Optimal Amikacin Levels for Patients with Sepsis in Intensive Care Unit of Cipto Mangunkusumo Hospital, Jakarta, Indonesia

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ABSTRAK

Latar belakang: *Amikasin merupakan salah satu pilihan antibiotik untuk tatalaksana sepsis dan syok septik. Kondisi sepsis dapat mempengaruhi farmakokinetik amikasin yang juga dapat berefek pada farmakodinamiknya. Saat ini belum pernah dilakukan penelitian untuk mengevaluasi kadar puncak (Cmax) amikasin dengan dosis standar pada pasien sepsis dewasa di Indonesia. Tujuan penelitian ini adalah untuk mengetahui ketercapaian kadar amikasin optimal pada pasien sepsis dengan dosis standar.* ***Metode:*** *semua pasien sepsis di ICU RSCM periode Mei-September 2015 yang mendapat amikasin dosis 1 g/hari IV diikutkan dalam penelitian. Data hasil kultur mikrobiologi dan* minimum inhibitory concentration *(MIC) didapatkan dari pemeriksaan mikrobiologi. Dilakukan pengukuran Cmax amikasin dan penghitungan Cmax/MIC. Kadar optimal amikasin dinyatakan tercapai bila Cmax/MIC >8.* ***Hasil:*** *rerata Cmax amikasin adalah 86,4 (kisaran 43,5-238) µg/mL, dengan 87% pasien memiliki Cmax >64 µg/mL. Data MIC didapatkan dari 7 dari 23 pasien. Bakteri yang banyak ditemukan dari hasil kultur pasien sepsis di ICU RSCM ialah K. pneumonia, A. baumanii, P. aeruginosadan E. coli. Rentang nilai MIC untuk patogen tersebut berturut-turut yaitu 0,75 - >256 µg/mL, 0,75 - >256 µg/mL, 1,5 - >256 µg/mL dan 0,75 - 16) µg/mL. Sebanyak 4 dari 7 pasien mencapai kadar amikasin yang optimal.* ***Kesimpulan:*** *Cmax amikasin yang dicapai dengan dosis 1g/hari sangat bervariasi. Hanya sebagian pasien mencapai kadar amikasin optimal meskipun kadar puncak yang dicapai cukup tinggi. Pengukuran kadar puncak dan MIC bakteri sangat penting dalam mencapai terapi yang optimal.*

Kata kunci: *Amikasin, Cmax, intensive care unit (ICU), minimum inhibitory concentration (MIC), sepsis.*

ABSTRACT

Background: *Amikacin is one of the antibiotics of choice for sepsis and septic shock. Pharmacokinetic of amikacin can be influenced by septic condition with subsequent effect on its pharmacodynamic. At Cipto Mangunkusumo Hospital (RSCM), Jakarta, adult patients in the ICU were given standard amikacin dose of 1 g/day, however the achievement of optimal plasma level had never been evaluated. This study aimed to evaluate whether the optimal plasma level of amikacin was achieved with the use of standard dose in septic conditions.* ***Methods:*** *all septic patients admitted to the intensive care unit of a national tertiary hospital receiving standard*

dose of 1g/day IV amikacin during May-September 2015 were included in this study. Information of minimum inhibitory concentration MIC was obtained from microbial culture. Cmax of amikacin was measured 30 minutes after administration and optimal level was calculated. Optimal amikacin level was considered achieved when Cmax/MIC ratio >8. ***Results:*** *average Cmax achieved for all patients was 86.4 (43.5-238) µg/mL with 87% patients had Cmax of >64 µg/mL.MIC data were available for 7 of 23 patients. MICs for identified pathogens were 0.75 - >256 µg/mL (K. pneumonia), 0.75 - >256 µg/mL(A. baumanii), 1.5 - >256 µg/mL (P. aeruginosa) and 0.75 – 16 µg/mL(E. coli). Four out of seven patients achieved optimal amikacin level.* ***Conclusion:*** *despite high Cmax, only half of the patients achieved optimal amikacin level with highly variable Cmax. This study suggests that measurement of Cmax and MIC are important to optimize septic patients management.*

