Evaluation of amikacin dosing schedule in critically ill elderly patients with different stages of renal dysfunction

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ABSTRACT

Objectives Amikacin is still a widely used aminoglycoside for the treatment of life-threatening infections. The pharmacokinetic parameters of this antibiotic may be altered in critically ill conditions. Moreover, in the elderly population, pathophysiological changes affect these pharmacokinetic variables, making it difficult to predict the appropriate dose and dosing schedule for amikacin. This study aimed to characterise the pharmacokinetics of amikacin in critically ill elderly patients with renal dysfunction, and to evaluate if the available dose adjustment schedules dependent on renal function would be appropriate for empirical dosing.

Methods Critically ill patients aged >60 years with a creatinine clearance of >20 mL/min in need of treatment with amikacin were randomly enrolled. All the patients received approximately 25 mg/kg amikacin. The patients were then divided into three groups according to the stages of their renal dysfunction based on creatinine clearance, and the optimum time to re-dosing was calculated for each group. The pharmacokinetic parameters of the patients were calculated and estimated as population pharmacokinetic data.

Results Of 30 patients, only 20% attained the target peak levels of amikacin of >64 mg/L. In addition, the mean volume of distribution was 0.47 L/kg. There was a poor correlation between amikacin clearance and creatinine clearance. The difference in amikacin half-life was not statistically significant among any of the stages of renal impairment.

Conclusions The initial dosing of amikacin in critically ill elderly patients should not be reduced, even in the context of renal impairment. Regarding the dose adjustment in renal impairment, dosing intervals estimation, no decision can be made based on the creatinine clearance and the first dose individualisation method in terms of the two-sample measurements may be considered as an appropriate strategy.

INTRODUCTION

Despite the introduction of new antimicrobial agents, amikacin and other aminoglycosides are still valuable drugs as first-line empirical therapy in critically ill patients for the treatment of life-threatening infections. Amikacin is a concentration-dependent bactericidal antibiotic with several post-antibiotic effects.[1 2] The optimised dose of this agent is based on the ratio of maximum concentration (C_{max}) to minimum inhibitory concentration. It is suspected that, for optimum bactericidal effects, this ratio must be between 8 and 10, especially if highly resistant bacteria are responsible for the infection.[3–5]

On the other hand, to achieve the target dose, the risk of nephrotoxicity should also be considered. Accordingly, it is more important when concomitant renal impairment is present due to a reduction in renal clearance and an increase in the accumulation of drugs in the human body.[6] Data supporting the specific criteria to evaluate the nephrotoxicity of amikacin are limited.[5] However, the accumulation of the drug in the renal cortex is directly linked to nephrotoxicity.[7] Therefore, concentrations just before the next dose are intended to assess the risk of nephrotoxicity. Regarding this claim, it was shown that the risk of nephrotoxicity could be managed by optimising the dosing schedule due to the target trough level.[4 8 9] The French guideline[10] has considered the level of 2.5 mg/L as a maximum trough level. However, none of the studies provided an optimised dosing schedule by considering the status of renal dysfunction in critically ill elderly patients.

In critically ill conditions, due to pathophysiological changes, the pharmacokinetic properties of amikacin may be altered. The change in the volume of distribution (V_d) can be as much as twice that of the normal population under these conditions.[11 12] These changes may cause a failure in achieving the target dose, and subsequently lead to a failure in treatment. Although an appropriate initial dose can have a significant effect on the optimal microbial and clinical responses by these unpredictable and complex variables, the optimised dose for amikacin in critically ill patients is still challenging.[13 14]

Ageing is accompanied by many complex physiological changes in the human body, and these changes can affect various pharmacokinetic and pharmacodynamic processes. Since amikacin is water-soluble and is almost completely eliminated from the kidneys, ageing changes such as the decreased elimination rate and decreased extracellular fluid have a greater impact on it. These changes affect both the V_d and amikacin clearance and make this particular population more susceptible to nephrotoxicity. On the other hand, the extent of the decline in renal function in the ageing process is not predictable. It is even considered that there is a subpopulation not affected by glomerular ageing.[15–21]

As old age and reduced renal function are two factors increasing the incidence of nephrotoxicity, it is crucial to have a well-matched dosing schedule for this particular population.

