PHARMACOKINETIC BEHAVIOR OF AMIKACIN IN 31 IRANIAN CRITICALLY ILL SEPTIC PATIENTS

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ABSTRACT

The pharmacokinetic behavior of amikacin and predictive performance of Sawchuk-Zaske dosing method, have been prospectively evaluated in 31 (16 male, 15 female) critically ill septic patients of mean (± SD) age of 58 ± 23 years, mean ideal body weight of 59.6 ± 6.4 kg, mean creatinine clearance of 52 ± 21.5 ml/min., mean serum albumin of 3.1±0.5 mg/dl and median APACHE (acute physiology and chronic health evaluation) II score of 26 (with a range of 18 to 33). In this cross–sectional study, critically ill patients who met the Bone criteria for spesis but had stable creatinine clearance (serum creatinine change <0.5 mg/dl of the baseline) received the ordered dose of amikacin in one hour infusions.Blood sample were collected 30 minute after the third dose, half an hour before the fourth dose which was 1.5 times of the predicted half life of amikacin after the third dose. Cirrhotic patients and patients with renal failure requiring any mode of dialysis were excluded. Vital signs were recorded at each time of blood sampling; serum Mg^{+}, serum albumin and APACHE score were recorded at the time of the first blood sampling. Mean (± SD) of the pharmacokinetic key parameters of amikacin in this population was as follow: V_d=0.390.045 l/kg; Ke=0.141 ± 0.057 /h; half-life=5.7 ± 2.06 h; Clearance=54.2 ± 25.2 ml/min. There was a good correlation between V_d and serum albumin and also APACHE score II (r^2=0.83, P=0.033; r^2=0.82, P<0.001 respectively). Mean measured peak and trough amikacin concentrations were 20.9 and 3.2 μg/ml respectively which were significanthy different (P<0.05 paired t test) from levels, predicted by Sawchuk–Zaske method (33.5 and 4.6 μg/ml respectively). Ke, $t_{1/2}$ and cledrane did not show any statistically significant changes (P>0.05 repeated measure test) amongst three times of blood sampling, but V_d was significanly different (p<0.05). The overall predictive performance of Sawchuk-Zaske method was poor; in spite of good correlation between predicted and measured parameters when using pooled data.

Key words: Amikacin, Pharmacokinetics, Sepsis, Critically ill patient, ICU

INTRODUCTION

Sepsis remains as one of the most important causes of morbidity and if not managed results in high mortallity, in critically ill patients. Aminoglycosides in association with a β-lactam antibiotic are commonly prescribed as the first–line combination emperic therapy as soon as this syndrome has been diagnosed, and it has been documented that the survival rate of patients with gram-negative infections significantly increase if therapeutic aminoglycoside serum concentrations are achieved in the early course of treatment (1). Amikacin has a unique role in aminoglycoside antibiotic family due to its remarkable effect in resistant cases and interestingly, its antibacterial activity is highly concentration dependent and does not plateau (2).This drug has a long post-antibiotic effect, the duration of which is also dependent upon the peak concentration in serum (3). However, like the other aminoglycosides, amikacin has a very narrow therapeutic index, and in concentrations needed for optimal efficacy it has a high risk of toxicity. Moreover, large inter-individual variations in the concentrations and pharmacokinetic parameters of amikacin in intensive care unit patients are noted(4).

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Consequently, amikacin is a drug for which therapeutic drug concentration monitoring has an established role, and an individualized optimal dosage regimen should be proposed and initiated as early as possible (5). In the critically ill septic patient there are physiological and metabolic changes that modify amikacin pharmacokinetics (6). The septic response has the characteristic of increased cardiac output, altered vascular permeability, increased vascular capacitance and an increased extracellular/interstitial water volume ratio (7). Metabolic changes including hypermetabolism, protein catabolism, accelerated gluconeogenesis, and cytokine-mediated down regulation of hepatic albumin synthesis, results in a reduced plasma oncotic pressure. Reduced oncotic pressure causes volume shifts from the plasma to the extracellular compartment. For most aminoglycosides, the increase in extracellular water results in a dramatic expansion in the volume of distribution. The increased volume of distribution means that a given dose of these antibiotics will be distributed within a much larger water volume, and the peak concentration of the drug will be reduced. Obviously, this reduction of the volume of distribution is very important for the drug which its bactericidal effect is concentration dependent (6-7).
The aim of the present study was to determine the pharmacokinetic parameters of amikacin in patients under study by using a one comparmental open pharamacokinetic model and also to compare these measures with their estimates which were calculated on the basis of population pharmacokinetics as suggested by Sawchuk and Zaske(8).

