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Influence of sepsis on higher daily dose of amikacin pharmacokinetics in critically ill patients

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Abstract. – BACKGROUND AND OBJECTIVES: Severe sepsis is a major problem as cause of high rates morbidity and mortality in intensive care units (ICU). Aminoglycosides are an important group of antimicrobials used for severe sepsis. However, aminoglycoside pharmacokinetics in ICU patients may be altered during sepsis, which can affect the drug concentrations. Therefore, this study was undertaken to examine the relationship between amikacin disposition kinetics after a 25 mg/kg loading dose and hemodynamic response to sepsis, as well as clinical parameters, in a population of critically ill patients.

METHODS: In this work, 30 patients who were candidate to amikacin therapy following Gram negative sepsis were enrolled. The pharmacokinetic profile of amikacin by a non-compartmental model was calculated for each patient.

RESULTS: Mean volume of distribution was 0.36 ± 0.07 L/kg and mean serum amikacin clearance was 3.88 ± 0.97 ml/min/kg. In the case of Vd, APACHE II score correlation was significant. In the case of amikacin clearance, two covariates including creatinine clearance and Sr Cr significant correlation was found.

CONCLUSIONS: It appears necessary to use higher amikacin dosage (≥ 25 mg/kg) considering hemodynamic response of patients to sepsis. To achieve therapeutic drug concentration a close drug monitoring and a shift from the population mean toward a value more representative of the critically ill patient subpopulation is crucial.

Key Words:
Amikacin, Pharmacokinetics, Sepsis, Critically ill patients, Aminoglycosides.

Introduction

Treatment of infections in critically ill patients is a serious challenge for intensive care unit (ICU) physicians, because these infections are associated with high rates of mortality and morbidity[1]. Up to 50% of all patients diagnosed with severe sepsis will die during their hospital admission[2]. Selection of appropriate antibiotic is the mainstay of treatment, since an inappropriate initial choice may be responsible for higher therapeutic failure and higher mortality rates[3,4].

Aminoglycosides are an important group of antimicrobial agents for severe sepsis and septic shock due to the desirable properties not exhibited by other classes of antibiotics[5]. Amikacin is a highly potent aminoglycoside, extensively used in ICUs to treat patients with life-threatening Gram-negative infections, with an excellent therapeutic value[6]. Amikacin has structural differences from the rest of aminoglycosides that makes it a more suitable option for the treatment of serious infections. Because of these structural differences, amikacin is not inactivated by common bacterial enzymes and a lower appearance of resistance has been observed with its use[7].

Pharmacokinetic (PK)/pharmacodynamic (PD) relationship of amikacin, like other aminoglycosides, is concentration dependent and the ability to treat infections is strongly associated with a high peak serum concentration[8]. Therefore, clinical estimates of amikacin dosage based on aver-

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age drug characteristics are inaccurate in critically ill patients, since aminoglycoside PK may be altered in ICU patients during sepsis, which can affect the drug concentrations[9]. These PK alterations may lead to unpredictable and variable exposure to amikacin when administered to these patients at conventional doses. Thus, optimizing amikacin dosing regimen to enhance antibacterial activity and therapeutic response might need higher doses of aminoglycosides[10].

Although the PK disposition of aminoglycosides has been studied before[7,11,12], limited PK data are available on higher dose amikacin in critically ill septic patients[10,13]. Moreover, the interpretation of this data is complicated since usually patients admitted to ICUs are not a homogenous population, due to diverse underlying diseases and severities of the illness[14]. Therefore, this study was undertaken in a population of critically ill patients to examine the relationship between the amikacin disposition kinetics after a 25 mg/kg loading dose and the hemodynamic response to sepsis, as well as clinical parameters.

Methods

Study Population

In this study, 30 patients with a diagnosis of severe sepsis[15] hospitalized in a general ICU between March 2010 and March 2011 were recruited. The legally authorized representative of each eligible patient was informed about the objectives of study and a written consent was obtained. This study was approved by our Institutional Investigational Review Board for human and animal studies.

Patients, who were candidate to receive amikacin following Gram-negative sepsis, were enrolled. Patients were excluded according to the following criteria: age under 18 or over 65 years, pregnancy, extensive burns (≥ 20% of body surface area), ascites, inadequate renal function (creatinine clearance < 60 mL/min), known cochleovestibular abnormalities, myasthenia gravis, and allergy to aminoglycosides, meningitis, endocarditis, immunodeficiency, and treatment with aminoglycosides in the previous 2 weeks.