Keywords: *Amikacin, Cmax, intensive care unit (ICU), minimum inhibitory concentration (MIC), sepsis.*

INTRODUCTION

Septic shock and severe sepsis are among the causes of high mortality in Intensive Care Unit (ICU) patients.[1,2] The incidence of sepsis and severe sepsis varies all around the world, ranging from 20 to 80%.[2,3] Mortality rate for sepsis is 20-50% worldwide, and 44.5% in Asia. Surviving Sepsis Campaign have recommended resuscitation in 6 hours to decrease mortality; including blood culture and antibiotic therapy.[3,4]

A study involving 13.796 subjects in 75 countries showed that pathogens causing infections in ICU were mostly gram-negative organisms (62%).[5] Amikacin is an aminoglycoside antibiotic that kills Gram-negative bacteria, including in severe infection.[6,7] Amikacin is effective in killing 88% bacteria resistant to gentamicin.[8] Resistance to amikasin is lower than gentamicin, because some enzyme produced by bacteria could not inactivate amikacin.[6,9]

The killing potency of amikacin depends on its peak concentration (Cmax) in plasma.[9] Cmax/MIC ratio is one of pharmacokinetic-pharmacodynamic (PK-PD) parameter used for an antibiotic with concentration dependent killing activity and Cmax/MIC ratio above 8 is required for it to be clinically effective.[10] MIC of bacteria varies, so therapy should be based on bacteria endemic pattern in each clinical setting. In the ICU, where Enterobacteriaceae and Pseudomonas aeruginosa were the most common pathogen, the clinical breakpoint of MIC is 8 µg/mL.[11,12] Clinical breakpoints are used in the clinical laboratory to advise the therapy of patients, by classifing the microorganism as clinically susceptible, intermediate or resistant based on MIC value.[12] Thus, Cmax should be at least 64 µg/mL to reach the optimum therapy.[11] Pharmacokinetic of amikacin can be influenced by septic condition due to the increase of volume distribution and clearance alteration.[13,14] Study by Duszynska et al.[15] on 63 ICU patients showed that 36% patients needed higher doses to reach optimal levels of amikacin, while in 38% patients the dose should be decreased.

Amikacin is one of the drugs of choice for infectious disease at intensive care unit of Cipto Mangunkusumo Hospital (RSCM), Jakarta, Indonesia. For practical reasons, this drug is administered 1g once daily intravenously for every patient, irrespective of body weight (BW). There is no data about achievement of optimal blood levels related to MIC with this regimen dosing. The aim of this study was to evaluate the peak levels (Cmax) and Cmax/MIC ratio of amikacinin septic patients following administration of 1 g amikiacin IV in ICU RSCM.

METHODS

This cross sectional study was conducted from May to September 2015 in the internal care unit (ICU) of RSCM Jakarta, Indonesia. The subjects were adult patients with sepsis in the ICU. Inclusion criteria were patients aged 18-65 years old, and receiving amikacin as antibiotic for sepsis. Patients with creatinin clearance below 60 mL/minutes were excluded. The study protocol was approved by the Ethics Committee of Faculty of Medicine, Universitas Indonesia – Cipto Mangunkusumo Hospital (FMUI-RSCM). Informed consents were taken from closest relatives in case where patients were unable to communicate.

Pharmacodynamic parameters of amikacin can be determined from Cmax/MIC ratio and AUC/MIC ratio. In this study, Cmax/MIC ratio was used to determine optimal amikacin levels. Cmax/MIC ratio of 8 or more was considered as the optimal amikacin levels. The susceptibility rate was counted based on Clinical and Laboratory Standards Institute (CLSI), which susceptibility for *Enterobacteriaciae (Klebsiellapneumoniae, Escherichiacoli)*, *P. aeruginosa* and *Acinetobacter spp*. were 16 µg/mL or less.[15]

The proportion of patients who reached the therapeutic levels of amikacin was determined. Most of the common pathogen in ICU had the clinical breakpoint of MIC of 8 µg/mL.[11,12] So, amikasin therapeutic levels is reached when Cmax >64mg/dL. Amikacin dose was analyzed by normalization of dose given (1 g) with patient's body weight to fulfill the recommended amikacin septic dose of 25 mg/kgBW. It was defined as underdose if patients received amikacin below 25 mg/kgBW.