MATERIALS AND METHODS

This research was a repeated measure cross-sectional study in which the pharmacokinetic, characteristics of amikacin were investigated in 31 (16 male and 15 female) adult critically ill septic patients whom were admitted to general intensive care unit (G-ICU) of a teaching referral hospital affiliated with Tehran University of Medical Sciences. The diagnoses of sepsis was estabished according to the criteria previously reported by Bone et al (9) and confirmed by the American Society of Critical Care Medicine and the American College of Chest Physicians (10). Hence, all critically ill patients who met at least 2 criterion (body temperature more than 39 °C; Heart rate more than 90 beat per minute ; WBC more than 12000 or less than 4000 cells per cubic millimeter; respiratory rate more than 20 breath per miniute or $PaCO_2$<32 mmHg) were included. Patients with established diagnosis of hepatic cirrhosis, renal failure requiring hemodialysis, hemoperfusion or peritoneal dialysis, unstable creatinine clearance which defined as serum creatinine changes more than 0.5 mg/dl in 24 hours and also patients with infections resistant to amikacin were excluded. This study was approved by the research committee for human study at Tehran University of Medical Sciences. The need for informed consent form was waived because all invasive procedures used, were already undertaken for clinical purpose. The severity of the condition of each patient was characterized globally by using the Acute Physiology and Chronic Health Evaluation (APACHE II Score) (11). This score was calculated for each patient seperately at the time of first amikacin blood sampling. Amikacin was administered intravenously over a 60 minutes infusion period by a microinfusion set. After infusion, tubing was flushed with 10 ml of normal saline solution to ensure complete drug administration. Amikacin dosage (dose amount and dosing interval) was ordered by the attending physician and ranged from 600 to 1450 mg/day. For all patients, there were at least three times of serum amikacin determinations: The first was taken 30 minutes after the end of the third dose infusion. The second blood samples were taken between the third and the fourth doses, when the time elapsed from the third dose was equal to 1.5 times of the predicted half-life of the drug in each patient seperately ($1.5\times t_{1/2}$ predicted); for example, if the predicted $t_{1/2}$ of amikacin was 2 hours in a patient, the second blood sampling was taken 3 hours (1.5×2) after the end of the third infusion (12). The predicted half-life of amikacin was equated with $0.693/K_e$ where: $K_e = 0.0028\times Cl_{cr} + 0.014$ (8). The third blood samples due to some instrumental limitations (e.g. detection limits) was taken half an hour before the fourth dose. Regarding to the average half life of amikacin which is about 2-4 hours and its dosing interval which was about 8-24 hours, it was assumed that at the time that samples were taken the drug had been reached to it steady state concentration (after the third dose). The dose's amounts, dosing intervals and sampling times were recorded exactly and accurately. Vital signs and other physiologic and paraclinical parameters were recorded exactly at the time of each blood concentration determination for amikacin (Table 1, 2). Serum Na^+, K^+, Mg^+ were

measured at the first and the third time of blood samplig and serum albumin and APACHE score were determined at the time of first blood sampling for amikacin.