During the empiric antibiotic therapy, amikacin with a loading dose of 25 mg/kg (intravenously over 60 minutes) was co-administered with a β-lactam antibiotic or carbapenem.

Drug Assays

In each case, 5 ml of blood was collected by infusion set following establishment of good laboratory practices at 0, 0.25, 0.5, 1.5, 4.0, 8.0, 12.0, 18 and 24 hours after the start of i.v. infusion in a 5-ml plain tube (without anticoagulant). When a clot had completely formed (15 to 30 min), the sample was centrifuged at 4°C, and the serum was stored at –80°C until analysis.

Serum concentrations of amikacin were quantified at the end of the study by means of fluorescence polarization immunoassay with the TDx analyzer (Abbott GmbH, Wiesbaden, Germany). According to the manufacturer, the limit of quantitation for this assay was 0.6 mg/L and the analytical precision was 3.18%, 2.62%, and 2.50% for low (5 mg/L), medium (15 mg/L), and high (30 mg/L) concentrations, respectively.

Data Collection

Whenever a blood sample was taken, all relevant demographic data (e.g. age, gender, total body weight (TBW), disease severity as characterized by the Acute Physiology and Chronic Health Evaluation (APACHE) II score[16], central vein pressure (CVP) were recorded.

In addition several laboratory tests including complete blood count (CBC), serum creatinine (Sr Cr), blood urea nitrogen (BUN), liver function tests, and electrolytes were performed at inclusion and at 24 hours.

Creatinine clearance (CrCl) was estimated with the Cockcroft and Gault equation by using TBW[17].

Pharmacokinetic

The pharmacokinetic profile of amikacin was analyzed by a non-compartmental model[18] and following pharmacokinetic variables were calculated for each patient. Total volume of distribution (Vd), total body clearance (Cl), elimination half-life ($t_{1/2}$), area under the curve (AUC) during the 24 hours, Peak (amikacin level measured 30 min after the completion of infusion) and trough (concentration 24 h after the start of infusion). Peak > 64 μg/ml was considered optimal concentration by expectance a mean Vd of 0.4 L/kg and the threshold of toxicity was determined by a trough > 5 μg/ml[10,12].

Statistical Analysis

Descriptive statistics were computed for all study variables. All data were entered to a database system. Correlation between groups was an-

alyzed by using the Pearson correlation test and comparison between two groups was analyzed by the use of one sample t-test. (SPSS software for windows, version 11.5; SPSS Inc., Chicago, IL, USA). *p* value less than 0.05 was considered significant.

Results

Characteristics of the Study Population

The study population consisted of 30 critically ill patients with the diagnosis of severe sepsis in which amikacin treatment was indicated.

Demographic and laboratory tests of the patients are shown in Table I.

Pharmacokinetic Data

The median amikacin dose was 1500 mg (1300-2000) which was administered intravenously over 60 minutes. Main PK parameters for amikacin are presented in Table II. The mean value (± standard deviation) of amikacin plasma concentration-time profiles of patients are shown in Figure 1.

The current value of Vd[19] and Cl[20] of amikacin observed in critically patients were 0.36 ± 0.07 L/kg and 3.88 ± 0.94 ml/ min/kg respectively, in comparison with a Vd of 0.25 L/kg and Cl of 1.37 ml/min/kg in non-critically ill patients, by using one sample t-test ($p < 0.05$).

Therapeutic Drug Monitoring of Amikacin

The peak serum concentrations were > 64 µg/ml in 75% of patients (Figure 2). No patient had trough concentration > 5 µg/ml (Figure 3).

Table I. Characteristics of the study population.

Characteristics	Value
Demographic data	
Age (years)	44.43 ± 14.2
Total Body Weight (kg)	69.47 ± 9.57
Male/ Female (%)	70/30
APACHE II score	18.45 ± 5.54
Mean arterial pressure (mmHg)	78 ± 11
Central venous pressure (mmHg)	12 ± 4
pH	7.41 ± 0.06
$PaCO_2$ (mmHg)	34.95 ± 7.18
HCO_3 (mmol/L)	21.92 ± 3.82
Laboratory tests	
AST(U/L)	68.55 ± 54.78
ALT(U/L)	66.30 ± 52.33
Sr Cr(mg/dl)	0.82 ± 0.18
BUN(mg/dl)	19.60 ± 14.12
Cr Cl (ml/min/1.73 m^2)	69 ± 7.53
WBC (/µl)	12962 ± 4094.8
Hb (g/dl)	9.93 ± 1.48
Platelets (/µl)	217.65 ± 82.86
Na (meq/L)	141.17 ± 4.32
K(meq/L)	3.40 ± .52
Albumin(mg/dl)	2.97 ± 0.47
Urine output (ml/24 h)	3887.50 ± 1131.47

Data are expressed as percentage or mean ± SD, Sr Cr: serum ceratinine, BUN: Blood Urea Nitrogen, APACHE: Acute Physiology and Chronic Health Evaluation, Cr Cl: creatinine clearance, Alb: serum albumin concentration.

