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Therapeutic Drug Monitoring and Safety of Amikacin in Patients with Febrile Neutropenia

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Abstract

Objective: To evaluate AMK TDM in hematology-oncology patients with neutropenic fever and to explore the effects of cachexia, demographic, anthropometric, and renal function variables on AMK PK parameters.

Methodology: In this prospective observational study, 68 febrile neutropenic patients aged ≥13 years at the Armed Forces of Bone Marrow Transplant Centre, Rawalpindi, received daily intravenous amikacin (15 mg/kg/day). Patients were classified into cachexia (n=34) and non-cachexia (n=34) groups. Peak (Cmax) and trough (Cmin) AMK concentrations were measured at steady state, and PK parameters were calculated using a one-compartment model. Data were analyzed using SPSS.25.

Results: Patients with cachexia had low body weight, body mass index, albumin, and creatinine. More than 70% of patients achieved their therapeutic levels, and both groups' Cmax and Cmin amikacin levels were comparable. While weight-normalized PK parameters did not significantly vary, the individuals in the cachexia group's absolute clearance was significantly higher (127.8±63.66 mL/min vs. 118±53.49 mL/min, p <0.001). The cachexia group experienced a longer time to effervescence (p=0.01), while nephrotoxicity was more common in the non-cachexic group; ototoxicity was not observed in any group.

Conclusion: In neutropenic hematological populations with and without cachexia, weight based amikacin dosage with TDM is safe and effective. Individualized monitoring is still essential because cachexia causes pharmacokinetic alterations, especially in renal clearance. Larger, multi-center clinical investigations are necessary to further develop dosage methods for these patients.

Keywords: Amikacin (AMK), Therapeutic drug monitoring (TDM), Peak (Cmax), Trough (Cmin).

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Introduction

In clinical situations where the clinical effect is strongly correlated with the drug's plasma concentration but cannot be measured directly, therapeutic drug monitoring (TDM) is advised.[1] In order to offer safe and effective therapy for patients who are neutropenic, TDM of amikacin (AMK) plasma or serum concentrations is thought to be the most feasible way to determine optimal antibiotic exposure. [2]

To define the best pharmacological plan and to adjust therapy when pathological conditions or pharmacological treatments change, amikacin TDM entails measuring and interpreting the drug's concentrations in plasma (or serum) and estimating its pharmacokinetic (PK) parameters, such as the volume of distribution (Vd) and the total clearance.[3,4] Aminoglycosides were generally administered in two or three doses per day. However, the extended interval dosing strategy has proven to be beneficial since it maximizes antibacterial activity and reduces toxicity, particularly when large residual concentrations are linked to nephrotoxicity. With this regimen, the intervals are prolonged to enable the complete elimination of amikacin. [5] AMK concentration of 3 µg/mL between administration of 2 doses (Cmin) was identified as the probable toxicity threshold for neutropenic individuals on an extended interval dosing regimen, while the optimum AMK peak (Cmax) was found to be between 20 and 50 µg/mL and trough (Cmin) level of 1 to 5 µg/mL.[6,7]

Intravenous AMK is administered as a first-line antibiotic to combat life-threatening gram-negative infections in neutropenic haem-oncology patients. No recent study on TDM of amikacin in neutropenic patients is done in Pakistan and only few are available for Asian populations.[1]

The primary objective of this study was to study amikacin TDM in neutropenic hematology oncology patients and to evaluate the effects of demographic and anthropometric variables, as well as renal function, on amikacin concentrations and to analyze alterations in PK parameter in haem-oncology patients who are cachectic.

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Methodology

In this prospective study, 68 patients with hematological disorders and febrile neutropenia (FN) who were admitted to the Armed Forces Bone Marrow Transplant Center (AFBMTC), Rawalpindi were included. The study was approved by the institutional review board (Letter No: IRB-029/AFBMTC/Approval/2022), and informed consent was obtained from all participants. The target population were patients aged ≥13 years who received intravenous amikacin at a dosage of 15 mg/kg once daily for more than 48 hours during the research period from Dec 2022 to Dec 2024. Patients under the age of 12 years, those with a temperature below 38°C, renal insufficiency, and in need of hemodialysis were excluded.