Amikacin serum concentrations were analyzed by a fluorescence polarization immunoassay technique (Éclair Vitalab, Merck diagnostica, D-6100 Darmstadt 1, Germany). Intra-assay and inter-assay coefficent of variation were <5% for serum concentrations ranging from 1 to 40 μg/ml. The detection limit was 0.5 μg/ml. The one-compartmental open linear pharmacokinetic model was used to determine the actual volume of distribution of amikacin (12).

$$V_d = \frac{Dose/t_{inf}}{Ke \times C_{pssf_2}} \times \frac{(1-e^{-Ke.t_{inf}})}{(1-e^{-Ke.\tau})} \times e^{-Ke(t_2-t_{inf})}$$

t_{inf} was the time of infusion and V_d, Ke, C_p, t_2 were volume of distribution (L/kg), elimination constant (/h), plasma concentration of amikacin (g/ml) and the time elapsed from the start of the drug's infusion(h), respectively. Sawchuk and Zaske suggested that the volume of distribution of amikacin in dehydrated edematous, normal and edematous patients may be considered as 0.2, 0.25 and 0.3 l/kg, respectively (12) and the drugs plasma concentration may be calculated with the same formula.

$$C_{pssf_2} = \frac{Dose}{t_{inf}} \times \frac{(1-e^{-Ke.t_{inf}}) \times e^{-Ke(t_2-t_{inf})}}{Ke \times V_{d\ predicted} \times (1-e^{-Ke.\tau})}$$

The ideal body weight (IBW) was calculeted for each patient as described by Devine (13):

$$IBW_{kg} = 50_{male}(45_{female}) + 2.3(Height_{inch}-60)$$

The pre and post dose levels and the serum level between them were used to calculate elimination constant regarding to time interval between them and elimination half-life was equated with $0.693/K_e$. Total body clearance was calculated by multiplying either predicted or measured volume of distribution by the elimination constant of amikacin at each time of blood sampling. Demographic, clinical, physiological and pharmacokinetic data are expressed as mean ± standard deviation (Table 2,3). All data were evaluated for normality of distribution, using Kolmogrov - Smirnov test. The two-tailed paired student's t-test was used to analyze the significance between the means of each pharmacokinetic parameter for both set of data (Sawchuk and Zaske population pharmacokinetic predicted parameters and corresponding measured data). Differences were considered to reach statistical significance with $P<0.05$. The absolute predictive performance of the Sawchuk and Zaske model for prediction of the volume of distribution of amikacin was assessed as proposed by Sheiner and Beal (14,15). The mean error was used to measure the bias and the root mean squared error was used to estimate the precision. To compare the predictive performance of the model, the relative bias and precision were estimated as the mean difference of the mean error and root mean squared error. If confidence interval did not include zero, it was concluded that the difference between model and measured values was statistically significant.

$$\text{Bias} = \frac{1}{n}\sum_{i=1}^{i=n}(X_{measured(i)} - X_{model(i)})$$

$$\text{Precission} = \sqrt{\frac{1}{2}\sum_{i=1}^{i=n}(X_{measured(i)} - X_{model(i)})^2}$$

In these expressions, the index "i" refers to an individual pharmacokinetic parameter value and "n" is the total number of sample size. Confidence intervals for bias and precision were also computed by the statistical method.

RESULTS

A total of 43 patients who met the inclusion criteria were enrolled in the study and 12 of them were excluded due to inaccurate documentation of the time of drug infusion or blood sampling, lack of complete laboratory data (which was needed in data analysis) and death of the patients. The main clinical, laboratory and physiological parameters of the patients are shown in Table 1.

Eighteen patients (57%) were on controlled mechanical ventilation mode, seven patients (23%) on assisted ventilation, five patients (17%) on nasal oxygen and one patient had normal spontaneous respiration.

Thirteen patients (42%) had positive blood culture (*Klebsiella* 13%, *Eschershia coli* 10%, *Pseudomonas aeroginosa* 10%, *Serracia spp.* 6%, *Acinetobacter* 5%) and eighteen patients (58%) had negative blood culture. 27 patients (87%) had

Table 1. Demographic data of the study patients

	MEAN	SD	SEM	MAX	MIN	MEDIAN	MODE
Age (years)	58	23	4	82	20	63	67
Height (cm)	165.5	7.1	1.3	181	150	167	172
IBW (kg)	59.6	6.4	1.2	75.9	45	61.4	45.5
APACHE II Score	25.8	4.9	0.9	33	18	26	24
Serum Albumin (g/dl)	3.1	0.5	0.1	4.2	2.2	3.1	3.1

IBW= Ideal Body Weight, APACHE= Acute Physiology and Chronic Health Evaluation Score II, SD= Standard Deviation, SEM= Standard Error of Mean