Relationship Between Amikacin Pharmacokinetic Values and Patients Variables

Relationship between amikacin Vd and Cl and patient's age, TBW, APACHE II score, Cr Cl and Sr Cr, as determined by Pearson correlation test, is shown in Table III. The APACHE II score's correlation was significant with amikacin Vd ($p < 0.05$). In the case of amikacin Cl, two covari-

Table II. Pharmacokinetic parameters of the studied population.

Parameter	Minimum	Maximum	Mean ± SD	CV (%)
AUC (mg hr/ml)	199.88	584.65	394.17 ± 124.14	31.50
AUMC	672.44	3611.83	1835.58 ± 922.12	50.24
MRT (hr)	2.55	6.31	4.42 ± 1.14	25.80
$t_{1/2}$ (hr)	1.42	4.03	2.72 ± 0.79	29.04
Cl (ml/min/kg)	2.40	5.30	3.88 ± 0.94	24.23
Vd (L/kg)	0.28	0.65	0.36 ± 0.07	19.44
Peak (µg/ml)	36	89	71.46 ± 12.45	17.42
Trough (µg/ml)	0.3	4.40	1.22 ± 1.07	87.70

AUC: area under the serum level-time curve, AUMC: area under the moment versus time curve, MRT: mean residence time, $t_{1/2}$: elimination half-time, Cl: total body clearance, Vd: volume of distribution, CV: coefficient of variation

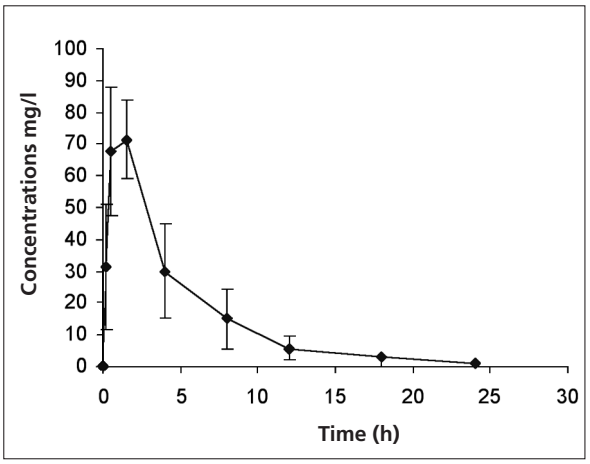

Figure 1. Mean concentration-time (± SD) profile of amikacin.

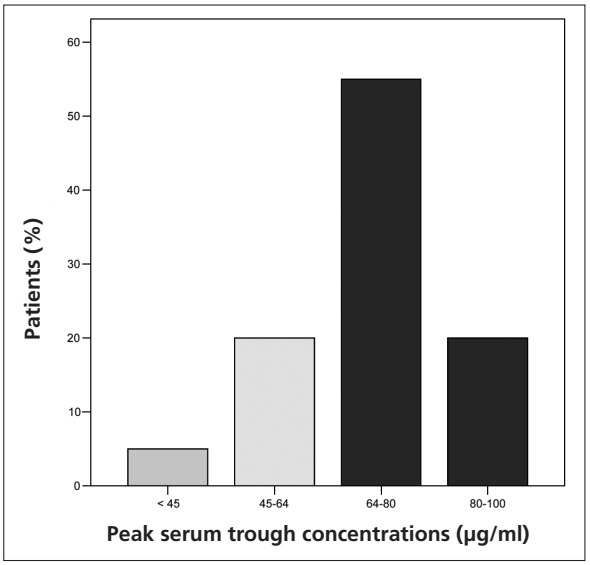

Figure 2. Distribution of peak concentrations. Black bars, peak > 64 µg/ml; gray bars, peak < 64 µg/ml. Patients (%).