All patients included in the study received 1 g amikacin by slow infusion for 30 minutes. Blood samples were taken at 30 minutes after infusion. Blood was collected in a 5-mL tube with EDTA. The samples were centrifuged for 10 minutes and the serum was stored at –20°C until analysed further. To quantify amikacin serum levels Liquid Chromatography Tandem Mass Spectrometry (LC-MSMS) was used in Laboratorium Kesehatan Daerah Provinsi DKI Jakarta.

The pathogens that infected the patients whenever possible and pooled samples from ICU patients in RSCM during study period were determined by culture, as well as the MIC. The method to determined MIC was E-test with MIC evaluator from Liofilchem®. Optimal amikacin levels was calculated from Cmax and MIC. Bacterial culture and MIC tests were done in Clinical Microbiology Labotarorium of FMUI-RSCM. Data were analyzed by using SPSS version 20.0.

RESULTS

Twenty four patients were enrolled during the study period. One patient died before blood sample was taken, so only 23 patients were included in analysis (**Tabel 1**). The median age was 39 years old (range 18-64). Most of the patients had decreased renal function (i.e. creatinin clearance 60-90 mL/min). In about 48% (11/23) of the samples, the focal infection of sepsis were lung origin, such as community acquired pneumonia (CAP), health care-associated pneumonia (HCAP) and hospital-acquired pneumonia (HAP). Mixed infection was defined when a patient has more than one source of infection. There were 2 patients with lung and urogenital infection and 2 patients with lung and wound infection).

Table 1. Characteristics of subjects at Intensive Care Unit, Cipto Mangunkusumo Hospital (N=23)

Variables	Value
Gender, n (%)	
- Male	11 (47.8)
- Female	12 (52.2)
Age (years), median (range)	39 (18-64)
Body Mass Index (kg/m^2), mean (SD)	22.1 (5.5)
- <18,5 (underweight), n (%)	6 (26.1)
- 18,5 – 24,9 (normal), n (%)	12 (52.2)
- 25 – 29,9 (overweight), n (%)	3 (13.0)
- > 30 (obese), n (%)	2 (8.7)
Creatinin clearance, n (%)	
- 60-90 mL/min	19 (82.6)
- >90 mL/min	4 (17.4)
Focal infection, n (%)	
- Lung	11 (48.0)
- Wound	7 (30.0)
- Urogenital	1 (4.0)
- Mixed infection	4 (18.0)

Optimal Amikacin Serum Levels

Cmax/MIC ratio was calculated from Cmax and MIC data. As shown in **Table 2**, the peak levels of amikacin were 86.4 (43.5-238) µg/mL, and the proportion of patients with peak levels >100 µg/mL was the largest (**Figure 1**).

If Cmax/MIC ratio >8 was used as the cut-off of optimal regimen, the peak levels above 64 µg/mL be considered optimal for pathogen with MIC 8 µg/mL. Twenty patients (87%) reached peak serum concentrations above 64 µg/mL.

Samples were collected for MIC of pathogens that infected patients in ICU during the study period. Data were collected from 7 patients

Table 2. Peak level compared to therapeutic target (Peak ≥64 µg/mL) and amikacin dose received/kgBW compared to recommended dose for sepsis (25 mg/kgBW)

Patient No.	Body weight (kg)	Received dose (mg/kgBW)	Peak (µg/mL)	Within therapeutic level	Dosing category
1	40	25	96.46	Yes	Appropriate
2	70	14.3	181.5	Yes	Underdose
3	55	18.2	223.04	Yes	Underdose
4	50	20	103.31	Yes	Underdose
5	51	19.61	91.78	Yes	Underdose
6	65	15.38	71.7	Yes	Underdose
7	60	16.67	238.01	Yes	Underdose
8	60	16.67	45.17	No	Underdose
9	45	22.22	74.48	Yes	Underdose
10	46	21.74	66.82	Yes	Underdose
11	35	28.57	143.46	Yes	Overdose
12	55	18.18	43.53	No	Underdose
13	60	16.67	128.2	Yes	Underdose
14	70	14.28	86.4	Yes	Underdose
15	51	19.61	83.39	Yes	Underdose
16	60	16.67	45.87	No	Underdose
17	60	16.67	86.49	Yes	Underdose
18	60	16.67	147.93	Yes	Underdose
19	90	11.11	69.56	Yes	Underdose
20	45.7	21.88	68.60	Yes	Underdose
21	40	25	75.16	Yes	Appropriate
22	70	14.28	114.02	Yes	Underdose
23	63	15.87	75.80	Yes	Underdose
Median/mean	56.6 (SD12.3)	18.5 (SD 4.1)	86.4 (43.5-238)		
CI 95%	51.3-61.9	16.7-20.3			