Table 2. Clinical and para-clinical data of the study patients

	AT THE TIME OF PEAK SAMPLING		AT THE TIME OF 2nd SAMPLING		AT THE TIME OF TROUGH SAMPLING		STATISTICAL ANALYSIS
	Mean	SD	Mean	SD	Mean	SD	p value
Temprature (°C)	38.9	0.38	38.9	0.31	38.6	0.48	0.205*
Mean Arterial Pressure (mmHg)	79	12	80	8	88	6	< 0.05*
Hear Rate (bpm)	110	21	111	18	93	15	< 0.05*
pH	7.27	0.12	7.31	0.07	7.35	0.07	< 0.05*
Serum Bicarbonate (meq/L)	17.7	6	19.9	4.8	22	4	< 0.05*
Oxygen Saturation (%)	89.3	6	92.1	5	93.9	7	0.519*
Oxygen Content (ml / dL)	15.5	2.3	16.3	1.7	17	1.8	< 0.05*
Serum Creatinine (mg/dL)	1.31	0.48	1.33	0.48	1.31	0.48	0.803*
Creatinine Clearance (ml/min.)	52	21.5	51.2	21.8	51.6	21.5	0.121*
Serum Sodium (meq/L)	139	5	-	-	137	3	0.098**
Serum Potassium (meq/l)	4.2	0.5	-	-	3.9	0.6	< 0.05**
Serum Magnesium (meq/L)	2.3	0.3	-	-	2.1	0.2	< 0.05**

* Repeated Measure Test, ** Student paired T Test

Table 3. Statistical description of the measured & calculated pharmacokinetic parameters of Amikacin in the study patients

	MEAN	SD	SEM	CI		MEDIAN	MODE	MAX	MIN
$V_{distribution}$ (l/kg)	0.39	0.045	0.008	(0.373	0.405)	0.39	0.39	0.49	0.30
$K_{elimination}$ (/h)	0.141	0.057	0.01	(0.121	0.161)	0.13	0.098	0.323	0.059
Half Life (h)	5.7	2.06	0.37	(4.95	6.40)	5.6	4	12.3	2.1
Clearance (ml/min)	54.2	25.2	4.5	(45.3	63.1)	50	40	134.1	21.2
Half Life (h)	5.7	2.06	0.37	(4.95	6.40)	5.6	4	12.3	2.1

SD= Standard Deviation, SEM= Standard Error of Mean, C I= Confidence Interval

leucocytosis and the rest of them had white blood cell count within the normal range.

The mean APACHE score II of study patients was 25.8 (Range: 18-33) with a median and mode of 26 and 24 respectively.

Pharmacokinetic parameters of amikacin in patients under study are shown in Table 3.

The volume of distribution of 5% of Patients were more t han 0.40 l/kg, 49% were between 0.3–0.4 l/kg and no patient had a volume of distribution less than 0.3 L/kg.

Body temperature, serum creatinine, creatinine clearance and serum sodium of patients under study were not significantly different at three times that amikacin blood concentration were determined ($p > 0.05$ repeated measure analysis of variance test). In contrast, mean arterial pressure, heart rate, pH, serum bicarbonate, serum potassium and

Table 4. Statistical analysis of the predicted and measured Amikacin pharmacokinetic parameters in the study patients

p Value ($t_{student}$ test)	Measured	Predicted	
< 0.05	0.045 ± 0.39	0.039 ± 0.253	$V_{distribution}$ (l/kg)
> 0.05	0.057 ± 0.141	0.060 ± 0.151	$K_{elimination}$ (/h)
> 0.05	25.2 ± 54.2	16.6 ± 37.8	Clearance (ml/min.)
> 0.05	2.06 ± 5.7	1.78 ± 5.15	Half life (h)
< 0.05	3.3 ± 20.9	5.3 ± 33.5	C_{peak} (μg/ml)
< 0.05	1.6 ± 8.4	2.0 ± 13.0	$C_{2nd\ sample}$ (μg/ml)
< 0.05	1.8 ± 3.2	2.6 ± 4.6	C_{trough} (μg/ml)
< 0.05	2.3 ± 10.8	3.3 ± 17.0	$C_{pooled\ data}$ (μg/ml)

serum magnesium were significantly different ($p<0.05$) (Table 2). As mentioned in the methodology section, individualized pharmacokinetic parameters of amikacin were calculated for each patient by using population pharmacokinetic estimation method suggested by Sawchuk and Zaske (8,12). Estimated and measured key pharmacokinetic parameters of amikacin are compared in Table 4.