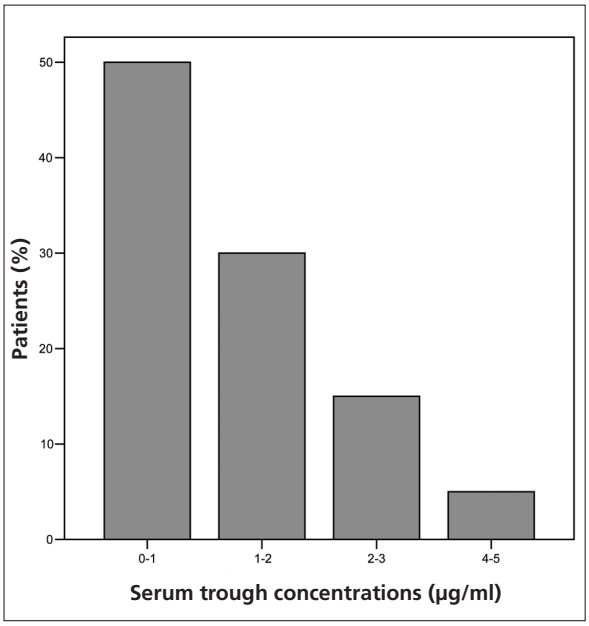

Figure 3. Distribution of trough concentrations. Patients (%).

ates including Cr Cl and Sr Cr significant correlation was found ($p < 0.05$). No significant correlations between other variables and amikacin Cl and Vd were found.

Discussion

As far as we know, limited studies have described higher dose amikacin in ICU septic patients[10,13]. Our study shows the pharmacokinetic values of a 25 mg/kg loading dose of amikacin and the influence of patients' variables on this higher dose in a population of severe septic patients.

Table III. Relationship between amikacin PK values and patients variables.

Variable	Vd	Cl	$t_{1/2}$	C_{max}
Age	0.36 (0.122)	0.12 (0.424)	0.13 (0.596)	-0.50 (0.026)
TBW	-0.14 (0.568)	0.40 (0.079)	-0.61 (0.004)	-0.21 (0.370)
APACHE II	0.45 (0.044)	0.14 (0.567)	0.24 (0.309)	-0.27 (0.244)
Cr Cl	-0.26 (0.279)	0.49 (0.027)	-0.75 (0.001)	0.12 (0.627)
Sr Cr	-0.20 (0.932)	-0.50 (0.025)	0.45 (0.047)	0.63 (0.003)

Data are expressed as Pearson Correlation: r2 (*p* value), Vd: volume of distribution, Cl: total body clearance, $t_{1/2}$: elimination half-time, C_{max}: peak concentration, TBW: total body weight, BUN: blood urea nitrogen, APACHE: Acute Physiology and Chronic Health Evaluation, Cr Cl: creatinine clearance, Sr Cr: serum creatinine.

The present study demonstrated that a profound change in amikacin disposition kinetics happens in response to sepsis in critically ill patients. Therefore, a higher dose schedule of amikacin might be needed to achieve optimal serum concentrations.

Critically ill patients normally are not a homogenous population, because there are varieties in the patient presentation, differences in underlying disease, levels of disease severity and organ function[14]. Most dosing regimens applied in ICU patients are founded on clinical trials involving non-ICU patients or healthy volunteers, based on the assumption that PK variables are similar between these two groups[21,22].

However, several pathophysiological changes occurring in ICU patients with sepsis can affect drugs PK behavior[10]. Hyperdynamic conditions, including an increased basal metabolic energy expenditure (BEE), cardiac output and oxygen consumption, frequently occur in the early phase of sepsis in response of body to infective insult[12]. Moreover, dynamic changes in volume status and end organ dysfunction can lead to altered PK properties of many drugs[22].

Various factors concerning the disease are correlated to aminoglycoside pharmacokinetics in the critically ill patients[23] who often display an increased Vd for aminoglycosides and this leads to a decreased peak serum concentration[6].

In our investigation the mean Vd was 0.36 ± 0.07, significantly higher than the Vd of 0.25 L/kg in non-critically ill patients[19]. This finding was consistent with most reported values in septic patients, confirmed that sepsis induced Vd change under similar conditions. Changes of Vd in critically ill patients were reported by Triginer et al[24]. In this study, in a group of critically ill patients, Vd in the first phase of the research was 0.43 ± 0.12 L/kg. Lugo et al[12] evaluated amikacin disposition in 30 critically ill patients and reported that mean Vd of amikacin was 0.47 L/kg, a value significantly increased in comparison with healthy volunteers. Taccone et al[10] and Marik et al[25], using amikacin in ICU patients with severe Gram-negative infections, referred that the mean Vd of amikacin was 0.37 L/kg and 0.41 L/kg respectively.