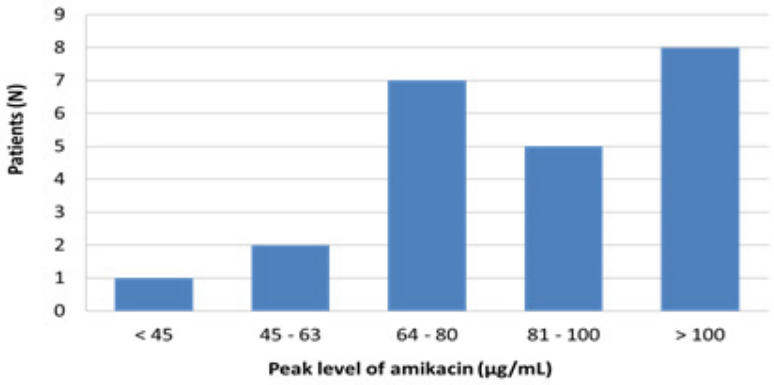

Figure 1. Distribution of serum peak levels (n=23)

included in this study. Four out of those seven patients (57%) had optimal amikacin levels against pathogen causing their sepsis (Cmax/MIC ratio >8). (**Table 3**)

There were interesting finding in this study where three patients reached therapeutic levels but not optimal levels and one patient had optimal levels but did not reach therapeutic levels.

Table 3. Patients with optimal amikacin level (Cmax/MIC ratio ≥8), according to Cmax and MIC data

Patient No.	Cmax (µg/mL)	Bacteria	MIC (µg/mL)	Cmax/MIC Ratio	Optimal
4	103.31	*K. pneumonia*	2	51.66	Yes
5	91.78	*K. pneumonia*	1.5	61.19	Yes
11	143.46	*A. baumanii*	256	0.56	No
13	128.2	*A. baumanii*	256	0.50	No
16	45.87	*K. pneumoniae*	3	15.29	Yes
		P. aeruginosa	2	22.94	Yes
18	147.93	*K. pneumoniae*	3	49.31	Yes
		P. aeruginosa	32	4.62	No
19	69.56	*A. baumanii*	0.75	92.75	Yes
Total	7 patients	9 bacteria			

Regimen and Peak Levels of Amikacin

All patients received amikacin 1 g once daily. If the dose was calculated to patient's body weight, in average the patients received 18.5 + 4.1 mg/kgBW/day (**Table 2**). This dose was lower than the usual recommended daily dose (15 mg/kgBW) and higher than recommended dose for sepsis (25 mg/kgBW). Only 2 patients received amikacin with the recommended dose.

Most of the patients (17/23) received the dose of <25 mg/kg/day, but still reached therapeutic levels. Most of the patients (18/23) received amikacin in the range of 15-25 mg/kgBW, whereas only 4 out of 23 received dose less than 15 mg/kgBW and only one received more than 15 mg/kgBW. Only three patients received sub-therapeutic levels of amikacin (**Table 4**).

Table 4. Numbers of patients achieving therapeutic level of amikasin related to dose

Regimen	Peak ≥64µg/mL, n (%)	Peak <64 µg/mL, n (%)
<25 mg/kgBW	17 (74)	3 (13)
25 mg/kgBW	2 (9)	0 (0)
>25 mg/kgBW	1 (4)	0 (0)

Minimum Inhibitory Concentration (MIC)

K. pneumoniae, A. baumanii, P. aeruginosa and *E. coli* were the most common gram-negative bacteria found in the microbial culture from patients in ICU RSCM from May-August 2015. Data of MIC can be seen at **Table 5**. Seventy two isolates were found with *K. pneumoniae* was the most frequent bacteria (44%).