Bias and precision of the Sawchuk-Zaske method in predicting amikacin volume of distribution and consequent calculated pharmacokinetic key parameters is shown in Table 5.

DISCUSSION

Several drug administration variables can affect aminoglycoside disposition. Method of administration, as well as length of the infusion, can affect the estimation of the drug's pharmacokinetic parameters, especially the volume of distribution. Pleasant et al (21) suggested that apparent changes in volume of distribution may be secondary to the method of drug administration and gathering of serum concentration data, rather than a physiological mechanism. Interestingly they are the only group who found a smaller volume of distribution (0.27 l/kg) in critically ill patients compared with that reported by ward (0.33 l/kg). In their study, aminoglycosides were delivered by infusion using a volumetric pump in the ICU setting, while in the reported by ward, aminoglycosides were delivered by gravity flow which was slower.The difference in drug delivery time plus residual drug left in tubing may explain differences. In the present study for all critically patients a microinfusion set was used for amikacin delivery; which is commonly used in similar real situations. It seems that the most striking aminoglycoside pharmacokinetic changes in critically ill patients are variability in volume of distribution. Generally, the V_d in ICU patients is larger than that observed in patients used to develop standard dosing nomograms (at least 0.3 vs 0.2-0.25 l/kg). In our study the mean (±SD) of V_d were 0.39 ± 0.045 (l\kg) which were within the range of 0.30-0.49 (l/kg). Half of the patients had a V_d of more than 0.39 (l/kg).

Chelluri et al (19) reported the pharmacokinetic parameter values in two groups of medical and surgical ICU patients (M-ICU & S-ICU). Twenty seven patients recieved aminoglycoside infusions; and serum concentrations were collected to calculate pharmacokinetic parameter values using the Sawchuk-Zaske method. The increase in V_d in both groups was attributed to volume resuscitation. Data consistent with this theory in their study were, tobramycin peak concentrations greater than 10 μg/ml in 4 patients who had clinical signs of dehydration (mean V_d 0.21 l/kg ± 0.024). In our study there were 8 dehydrated patients at the time of peak sampling that had a mean V_d of 0.36 l/kg ± 0.032 versus 0.2 l/kg in standard dosing regimens for dehydrated patients. Moreover, peak concentrations for amikacin had a range of 17-30 μg/ml in contrast to the V_d of 0.2 l/kg for dehydrated patients in standard dosing regimens, as described by Sawchuk and Zaske (8). Triginer et al (22) also reported their experiences whith fourty critically ill medical patients who had serum gentamicin concentrations on days 2 and 7 of therapy. Interestingly, the V_d decreased from 0.43 to 0.29 l/kg on the day 7, although the changes in weight and fluid conditins were not statistically significant. The authors suggested that the percentage of water weight increases secondry to muscle mass waste occurring in sepsis. As sepsis resolves mobilization of fluid excess would cause the V_d to decrease regardless of total body muscle mass. Several factors, including capillary leakage, may help to explain the larger V_d in ICU patients. During sepsis the ratio of extracellular to intracellular fluid increases, due to th leak of fluid into the extravassular space. Accordingly, aminoglycosides would be distributed in to this increased extracellular volume. The increased V_d

Table 5 – Prediction performance of the population pharmacokinetics of Amikacin base on Sawchuk-Zaske dosing method