Different factors are responsible of changes in Vd in critically ill patients. Endotoxins from bacteria can lead to the production of numerous mediators affecting vascular endothelium and increased permeability[26]. Edematous status may cause clinical failure of antimicrobial therapy via increasing Vd and lowering antimicrobial concentrations[27]. Furthermore, capillary permeability, fluid therapy and total parenteral nutrition (TPN) may contribute in critically ill patients to expand the extracellular fluid and Vd and, as a result, a greater dilution of the aminoglycosides[28].

Increased sickness severity, as measured by the APACHE II score, has been shown to be related to higher Vd for aminoglycosides[29]. According to our findings, amikacin Vd was affected by patients' APACHE II score. Data reported by Marik et al[29] and Lugo et al[30] as well as our data, support an association between sepsis severity, as estimated by the APACHE II score, and the expansion of the aminoglycoside Vd.

According to our results, the amikacin Cl in septic patients was significantly higher than amikacin Cl in non-ICU patients likewise to Tang et al[23] who found that the clearance of gentamicin was 1.5-fold higher in hyperdynamic septic patients.

In the critically septic patients, physiopathologic changes determined by sepsis and associated stress, hemodynamic status and medical interventions determine a wide variability in aminoglycoside Cl. The body response to infection and injury lead to the increase of BEE, oxygen consumption, and higher cardiac output, blood flow and organ perfusion. In severe sepsis cardiac index is normal or even increased compared with that in the absence of organ dysfunction; renal artery blood flow is also increased resulting in the enhanced delivery and excretion of hydrophilic agents like aminoglycosides[31].

Amikacin is primarily eliminated by glomerular filtration and, thus, modifications in renal function should directly affect the drug's clearance[32]. In our results, there was a significant correlation between amikacin Cl and Cr Cl that was similar to other researches[12,33].

The loading dose is directly proportional to the drug Vd[34], and an optimal regimen for aminoglycoside therapy would assure an adequate initial drug level, thus minimizing the opportunity for adaptive resistance[35]. According to Jackson et al[35], the primary bactericidal phase is rapid and drug concentration dependent. During this initial phase, the killing rate is directly related to the initial drug concentration.

75% of our patients achieved the target peak concentration of > 64 μg/ml by using a 25 mg/kg dose of amikacin. But still 25% of them had a peak concentration below the target level and it shows the necessity of using even higher doses in these patients.

Nephrotoxicity of aminoglycosides has been associated with elevated trough concentrations[36]. In our work, trough concentrations were well below 5 μg/ml for all patients.

Optimizing aminoglycoside concentrations according to patient pharmacokinetic model is crucial to enhance efficacy while minimizing complications due to toxicity[5]. Therefore, based on our findings, by using amikacin dose of 25 mg/kg, although most of patients reached optimal peak level, we couldn't achieve target peak concentration in a portion of our patients. Since amikacin is known to be a concentration-dependent antimicrobial drug, it shows that by individualizing dosage regimen, and probably using a dose of ≥25 mg/kg, we may enhance efficacy by optimizing peak concentration. Meanwhile, because of low trough levels in this regimen it could help reducing the risk of amikacin nephrotoxicity.

Two major limitations exist in our investigation. First, a control group without sepsis was not included, because administration of a higher dose of a potentially toxic antibiotic to nonseptic patients was not ethical. Second, our study was limited to first 24 hours of amikacin administration. However, resolution of sepsis resulted in decline of Vd and Cl.

In conclusion, our study have showed the importance of factors associated with physiologic response of patients due to sepsis, and their clinically relevant influence on the variability of pharmacokinetic profile of amikacin. Subtherapeutic levels of amikacin possibly due to the increase in Vd and Cl, represents a serious challenge for achieving target concentrations rapidly and efficiently, and thus control of the septic process. Therefore, it appears necessary to adjust amikacin dosage considering hemodynamic response of patients and a shift from the population mean toward a value more representative of the critically ill patient subpopulation. To maximize amikacin antibacterial effect, a close drug monitoring and dosing of amikacin at high doses (≥25 mg/kg) is probably required. This will help in defining more precisely optimal peak concentrations of amikacin that provide the greatest effectiveness with least toxicity.

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