The demographic data included age and gender while the laboratory parameters were complete blood count, urea, creatinine, bilirubin, ALT, CRP, albumin, height, sex, age, primary diagnosis, anorexia, diet intake during therapy and body weight (BW) at initiation of amikacin therapy. We computed lean body weight (LBW) and BMI by the formula.[8, 9] BW was used to determine CrCl using the Cockcroft-Gault equation [10]. Clinical signs of neutropenia in hematology patients included a single axillary/oral temperature >101.3°F (38.5°C) or persistent temperature of ≥100.4°F (38°C) for one hour, an absolute neutrophil count (ANC) < 500 cells/mm^3 or an expected decease in ANC to < 500 cells/mm^3 within 48 hrs. Under these conditions, patient's blood cultures were obtained and inpatient treatment with empirical antibiotics were commenced until they were afebrile for 48–72 hrs and ANC of ≥500 cells/mm3 for 72 hrs was achieved.[11] Weights and laboratory results were collected as soon as possible or within 48 hours of the day the AMK concentrations were measured. Renal injury was defined as an elevation of serum creatinine level by >1.5 times during the therapy as per RIFLE criteria.[12] Patients were classified into two groups using criteria of Fearon and Blum for cancer cachexia.[13,14] .Cachexia was defined as involuntary weight loss (>2%) along with anorexia. [15]

The initial dose of amikacin was administered intravenously as a 30-minute infusion. Peak (Cmax) and trough (Cmin) samples were collected daily after the steady-state was achieved, with Cmax samples taken 30 minutes after the infusion ended and Cmin samples collected prior to the next scheduled amikacin dose. For each patient, the exact timing of administration and sampling was meticulously recorded. AMK levels were measured in the AFBMTC laboratory by using a COBAS c501 chemistry analyzer by using spectrophotometric analysis. The calibration range was 0 to 50 ug/ml. Samples exceeding 50ug/mL were diluted using a dilution buffer according to the manufacturer's dilution protocol.

For each patient, plasma amikacin concentration-time data were analyzed using 1-compartment model.[16] PK parameters such as the elimination constant (kel) ,half-life($t_{1/2}$), volume of distribution (Vd) and amikacin clearance (CL_{amk}) were determined according to the equations.[16]:

$$kel = \ln (Cmax / Cmin) / (\text{dosing interval-infusion time})$$

$$\text{Half-life } (t_{1/2}) = 0.693/ kel$$

$$Vd = k_o / kel \,.\, (1-e^{-kel\ t_{in}})/(Cmax - Cmin\ e^{-Kel\ t_{in}})$$

Where k_o is the constant infusion rate of amikacin and t_{in} is the duration of drug infusion.

$$CL_{amk} = Vd \times kel$$

Dose, Vd, CL_{amk} are expressed in absolute values and values are normalized by body weight.

Data analysis was performed using SPSS version 25.0. Frequencies and percentages were calculated for categorical variables. A Shapiro-Wilk test was used to demonstrate the normality of distribution of numerical variables; for continuous numerical data mean ± standard deviation or median (IQR) was calculated. Median values between both groups were compared by Mann-Whitney test while Fisher exact test was used for categorical data. *P*-value of less than 0.05 was considered statistically significant.

Results

We analyzed the TDM of 68 patients who received intravenous amikacin during the study period. The cohort was classified into cachexia and non-cachexia group with 34 (50%) patients in each group respectively. The demographic, anthropometric, and relevant clinical characteristics of these patients are summarized in Table I.

The cohort of both groups were given amikacin dose at 15mg/kg/day, median daily dose in cachexic group was 1000 mg (IQR: 780–1000) while in non-cachexia was 1000mg (IQR:1000) which was significant with $p < 0.05$ while infusion time of 30 minutes were same significantly

Table I: The Demographics, Anthropometric, and Relevant Clinical Characteristics.