	Bias	Confidence Interval		Precision	Confidence Interval		r^2	p value
$V_{distribution}$ (l/kg)	0.05	(0.01	0.10)	0.14	(0.09	0.19)	-	-
$K_{elimination}$ (/h)	0.032	(0.026	0.038)	0.115	(0.10	0.121)	0.94	< 0.001
Clearance (ml/min.)	16.6	(9.2	24.0)	20.2	(12.8	27.6)	0.86	< 0.01
Half life (h)	0.48	(0.21	0.75)	0.75	(0.48	1.02)	0.93	< 0.001
C_{peak} (µg/ml)	12.6	(7.8	14.7)	13.2	(8.4	18.0)	0.43	< 0.01
$C_{2nd\ sample}$ (µg/ml)	4.6	(2.8	6.4)	4.9	(3.1	6.7)	0.37	< 0.01
C_{trough} (µg/ml)	1.4	(0.8	2.0)	1.8	(1.2	2.5)	0.90	< 0.001
$C_{pooled\ data}$ (µg/ml)	6.2	(1.0	11.4)	8.2	(3.0	13.4)	0.95	< 0.001

observed in patients with ascites helps to validate this explanation (23). In addition, the correlation between weight gain and V_d reported by Dasta and Armstrong (24) support this supposition. Because the weight change in the patients was so rapid, it was most likely caused by the fluid (24). Patient-specific problems can also alter the V_d. Many ICU patients are at least 20 percent over their ideal body weights. Studies reporting V_d based on actual weight may not accurately represent changes in V_d. Several articles have documented the need for larger doses in this population based upon their increased V_d which were calculated on the basis of ideal body weight (25-27). Protein malnutrition may also play a role in increasing V_d. Zarowits et al (28) proposed that malnutrition increases extracellular body mass which contributes to the increase in V_d. Oparaoji et al (29) in their study on 23 surgical critically ill septic patients reported a correlation equation between V_d and serum albumin:

V_d (l/kg)= - 0.13 serum albumin conc.(g/dl) + 0.672, (r^2= 0.716).

Our septic patients had an approximately equal average serum albumin concentration compared to oparaoji's study (3.1 ± 0.5 vs. 3.1 ± 0.81). There were also a linear relationship between V_d and serum albumin in our setting

V_d (l/kg) = - 0.112 serum albumin concentration g/dl +0.811, (r^2 = 0.83 p=0.033).

Hypoalbuminemia and the resultant decrease in oncotic pressure may cause a shift of body fluid from the intravascular to the extravascular space. Because aminoglycosides are distributed in to the extracellular fluid compartment, a fluid shift could have a dramatic effect on V_d and on serum aminoglycoside concentrations.

Surgical procedures has suggested by kloth et al (30) may increase the mean V_d to 0.35 l/kg. Zaske et al (31) demonstrated a wide variability in V_d ranging from 0.06 to 0.63 l/kg (mean 0.2 l/kg) in 242 surgical patients. Fluid resuscitation after surgical procedures may be responsible for the observed variability of V_d. No patient in our study was surgical. Mechanical ventilation has been implicated as the cause for increased V_d in critically patients (32-33) and the use of positive end expiratory pressure mode of ventilation (PEEP) is a well-documented cause of reduction in cardiac index, hepatic and renal flow, glomerular filtration rate and urine output (34-35). Therefore, it has been suggested that the pharmacokinatic behavior of aminoglycosides which is predominantly eliminated through kidney, might be substantially affected by using this mode of ventilation(36). Lugo and Castaneda–Hernardez (37) have studied the relationship between hemodynamic measures and pharmacokinetic behavour of amikacin in 30 critically ill septic patients. They found a poor but significant relationship between the use of PEEP mode of ventilation and V_d (r^2=0.29, p=0.002) and the same was found about amikacin clearance and the use of PEEP (r^2=0.39, p=0.0001). In our study 57% of patients were on controlled mechanical ventilation and no patient was on PEEP mode of ventilation and till now there is no data about the relationship between V_d and controlled mechanical ventilation. However mechanical ventilation may not be an independent factor as recent surgery and sepsis may cause increased interestitial fluid (38). Peripheral edema and an increase in fluid requirment are observed during sepsis and septic shock. These features have been explained on the basis of an alteration in microvascular permeability due to release of cytokines (39), and have been related to multiple system organ failure and mortality rate (40). Thus a relationship between the intensity of the septic process and extracellular