Percentage of *K. pneumoniae* and *E. coli* that was susceptible to amikacin (MIC <16 µg/mL) was quite high, however the percentage was low for *A. baumanii* and *P. aeruginosa*.

DISCUSSION

Optimal concentration of amikacin is determined by Cmax/MIC ratio. MIC pathogen in ICU was 8 µg/mL.[7,11,16] There where no data about MIC of pathogens in our ICU. Based on the literatures, the amikacin levels in this study was targeted at Cmax >64 µg/mL. Most (87%) patients reached Cmax of >64 µg/mL. This finding was higher than data from Taccone et al.[11], in which 70% of the patients reached amikacin peak levels above 64 µg/mL.

Seven patients have complete data of Cmax as well as the MIC data from the isolates of these patients' specimen. Among these 7 patients, 4 patients (57%) had Cmax/MIC ratio above 8 or reached optimal amikacin concentration. It was not far from Duzynska et al.[16] who reported 63% (40/63) patients with sepsis reached Cmax/MIC ratio >8. In the future, studies with larger samples should be done in Indonesia.

In this study, all patients received amikacin 1 g, in accordance of local guidance. Taking into accounts patient's individual body weight, the dose range was 18.5 ± 4.1 mg/kgBW. This was different from Najmeddin et al.[17], who found mean dose of 22.4 (SD 0.4) mg/kgBW was given to septic patients in their study. Taccone et al.[11]

found that only 9% of all patients with 15 mg/kgBW dose reached the peak levels of >64 µg/mL, while 72% reached the peak levels with 25 mg/kgBW dose.

Duzynska et al.[16] concluded that patients in septic condition need loading dose of amikacin more than 25 mg/kgBW to reach its optimal levels. Similar results was found by Mahmoudi et al.[7], amikacin dose of more than 25 mg/kgBW was needed to reach the optimal levels in patients with increased volume distribution (Vd). This study found that with the mean dose of 18.5 (SD 4.1) mg/kgBW, the peak levels of >64 µg/mL could be reached in 87% patients. Most (18/23) patients got amikacin dose of 15-25 mg/kgBW. This difference can be associated with the relatively small Vd in our subjects, which can also be caused by dehydration.

Peak concentrations of amikacin in our samples were quite high and had wide range (median 86.4 [43.5-238] µg/mL). Dose and volume distribution could influence this

Table 5. M IC data of Gram-negative isolates from stock bacteria of FMUI-RSCM (N=72 isolates)

No. Isolate	MIC *K. pneumoniae* (µg/mL)	MIC *A. baumanii* (µg/mL)	MIC *P. aeruginosa* (µg/mL)	MIC *E. coli* (µg/mL)
1.	0.75	0.75	1.5	0.75
2.	0.75	0.75	2	1
3.	0.75	1	2	1
4.	0.75	1.5	3	1.5
5.	0.75	2	3	4
6.	0.75	2	16	16
7.	0.75	2	16	
8.	1	2	32	
9.	1	3	32	
10.	1	3	32	
11.	1	3	48	
12.	1.5	3	>256	
13.	1.5	48	>256	
14.	1.5	>256	>256	
15.	1.5	>256	>256	
16.	2	>256		
17.	2	>256		
18.	2	>256		
19.	2	>256		
20.	2			
21.	3			
22.	3			
23.	3			
24.	3			
25.	3			
26.	4			
27.	4			
28.	>256			
29.	>256			
30.	>256			
31.	>256			
32.	>256			
Total isolates (N)	32	19	15	6

Stock of bacteria were isolated from ICU patients in period May-August 2015

condition.[18] All subjects in this study received 1 g amikacin, not based on patient body weight. Another factor was volume distribution. Volume distribution is influenced by plasma binding protein, hydration, fever, sepsis, burn lesion, lean body mass, etc.[19] Sepsis can cause fluctuation of volume distribution.[20] Lugo et al.[21] found that the hemodynamic and vital support influenced the kinetics of amikacin in their patients. Three major factors which have impact on volume distribution were body weight, oxygen extraction, and serum albumin. The impact of albumin to amikacin could be neglected because of the insignificant amikacin protein binding.[22] Effect of dehydration could not be excluded due to limited data. Influence of body weight could be minimized by body weight dosing regimen.