Table 1 Categories of patients regarding dosing and sampling time

Category	CrCl (mL/min)	Dosing schedule	Times of sampling after the end of infusion
A	≥60	25 mg/kg every 24 hours	1, 3, 6 and 8 hours
B	≤40 to <60	25 mg/kg every 36 hours	1, 4, 8 and 10 hours
C	≤20 to <40	25 mg/kg every 48 hours	1, 6, 18 and 24 hours

CrCl, creatinine clearance.

The main objective of this study is to characterise the pharmacokinetics of amikacin in critically ill elderly patients at different stages of renal dysfunction to evaluate the appropriateness of the empirical dosing available for this population.

METHODS

This prospective randomised observational study was conducted in two ICU wards at Sina Hospital, affiliated to Tehran University of Medical Sciences (TUMS). Thirty elderly patients (aged ≥60 years) receiving amikacin as a part of their treatment were enrolled in the study.

All patients enrolled in the study had a creatinine clearance of >20 mL/min. Based on the definition of renal dysfunction,[22] their renal status did not change significantly for at least 1 week before inclusion in the study. Patients were excluded from the study if they had one of the following conditions: acute renal failure according to AKIN criteria,[23] severe burns, body mass index (BMI) ≥35 kg/m^2, dissatisfaction from family or patient, or any amikacin contraindications.

Amikacin was infused over 30 min at a dose of 25 mg/kg body weight (ideal body weight (IBW)). For patients whose weight was 30% greater than the IBW,[24] the dose was calculated based on the adjusted body weight (ABW). The patients enrolled in this study received all the standard treatments and amikacin was continued according to the physician's discretion.

Blood samples of the patients were collected to determine serum levels of amikacin. To determine the intervals of sampling based on creatinine clearance obtained from the Cockcroft–Gault equation (Equation 1), patients were divided into three groups (A, B or C; table 1).

$$CrCl = \frac{(140-AGE)\times IBW}{SrCr\times 72}(if\ female: \times 0.085) \quad (1)$$

where CrCl is clearance of creatinine (mL/min), AGE is the age of the patients (years), IBW is the ideal body weight (kg) and SrCr is the serum creatinine (mg/dL).

The samples were collected from the central venous line in 5 mL plain tubes. All blood samples were centrifuged for 10 min at 6000 rpm. After serum separation, all serum samples were stored at −70°C until performing the analyses.

Clinical and demographic data such as age, gender, weight, height and serum creatinine were recorded. The amikacin serum concentrations were quantified using a fluorescence polarisation immunoassay kit (Roche Diagnostics GmbH, Mannheim, Germany). Statistical analyses were performed using SPSS version 25.0.

Descriptive statistics were computed for all of the study variables. A Kolmogorov–Smirnov test was used and histograms and normal quantile plots were examined to verify the normality of continuous variable distribution. Discrete variables were expressed as counts (percentage) and continuous variables as mean±SD. The demographic and clinical differences between the study groups were assessed using the ANOVA test. The correlation between parameters was evaluated using the Pearson correlation test.

After determining serum levels, the elimination rate constant (K_{el}) of amikacin was calculated using the slope of the regression line of the natural logarithm concentration–time curve for each patient based on one-compartment linear pharmacokinetic analyses (Equation 2). The half-life ($T_{1/2}$) of amikacin was calculated according to Equation 3. The extrapolation of the individual concentration–time curve to time zero was performed to calculate C_0 and, subsequently, to calculate the V_d of amikacin (Equation 4). Finally, drug clearance (CL) was obtained by multiplying K_{el} and V_d (Equation 5).

$$K_{el}\ \frac{\sum(t.lnC)-\frac{\sum(t)\times\sum(lnC)}{n}}{\sum(t^2)-\frac{\sum(t)\times\sum(t)}{n}} \quad (5)$$

$$T_{1/2} = \frac{0.693}{K_{el}} \quad (6)$$

$$V_d = \frac{Dose\times(1-e^{-kt})}{k_{el}\times C_0\times t'} \quad (7)$$

$$CL = (K_{el})(V_d) \quad (8)$$

where t is the time from infusion to discontinuation, t′ is the infusion time, C is concentration and n is the number of measured concentrations.