fluid expansion can be assumed. The severity of illness in critically ill patients in present study was summed in APACHE score and had a strong relationship with amikacin V_d (r^2=0.83 p<0.001), which is consistent with data obtained by Lugo (37) and Marik (41). Oparaoji et al (29) compared volume of distribution of seven postoperative septic shock patients with 12 control ones and blood sampling were given after the third dose and just prior to the fourth dose of gentamicin. They used Sawchuk and Zaske one compartmental model for aminoglycosides dosing and suggested a mean V_d of 0.41 l/kg in the septic shock group.These data encouraged authors to recommend gentamicin loading doses of 4 mg/kg in septic shock patients. In the present study, the mean ($\pm$SD) V_d of amikacin were 0.39 l/kg $\pm$0.045 (CI $_{95\%}$= 0.373-0.405). Interestingly the median and the mode of V_d in these patients were both 0.39 l/kg. There is no reliable pattern describing changes in renal clearance in ICU patients (42-43). In sepsic patients similar to other drugs, aminoglycoside renal clearance is dependent upon glomerular filtration rate and minimal tubular reabsorption (44).

Factors in critically ill patients which may affect the drug's clearance are: patients hemodynamic status, vasopressor usage, alternative methods of blood clearance (e.g.: slow continiuous ultrafiltration, continuous arteriovenous hemofiltration, hemodialysis), and specialized equipments (e.g., mechanical ventilation, cardiopulmorary bypass)(6,36,45). Disease states in ICU patients such as burns, trauma and hyperdynamic septic shock increase drug clearance and some drugs which frequently are used in this population such as low dose dopamine or vasopressor drugs could affect amikacin clearance (6, 30, 46, 47). In healthy volunteers, about 80% to 90% of variability in aminoglycoside elimination can be explained on the basis of changes in renal function (48).

Howerer in critically ill patients with sepsis, physiopathologic changes associated with stress caused by sepsis determine a wide variability in aminoglycoside elimination which is poorly explained by changes in renal function. Hence, Barza (49) reported that only 52% of variability in gentamicin elimination could be explained by changes in serum creatinine of septic patients. Kaye (50) by studies in a similar population reported that only 50% of variation in gentamicin elimination was explained by changes in renal function. Their results showed that none of these indices provided an acceptable precision value for prediction of the serum aminoglycoside clearance and dosage requirments in this patient population. However when all physiologic measurements including creatinine were included in a multiple regression model, the total explained variance increased to 73%. Our results show that the calculated creatinine clearance accounted for 89% of variability in amikacin clearance. More interestingly was the positive correlation between calculated creatinine clearance and amikacin elimination constant (r^2=0.93 p<0.001). The regression line equation for these two parameter was as following:

$Ke_{/h} = 0.0025 \times Cl_{cr\ ml/min} + 0.0101$ which is higly consistent with similar studies (8).

As shown in Table 4, measured amikacin serum levels were significantly (p<0.05) different from the drug's predicted levels which were calculated by using the predicted volume of distribution and elimination constant as suggested by Sawchuk – Zaske (8). Predicted and measured volume of distribution of amikacin were also statistically different (p<0.05). In contrast, the difference between predicted and measured amikacin elimination constant, half life and renal clearance were not statistically significant (p<0.05). The predictive performance of Sawchuk–Zaske population pharmacokinetic was also tested and is shown in Table 5. Bias was statistically different from zero (p<0.05 t test), and the 95% confidence interval did not include zero. The performance of such a method depends on the good estimation of the distribution parameters (mean and standard deviation) in the studied population. Unfortunately, mean population parameters estimated by the use of the standard compartmental model are not suitable to describe a complex kinetic process such as drug kinetic in critically ill patients which varies with time. Indeed in such a population, fluid and blood administrations are frequent; some patients present with hemodynamic instability, and deterioration in renal function attributed to the underlying disease process which occurs during treatment. It seems that the Sawchuk–Zaske's method of amikacin dosing has a poor predictive performance in critically ill septic patients, which may be attributed to the physiological instability of this population. Further studies are suggested to design a pharmacokinetic model with acceptable predictive performance in critically ill septic patients.

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