		Cachexia (n=34)	Non-cachexia (n=34)	*P*-value
		n (%)	n (%)	
Age (years)*		27(17-37)	30(20.5-43.2)	0.3
Gender	Male		27(79.4%)	19(55.9%) 0.06
	Female		7(20.6%)	15(44.1%)
BW at initiation of Amikacin therapy (Kg)*		62.2(38-113)	72.8(48-99)	0.001
Body mass index (Kg/m^2)*		21.7(19.4-24.8)	25.5(23.5-29.1)	0.001
Co-Morbids	No		34(100%)	28(82.4%) 0.02
	Diabetes		0(0%)	2(5.9%)
	Grave's disease		0(0%)	1(2.9%)
	Tuberculosis		0(0%)	1(2.9%)
	DM/HTN**		0(0%)	1(2.9%)
	Rheumatic fever		0(0%)	1(2.9%)
Hematological diseases	Acute Myeloid Leukemia		7(20.6%)	14(41.2%) 0.1
	Acute Lymphoblastic Leukemia		8(23.5%)	9(26.5%)
	Chronic Myeloid Leukemia		2(5.9%)	3(8.8%)
	Lymphomas		3(8.8%)	3(8.8%)
	Multiple Myeloma		1(2.9%)	2(5.9%)
	Waldenstorm's Macroglobinemia		1(2.9%)	0(0%)
	Myelodysplastic Syndrome		1(2.9%)	0(0%)
	Aplastic Anemia		9(26.4%)	2(5.9%)
	Paroxysmal nocturnal hemoglobinuria		2(5.9%)	0(0%)
	Neuromyelitis optica		0(0%)	1(2.9%)
Absolute neutrophil count (x10^9/uL)*		0.3(0.02-0.8)	0.1(0.02-0.8)	0.6
Hemoglobin (g/dL)*		8.6(8.1-9.2)	9.0(8.3-9.8)	0.07
Albumin (g/L)*		32.5(28-35)	35(34-37)	0.002
Serum Creatinine (mmol/L)*		68.5(51-87.5)	63(47.7-86.7)	0.8
Creatinine clearance (mL/min)*		121(36-253)	149.1(41-287)	0.04
Culture Growth	No growth		31(91.2%)	30(88.2%) 1.0
	Pseudomonas aeroginosa		1(2.9%)	2(5.9%)
	Acinetobacter baumannii		0(0%)	1(2.9%)
	MRSA		1(2.9%)	0(0%)
	Burkholderia specie		0(0%)	1(2.9%)
	Klebsiella pneumoniae		1(2.9%)	0(0%)
Concurrent drugs	Meropenem		31(91.2%)	29(85.3%) 1.0
	Tazobactum/Piperacillin		6(17.6%)	6(17.6%)
	Teicoplanin		24(70.6%)	25(73.5%)
	Cefipime		1(2.9%)	0(0%)
	Amphotericin-B		4(11.8%)	3(8.8%)
	Linezolid		2(5.9%)	1(2.9%)
	Tigecycline		2(5.9%)	0(0%)
	Ceftazidime/Azobactam		2(5.9%)	3(8.8%)
	Moxifloxicin		1(2.9%)	2(5.9%)
	Colomycin		4(11.8%)	6(17.6%)
	Chemotherapy		23(67.6%)	32(94.1%)
Time to defervescence (Days)*		4(3-7.2)	3(2-4)	0.01

Note: *= Median (IQR),**DM/HTN=Diabetes/Hypertension
Chi-square was applied. For non-parametric categorical data Fisher's exact test and Mann Whitney test for continuous variables was performed. *P*-value less than 0.05 was significant statistically

in both groups (p= 1.0). Amikacin PK parameters collected from patients with or without cachexia who received amikacin. (Table II)

The absolute creatinine clearance post-amikacin therapy in cachexia group was 127.8±63.66mL/min (20-288) with only 3 (8.8%) patients who had kidney injury while 118±53.49 was the absolute creatinine clearance in non-cachexic group with kidney injury in 8 (23.3%) cases,

only 1(1.47%) patient underwent hemodialysis while no ototoxicity was reported in both groups.

Table II: Pharmacokinetic and TDM parameters in Cachexia and Non-cachexia Groups.

	Cachexia		Non-cachexia	*P*-value
	n (%)		N (%)	
Duration of amikacin therapy*	7(6-10)		7(5-8)	0.05
Cmax (mcg/mL)*	24.5(20.07-33)		23.3(19.2-34.2)	0.94
Cmin(mcg/mL)*	1(1-1.5)		1(0.2-2)	0.93
kel(h-1)*	0.50(0.42-0.63)		0.55(0.42-0.66)	0.45
Half-life(h)*	1.36(1.09-1.63)		1.2(1.04-1.65)	0.45
Weight normalized Vd(L/Kg)*	0.66(0.46-0.89)		0.68(0.45-0.85)	0.96
Absolute value of Vd (L)*	2.60(1.68-3.50)		2.63(1.50-3.31)	0.58
Weight normalized CLamk (mL/min)*	0.30(0.21-0.37)		0.20(0.20-0.44)	0.53
Absolute value of CLamk(mL/min)**	127.8±63.66		118±53.49	0.00
Therapeutic peak achieved	Yes	27(79.4%)	25(73.5%)	0.7
	No	7(20.6%)	9(26.5%)	
Therapeutic trough achieved	Yes	27(79.4%)	24(70.6%)	0.5
	No	7(20.6%)	10(29.4%)	
Kidney injury	Yes	3(8.8%)	8(23.5%)	0.1
	No	31(91.2%)	26(76.5%)	
Trough level >4ug/mL		2(5.9%)	2(5.9%)	1.0
Ototoxicity	Yes	0(0%)	0(0%)	
	No	34(100%)	34(100%)	
Dose adjustment	Yes	3(8.8%)	5(14.7%)	0.7
	No	31(91.2%)	29(85.3%)	
Infection subsided	Yes	27(79.4%)	31(91.2%)	0.3
	No	7(20.6%)	3(8.8%)	

Note:*:Median(IQR),**Mean± Standard deviation
Chi-square was applied. For non-parametric categorical data Fisher's exact test and Mann Whitney test for continuous variables was performed. *P*-value less than 0.05 was significant statistically.