Table 2 Baseline parameters of patients (N=30)

Demographic parameters	N=30
Sex (male/female)	14/16
Age (years)	73.6±9.1
Body weight (kg)	73.3±14.0
Height (cm)	163.7±9.2
eGFR (mL/min)	52.2±20.3
SOFA score (on amikacin day)	8.2±3.2

eGFR, estimated glomerular filtration rate; SOFA, sequential organ failure assessment.

Table 3 Pharmacokinetic properties of amikacin in all patients

Pharmacokinetic parameters	Mean±SD (range)
Dose (mg/kg)	24.5±5.3 (14.8–36.7)
C_{max} (mg/L)	53.6±11.0 (37.4–78.2)
V_d (L/kg)	0.47±0.14 (0.18–0.78)
CL (mL/min)	64.7±42.7
K_{el} (1 /hour)	0.14±0.06
$T_{1/2}$ (hour)	5.8±2.5

C_{max}, maximum serum concentration; V_d, volume of distribution; Cl, amikacin clearance; K_{el}, elimination constant rate; $T_{1/2}$, half-life.

RESULTS

Patient characteristics

Thirty elderly patients were enrolled in the study. Table 2 shows the baseline parameters as mean±SD values.

Pharmacokinetic properties of amikacin

Pharmacokinetic parameters were individually calculated for each patient based on the serum concentrations (table 3).

Based on CrCl values, patients were categorised into three groups and pharmacokinetic parameters were compared among

Table 4 Pharmacokinetic parameters by different stages of renal dysfunction

Pharmacokinetic parameters	Group 1 CrCl ≥60 (n=13)	Group 2 CrCl ≤40 to <60 (n=8)	Group 3 CrCl ≤20 to <40 (n=9)	F	P value
C_{max} (mg/L)	50.0±10.8	59.2±9.6	53.9±11.2	1.841	0.178
V_d/kg (L/kg)	0.51±0.17	0.43±0.09	0.45±0.12	0.993	0.383
CL (L/min)	85.5±56.2	56.7±17.8	41.8±15.4	3.473	0.045*
$T_{1/2}$ (hours)	5.2±2.3	5.5±2.8	6.8±2.2	1.336	0.280
K_{el} (1 /hour)	0.16±0.07	0.15±0.05	0.11±0.05	1.552	0.230

*Statistically significant

CL, amikacin clearance; Cmax, maximum serum concentration; CrCl, creatinine clearance; K_{el}, elimination constant rate; $T_{1/2}$, half-life; V_d, volume of distribution.

them. A significant difference was found only for amikacin clearance in these three groups (table 4).

There was a weak correlation between amikacin clearance and CrCl calculated by the Cockcroft–Gault equation (Pearson correlation=0.48, p=0.007) (figure 1A). No correlation was found between half-life and CrCl (Pearson correlation=0.25, p=0.188) (figure 1B).

To evaluate the appropriateness of the empirical treatment dosing interval adjustment schedule according to renal impairment, we classified the patients according to their amikacin half-life and then considered the optimum re-dosing time based on levels of <2.5 mg/L. They were estimated to take five half-lives to decline from the optimum maximum concentration of 80 mg/L.

Table 5 shows the success rate for an appropriate interval adjustment. The results were obtained from the patients based on their stage of renal dysfunction.

