48.22 m L/h/kg T1/2= 6.81 ± 2.51 h	Katarina Vuicevic et al. ²²
Amikacin Pharmacokinetics and Suggested Dosage Modifications for the Preterm Infant	-	$T_{max} = \left[\ln \left(\frac{C_{peak}}{C_{trough}} \right) \right] / k$, (ii) $C_{ave} = \frac{dose}{(T_{max})} (Cl)$, (iii) $dose = (C_{ave}) (Cl)$.	C peak= 21.88 ± 4.88	C trough= 9.10 ± 3.77	Vd=0.57 +0.11l Cl= 0.84 ±0.28 L/kg/hr T1/2= 8.42 ±2.55 h	Cynthia et al. ²³
Population Pharmacokinetics of Amikacin In Indian Paediatric Patients	Body weight, age	$CL = 1 \cdot (WT/14.2) \cdot EXP (-1)$ $V = 2 \cdot EXP (2)$	-	-	Cl=1.23 L/kg/h Vd=3.37 L/kg	Raju et al. ²⁴

* C_{trough} - Trough Concentration, C_{peak} - Peak Concentration, T_{max} - Time taken to reach the maximum concentration, C_{ave} - Average Concentration, Vd - Volume of Distribution, Cl - Clearance

Exclusion Criteria

The articles which did not have the information on pharmacokinetic aspects were excluded from the study.

RESULTS AND DISCUSSION

Population Pharmacokinetics of Amikacin

High variability in the primary pharmacokinetic parameters influenced by multiple covariates has been established in the paediatric population. Since amikacin excretion is through renal, GFR predominantly determines the clearance values.²³ Hence, in neonates there is a significant difference in the clearance of the drug when compared to adults. Gestational age is one such covariate as the preterm infants had higher drug levels than the full-term infants. The mean neonatal amikacin Vd, CL, and t1/2 were 0.78 ± 0.38 l/kg, 86.99 ± 48.22 ml/h·kg, and 6.81 ± 2.51 h, respectively.²² It was evident from a study that there was a decrease in half-life and increase in clearance with increase in the post-conceptual age. Variability has also been noted with the frequency of dosing, for instance, a study conducted by Katarina Vucicevic et al.,

revealed higher drug levels in the BID dosing viz peak concentration of 36.39 mg/ml and trough concentration of 5.67 mg/ml while the OD regimen produced a peak concentration of 21.79 mg/ml and trough concentration of 3.99 mg/ml respectively.²² The reported mean pharmacokinetic parameters and the influence of covariates among different pop pk studies are summarised in Table 1.

Dosage Adjustments and Pharmacokinetics of Amikacin in Various Disease Conditions

Amikacin has been used in various disease conditions and it is often co-administered with other antibiotics including Vancomycin, beta-lactam antibiotics. There is a higher inter-individual variability observed in ALL when compared to the normal healthy volunteers.¹² The mean peak serum concentrations were observed to be 36.30 ± 4.03 µg/ml. normal healthy volunteer- 19 to 43.8 mg/L. due to morphological changes in cancer patients, the renal clearance might be affected which has a direct effect on the clearance of the drug. The clearance and half-life tend to decrease in oncology patients which stated the importance of optimizing the dose of amikacin in paediatric ALL patients.