However, the simultaneous analysis of therapeutic levels and peak levels of amikacin in our study could only be performed in 7 subjects which was the limitation of the study. The optimal levels illustrates interaction between the drug levels in a patient (host) with the sensitivity of the organism (agent). The amikacin therapeutic levels in ICU is described as the amikacin blood levels that is regarded as sufficient to kill most of the bacteries that are commonly present in ICU, based on bacterial MIC data in a certain period. The therapeutic levels do not take into account the bacterial sensitivity of each patient.

Our study shows that 3 of 7 subjects had amikacin levels above 64 µg/mL but the Cmax/C ratio were below 8 (i.e. not optimal to kill the pathogens). From this data we can conclude that the consideration of amikacin dose cannot be done simply by using therapeutic levels, but also have to take account for the optimal levels. Therapeutic drug monitoring of an antibiotics must consider the optimal levels of each antibiotic for each individual patient, beside the drug plasma levels. There was one patient with drug plasma levels less than 64 µg/mL, with Cmax/MIC ratio >8. This finding might show the importance of analyzing drug requirement for each patients. Therefore, measurement of amikacin optimal levels should be done whenever a definite therapy is given.

In this study, four major Gram negative bacteria i.e. *K. pneumoniae, A. baumanii, P. aeruginosa* and *E. coli* were found. Lee et al.[23] reported that infection caused by *Enterobactericeae* (*K. pneumoniae* and *E. coli*) were increased during their study period (from 2003 to 2011) in Taiwan. Lee also found the increase of resistance levels of A. baumanii. This data was similar with our finding, in which *A. baumanii* had the highest resistance levels among other Gram negative bacterias.

An interesting finding in MIC is shown in **Table 5**. The MICs of *K.pneumonia, A. baumanii* and *P. aeruginosa* were not distributed normally. Some bacteria had low and, contrastingly, some of them had high MICs. This phenomenon could be caused by plasmid transfer from a resistant bacteria. An in vitro study by Vaidya[24] found a horizontal resistant transfer by conjugation from Enterobactericeae strain Extended Spectrum β-Lactamase (ESBL) against many antibiotics include amikacin. The same condition could occur naturally in hospital setting.

Susceptibility rate of some pathogens were still quite high for *E. coli* and *K. pneumonia* but were decreasing for *A. baumanii* (63%) and *P. aeruginosa* (47%). This finding was similar with data from Kizirgilet al.[25], which showed that the susceptibility rate of *K. pneumoniae* and *E. coli* strain ESBL were 83.3% and 94.5%, respectively.

Only 7 patients had complete data set for calculation of Cmax/MIC ratio. It was caused by our limited access to the specimen for susceptibility test. The calculation of Cmax/MIC ratio were performed only in a few patients. If we used MIC 8 µg/mL as a consideration to calculate target peak levels, the data would not represent real condition in our ICU.

Another limitation was patient recruitment. Amikacin was used as second line empirical therapy in this study site hospital. Some patients received amikacin after treatment failure with carbapenem or cephalosporin. Most of the septic patients had renal impairment, so they were excluded from this study.

Result of this study could be used for revising patient management in the hospital. Drug use study could improve patient safety and optimizing the benefit of antibiotic therapy.

Similar evaluation of other antibiotics should be done, espesially in critically ill patients.

CONCLUSION

By giving 1 g of amikacin, only 57% of patients with sepsis reached an optimal Cmax/MIC ratio of 8 or more, although most of the patients reached peak levels of >64 µg/mL. For optimal septic therapy, the evaluation of Cmax and MIC were needed. Optimalization of amikacin therapy could be achieved by monitoring plasma concentration because of its wide interindividual variability. Amikacin regimen based on body weight could be considered to minimize this variability.

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