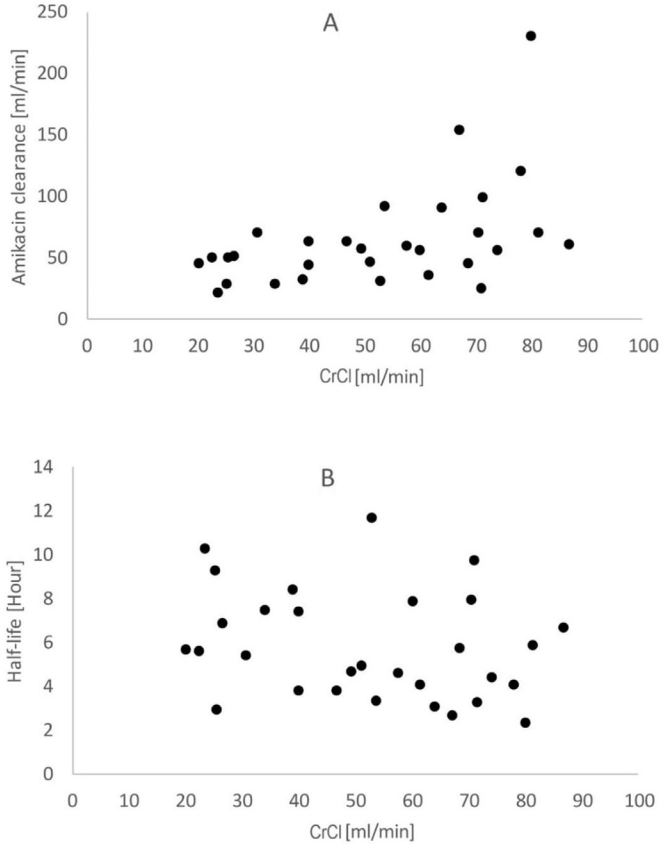

Figure 1 (A) Correlation between amikacin clearance and creatinine clearance (CrCl) for individual patients. (B) Correlation between amikacin half-life and CrCl for individual patients.

DISCUSSION

The first finding of the present study is that, even though the highest recommended adult doses of amikacin based on the latest available guidelines were prescribed, only six of the 30 patients (20%) attained the target peak plasma levels (C_{max} >64 mg/L). Among these, two were from group A, one from group B and three patients were from group C. Furthermore, no patient achieved the target peak levels of >80 mg/L. This finding may reflect the altered pharmacokinetics of amikacin in critically ill elderly patients and confirms that depending on renal function alone in designing dosage regimens for this drug to the specified patient population is not entirely reliable. In addition, it shows that, even with the administration of amikacin at an average dose of 24.48±5.31 mg/kg body weight, pharmacokinetic objectives in the elderly population hospitalised in the intensive care unit cannot be achieved significantly, so the dose reduction approach in the case of renal failure is completely contrary to the realisation of pharmacokinetic goals. Increased values of V_d can be considered to be the main reason for this result. Galvez *et al*[25] reported that only 39% of patients receiving 25 mg/kg amikacin reached the C_{max} of 60 mg/L. Some studies have suggested initial doses of >25 mg/kg (30–40 mg/kg) for critically ill patients.[9 11 25] However, these studies were not conducted on the elderly and renal-deficient population. In this study, the mean amikacin dose required to achieve the target dose (C_{max} >64 mg/L) was 23.8±7.7 mg/kg (range 18.3–43 mg/kg).

C_{max} in the study population had a SD of 11 mg/L. This SD shows that, as the population ages, the factors involved in pharmacokinetic parameters increase so much that the need for individualisation of treatment becomes more and more crucial. The mean V_d in our study was 0.47±0.14 L/kg, which is double that of the normal population (0.25 L/kg) and is in line with previous studies such as that by Lugo *et al*.[26] They reported a V_d of 0.47 L/kg in 30 critically ill adult patients. The V_d in a study by Sadeghi *et al*,[15] which was also performed in an elderly population, was 0.46 L/kg on the seventh day of treatment with amikacin. However, all of the patients included in that study had normal eGFR. The results of our study also specify that, in the older population, the V_d increased equally or more than in the studies conducted on the younger population.[11 12 25 27 28] Even though the water content of the body decreases with ageing and it is expected that water-soluble drugs have a lower V_d, the effect of changes in the glycocalyx may cause endothelial damage and capillary leakage due to critical illnesses. This leads to a larger extracellular volume, subsequently enhancing the V_d of amikacin.[15 29 30]

There was also a poor correlation between the amikacin clearance and CrCl. As amikacin is primarily eliminated by glomerular filtration with an insignificant portion of reabsorption, it can accurately reflect the actual glomerular filtration rate. This fact further emphasises that the Cockcroft–Gault equation in this

Table 5 Optimum re-dosing schedule based on the half-life of patients

CrCl (mL/min)	Empirical interval adjustment based on individual eGFR	Optimum re-dosing schedule (hours)				Success rate for empirical interval adjustment
		<24	24–36	36–48	>48	
≥60	Every 24 hours	7*	5	1	–	7/13
≤40 to <60	Every 36 hours	6	1*	–	1	1/8
≤20 to <40	Every 48 hours	2	5	2*	–	2/9