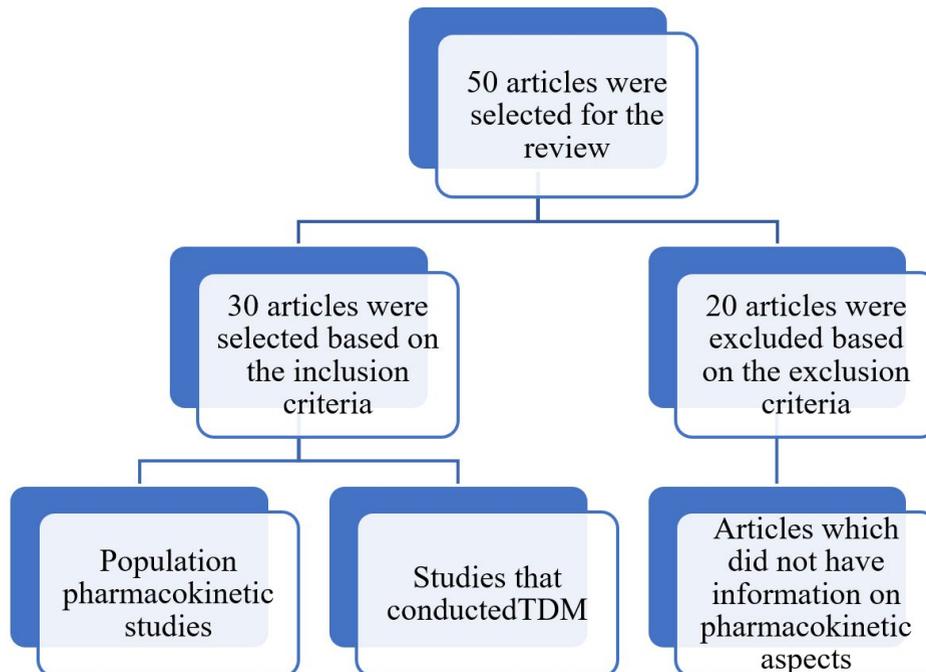


Figure. Literature survey

Table 2. Pharmacokinetic Parameters in Various Disease Conditions

Disease condition	Age	Body weight	Peak conc.	Trough conc. mg/mL	AUC (µg.hr/ml)	Clearance mL/min	Volume of Distribution	Half life (h)	Authors
Febrile	3-11	11.5-21.5	36.30 ± 4.03	0.41 ± 0.23	76.20±6.30	18.85±5.11	0.19±0.11 L/kg	1.76±0.55	Nadeem et al. ¹²
Neutropenia						mL/min			
Burn Patients	0.6-17	8-90	33.2 ± 9.4	3.8± 4.6	-	2.48 L/h	2.71 L	-	Catherine et al. ¹³
Sepsis	0.16-21.75 (h)	(0.9-5.2)	17.5 ± 9.3T 19.9(10.5) P	6.2± 3.4 9.2 ± 5.7	-	0.153L/h	2.94L	13.7	Amponsah et al. ¹⁴
Perinatal asphyxia treated with hypothermia	0.22 (8)	0.926 (2)	-	-	-	0.0495 (2)	0.832(1)	-	Sinziana et al. ¹⁵

* AUC- Area under the curve

In paediatric population, amikacin is widely used to treat sepsis and the patients at risk of sepsis. The burn patients' pathogenesis might result in altered vd, cl of amikacin.¹³ A total of 73 burn patients were included in a study to determine the pharmacokinetics of amikacin in burn patients. The multivariate analysis revealed that bodyweight-only had a significant effect on clearance and other covariates like age, sex, concomitant adm with vancomycin had no effect on cl or Vd. Also, pharmacodynamic studies should be conducted in burn patients to optimize the dosage. Drug characteristics such as weight, lipophilicity, and pH have an impact on the disease condition. In preterm and term neonates, at birth, the volume of distribution is increased but did not influence clearance. An increase in peak concentrations and lower trough concentrations suggested dosage adjustment in pre-term and term neonates.¹⁴

In Perinatal Asphyxia Treated with Hypothermia, there is a substantial decrease in the clearance of the drug by 40.6% but no change was noted in the volume of distribution. The percentage of neonates with toxic trough levels had decreased from 40 to 76% to 14 to 25% by increasing the dosing interval by 12h. Simulation of the study revealed that the neonates reaching the toxic trough levels has decreased by increasing the dosing interval by 12h which also increased the clearance. For children weighing 2.8kg, the dose recommended was 15mg/kg every 42h and 15mg/kg every 48hours for children weighing between 1.8kg to 2.8kg.¹⁵ Parameters of the above-discussed disease condition have been shown in the Table 2.