Discussion

This study represents the first prospective, observational research in a low-income country, Pakistan, that provides important information about PK, how safe and effective amikacin is for hematology patients with febrile neutropenia, particularly analyzing the results for patients with cachexia compared to those without. In the present study there is no significant difference in median age of both groups suggesting same age distribution across the cohort . [15-17]

One notable finding was the absence of chronic co-morbidities in the cachexia group compared to the non-cachexia group. Chronic diseases can have a substantial impact on PK by affecting drug metabolism, clearance, and potential toxicity, which highlights the importance of carefully assessing of comorbidity profile when interpreting TDM data, as the absence in cachectic patients may lead to biased treatment outcomes.

Individuals with cachexia were found to have significantly lower BW and BMI along with lower albumin levels, which are consistent with known features of cachexia like involuntary weight loss, muscle atrophy, edema, and systemic inflammation.[15] Although serum creatinine was comparable in both groups, the cachectic patients showed marked decrease in CrCl, likely due to decreased muscle mass, which affects the production of serum creatinine, which emphasizes the importance of more accurate and precise estimation of renal function in cachexia as creatinine based calculation may overestimate glomerular filtration rate (GFR) in such patients. [18]

A daily dose of 15mg/kg/day of AMK were administered to both groups. However, the median dose in the cachexia group was lower due to their lower body weights. Both groups achieved similar Cmax and Cmin concentration in spite of this discrepancy, suggesting that proper dosing according to actual body weight could help in achieving target concentrations even in cachexia patients. [19]

It's interesting to note that individuals with cachexia had significantly higher absolute clearance of amikacin than non-cachexic group due to changes in the dynamics of Vd and renal function in this cohort, or it could be a result of increased inter-individual variations. However, when considering weight-adjusted clearance and Vd, there were no significant difference between the groups, indicating that standard weight-based dosing is still suitable which are in accordance of previous research showing that hypoalbuminemia, increased capillary permeability, and fluid changes cause elevated Vd and clearance in critically ill or malnourished patients.[20-22] Additionally, there was no apparent difference in the half-life or elimination rate constant (kel) between the groups. This implies that careful dosing and monitoring may

lessen the clinical impact of cachexia, even while it somewhat changes distribution and clearance profiles.[15]

The PK were similar across groups; however, the patients in the cachexia group experienced a significantly longer time to defervescence, possibly indicating a compromised immune system or a more severe disease state while non-cachexic group has higher percentage of infection resolution.[23] More than 70% achieved significant therapeutic peak and trough concentration, which indicates the effectiveness of TDM in managing amikacin therapy in neutropenic patients with hematological malignancies. [21]

Similarly, the renal damage was more frequent in non-cachexia individuals, although not statistically significant which could be due to prolong chemotherapy exposure and also suggests that individuals with cachexia have higher renal reserve or compensatory abilities, which contradicts the assumptions about renal issues in this population. Since no patient experienced ototoxicity, AMK is safe when used with cautious TDM. Dosage adjustments were infrequent in both groups, with only one patient requiring hemodialysis. [15]

These results highlight the value of TDM in optimizing AMK therapy, particularly in hematology patients. Sub therapeutic peak levels, despite high dose, may be attributed to increased Vd or impaired absorption as a result of disease physiology.

Limitations: A small, single-center cohort limits the data's statistical power and generalizability. Dynamic renal indicators were not used, and limited PK data lacked thorough sampling and modeling. Long-term outcomes, including renal recovery and overall survival, were not evaluated, nor were inflammatory markers. Furthermore, there were differences in chemotherapy exposure between groups, which introduced confounding.

Conclusion

Despite physiological variations between cachectic and non-cachectic hematological patients, weight-based amikacin dose guided by TDM yields comparable therapeutic levels, clinical efficacy, and safety results.

Changed pharmacokinetic characteristics associated with cachexia, notably renal clearance, underline the importance of individualized monitoring. Large-scale, multicentric studies with comprehensive PK/PD modeling are needed to optimize aminoglycoside use in heam-oncology patients.

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