*Reference empirical interval adjustment based on CrCl.
CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate.;

population cannot be considered an accurate tool to evaluate renal function. Since this equation is based on the serum creatinine produced by muscles and the muscle content in elderly and critically ill patients is compromised, serum creatinine can overestimate the glomerular filtration rate.[19 31] Therefore, it should be used with caution among the elderly population.[1] A study by Shahrami *et al*[32] also confirmed the poor correlation between vancomycin clearance and creatinine clearance estimated by the Cockcroft–Gault method. They suggested using measurement of the area under the curve and creatinine clearance after 6-hour urine collection to calculate vancomycin empirical dosing.

The mean half-life in this study did not correlate with the CrCl due to both poor correlations between the drug and CrCl and variability in the V_d.

The mean time required to achieve trough concentrations of <2.5 mg/L was 25.21±10.28 hours. Surprisingly, 8/17 of our patients with a CrCl <60 mL/min required less than 24 hours to reach a trough concentration. On the other hand, this time was >24 hours for six of the 13 patients in group A (CrCl ≥60 mL/min). Therefore, no correlation was observed between the time to reach a trough concentration of <2.5 mg/L and CrCl. With regard to the optimum re-dosing schedule, our data had a range of 8.93–50.07 hours, which covers a wide range and emphasises the need for an individualised schedule. To reach a peak of 64 mg/L, 13 patients had to receive a dose of >30 mg/kg, four patients needed doses of 25–30 mg/kg, 10 needed a dose of 20–25 mg/kg and three patients needed doses of <20 mg/kg. As we know from the sepsis condition, either clearance and V_d or both may increase,[30] and this may result in a decrease or an increase in the half-life, respectively. Based on the data from our study, the intervals that follow target concentrations can be even less than 12 hours in elderly patients with impaired renal function. Therefore, this result further emphasises that, in the presence of a large amount of variability in the volume of distribution, critically ill patients cannot be divided into dosing schedule groups in terms of their renal function.

These results indicate a low rate of success with adjustment of the empirical dosing interval among critically ill elderly patients (10/30). On the other hand, individual pharmacokinetic parameter calculation based on the samples obtained from the first dose may guide the practitioner to the best dose with the most accurate schedule and may also reduce the risk of nephrotoxicity.[33 34] Accordingly, this could be achieved by a simple two-point sampling to calculate the individual half-life and V_d or with the assistance of the appropriate soft wares. Previous studies[35 36] also concluded that there is no need to reach steady-state in amikacin to start therapeutic drug monitoring. They also pointed out that, in first dose therapeutic drug monitoring, the time to reach the target dose is significantly reduced and the number of patients achieving the target dose is about twice that in the steady-state group. This strategy has been previously used for other antibiotics among critically ill patients.

Our study has several limitations. First, we only assessed the patients for a single dose of amikacin and trough concentrations for subsequent doses were not recorded. In the study conducted by Sadeghi *et al* in critically ill elderly patients with normal renal function, 30.3% of patients had trough levels of >6 µg/mL, which emphasises the important role of trough concentrations in this population.[8] Second, due to the small sample size we were not able to produce a reliable model for optimum interval adjustment based on the CrCl of the patients; however, because of the high variability in V_d and the poor correlation between amikacin clearance and the CrCl, it is unlikely than an appropriate method can be achieved even with larger sample sizes.

CONCLUSION

Our results show that ageing and renal dysfunction are not reasons for decreasing the initial dose of amikacin to <25 mg/kg in critically ill patients. Due to the variability in V_d and amikacin clearance, the dosing intervals should not be adjusted based on the CrCl. Thus, the first dose individualisation method can be considered as a reliable strategy.

What this paper adds

What is already known on this subject?

- Amikacin is a widely used aminoglycoside for the treatment of life-threatening infections.
- The pharmacokinetics of amikacin may be altered in critically ill conditions.
- Ageing and reduced renal function are two factors affecting pharmacokinetic variables, making it difficult to predict the optimum dosing schedule.

What this study adds?

- The first dose of amikacin in critically ill elderly patients should not be adjusted, even in the context of renal impairment.
- For dosing interval estimation, no decision can be made based on creatinine clearance and the first dose individualisation method using two-sample measurement should be considered.

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