Therapeutic Drug Monitoring of Amikacin to Assess Nephrotoxicity & Ototoxicity

Commonly reported toxicities of Amikacin are nephrotoxicity and ototoxicity. Several studies have been conducted to compare the safety and efficacy of once-daily and twice-daily dosing of Amikacin.¹⁶ It has been established that the trough plasma concentration of <10mg/L is safer and there exists a risk of ototoxicity when it exceeds 10mg/L and duration of therapy if it exceeds more than 7 days. The peak plasma concentration of up to 30mg/L is acceptable. Amikacin-induced ototoxicity is caused by damaging the cochlea in

the inner ear which is known as cochleotoxicity leading to permanent hearing loss. It also causes calcium influx by binding to the NMDA receptors. Tinnitus is used in the early diagnosis of ototoxicity in paediatric patients.¹⁷ Extremely low-birth-weight infants are at higher risk for ototoxicity compared to low birth-weight infants. Thus, dosage adjustments of Amikacin are needed based on the gestational age, birth weight.¹⁸

Nephrotoxicity is yet another familiar toxicity of Amikacin predisposed by the accumulation of the drug in the proximal renal tubule, which produces oxidative damage by emitting free radicals.¹⁹ The risk of toxicity is typically more with the coadministration of other nephrotoxic drugs such as loop diuretics, NSAIDs, Amphotericin B, etc. nephrotoxicity was assessed by serum creatinine levels if $>0.3\text{mg/dl}$ or 50% increase after the initial therapy. The simulation studies revealed significantly high variability between the plasma levels in preterm and term infants. Thus, higher risk in preterm infants than the term infants those with increased serum Amikacin levels in preterm infants have been concluded.²⁰

Monitoring of Ototoxicity and Nephrotoxicity

Ototoxicity is measured by an otoacoustic emission test and pure tone screening. It is screened by using audiometry, earphones. It is managed by audiological interventions such as hearing aids, educational interventions, and tinnitus therapy.¹⁸ For the prevention of nephrotoxicity, calculating creatinine clearance, baseline kidney function, and urinary alpha-1m excretion should be monitored in all the patients administered with Amikacin and therapeutic drug monitoring is essential in patients with abnormal renal function.²¹

Once Daily (OD) vs Twice Daily (BD) Dosing of Amikacin

There has been a conflicting view about the safety of once-daily vs twice-daily regimens. Studies have stated that mean peak and trough concentrations $21.79\ \mu\text{g/ml}$ and $5.67\ \mu\text{g/ml}$ in twice-daily regimen was significantly different from peak and trough concentrations of $36.39\ \mu\text{g/ml}$ and $3.99\ \mu\text{g/ml}$ of once-daily regimen but there was no change observed in the pharmacokinetic

parameters.²² Some studies have concluded that the OD regimen had higher peak concentrations and less trough concentration compared to the twice-daily regimen.¹⁶ When the peak plasma concentration is higher the activity of the drug will be higher, at the same time when the trough level is below $10\ \text{mg/L}$ ototoxicity can be prevented.²³ Thus, establishing the superiority of the once-daily regimen owing to higher bactericidal effect with higher peak plasma concentration and better tolerability with lower trough plasma concentrations.

CONCLUSION

Amikacin is a narrow therapeutic drug with high inter-individual variability. Pharmacokinetic modeling enables the individualization ratio of dosage regimens. High variability has been observed in the clearance and volume of distribution in preterm and term infants. Thus, this review article concludes that Amikacin should be administered only when it is indicated, and dosing should be rational as the Amikacin pharmacokinetic parameters. Therapeutic drug monitoring of Amikacin is necessary to optimize a safe and effective dose. Thus, further studies have to be conducted to recommend an appropriate dose for safe and effective treatment of Amikacin in paediatric population.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

KC and KPA have formulated the hypothesis. TN, HV and SNK collected the articles and wrote the manuscript. All authors read and approved the final manuscript for publication.

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DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

Not applicable.

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