한국인 성인 환자를 대상으로 한 1일 1회 요법 아미카신의 약물동태학

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Pharmacokinetics of Once-Daily Amikacin in Korean Adult Patients

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목적: 이 연구의 목적은 한국인 성인 환자를 대상으로 아미카신 1일 1회 요법을 시행하였을 때의 약동학적 파라미터를 평가하고, 신기능에 따른 아미카신의 약동학적 파라미터를 비교함으로써 최적의 개인화 약물요법을 설계할 수 있도록 하는 것이다.

방법: 그람 음성균 감염에 대해 1일 1회 요법으로 아미카신을 투여 받았던 353명의 한국 성인 환자를 대상으로 항정상태에서 아미카신의 농도를 2회(약물 투여 전 1시간 이내, 약물투여 종료 후 0.5~1시간 이내) 측정하였다. 각 환자의 약동학적 파라미터(분포용적, 청소율, 반감기) 및 혈중 최고 농도, 최저 농도는 환자의 나이, 체중, 신장, 성별, 혈중 크레아티닌 농도, 투여된 약물용량, 측정된 약물의 혈중농도, 감염의 종류 등을 감안하여 산출하였다. 크레아티닌 청소율에 따라 환자를 4군으로 분류하여 아미카신의 약동학적 파라미터를 비교분석하였다.

결과: 본 연구에서 아미카신 혈중 최저, 최고 농도의 평균 ± 표준편차는 각각 1.14±1.95 mg/L, 26.35±9.28 mg/L이며, 청소율, 분포용적 및 반감기의 평균 ± 표준편차는 각각 55.40±23.72 mL/hr/kg, 0.35±0.12 L/kg, 그리고 5.22±3.34 hrs로 산출되었다. 크레아티닌 청소율에 따른 아미카신의 청소율, 분포용적 및 반감기의 유의한 차이가 관찰되었다. 종합적으로 아미카신의 혈중 최저 농도는 크레아티닌 청소율이 40 mL/min 미만인 경우 40 mL/min 이상인 경우에 비해 유의하게 증가하였다.

결론: 아미카신의 약동학적 파라미터들은 신기능에 따라 유의한 차이가 있으므로 최적의 치료효과를 위해서는 환자의 크레아티닌 청소율에 따른 개인화 약물요법이 필요하다.

□ Key words - once-daily amikacin, pharmacokinetic parameter, creatinine clearance

Aminoglycosides are the major components for the empirical treatment of infections caused by gram-negative organisms.[1,2] Two major toxicities associated with the use of aminoglycosides are nephrotoxicity and ototoxicity.[3-5] Nephrotoxicity is related to the duration of exposure rather than the high serum levels. On the other hand, ototoxicity is related to the elevated trough concentration, which is sometimes irreversible.[3,4,6] A suggested approach to reducing these toxicities is to decrease the dosing frequency. As a result, a new dosage strategies for administering aminoglycosides, namely extended-dosing intervals and once-daily dosing regimen, are increasingly being practiced.[7,8] Unlike that of β-lactams, the rate and extent of aminoglycoside's capability against gram-negative bacteria are more a function of the concentration of the antibiotic. As a result, a higher peak concentration (C_{peak}) and a higher C_{peak}/MIC ratio produce a rapid and complete bactericidal effect and have been postulated to be the best predictors of therapeutic efficacy. Prolonged post-antibiotic effect, bactericidal activity, reduced potential for adaptive post-exposure, and decreased risk of nephrotoxicity and ototoxicity are all associated with the once-daily regi-

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men.[5,6,9] Many meta-analysis and clinical trials indicate that once-daily dosage of aminoglycosides is as effective as multiple-dosage regimen with similar or lower toxicity.[10-12]

The pharmacokinetics of amikacin has large intra- and inter-patient variations due to several factors such as creatinine clearance (CLcr), gender, age, body weight, serum creatinine (Scr), and the presence of sepsis or cirrhosis.[1,2,7,13-19] Interestingly, a recent study of the once-daily dose of amikacin with lower peak target concentrations in intensive care unit (ICU) patients reported good clinical responses (94%) and bacteriologic responses (84%) with no nephrotoxicity.[3,4]

All previous studies recommend that amikacin should be administered with individualized dosing regimens that take into account the factors that influence amikacin's pharmacokinetic parameters. However, these previous studies have several limitations in that they had insufficient population sizes, validation problems, and restricted-population patients' groups, among many others.[19] Although the use of once-daily aminoglycoside is becoming increasingly prevalent in Korea, the optimal once-daily dosing strategy remains unknown and no clear guideline for its monitoring is available. Dosing strategies in Korean patients have been based on pharmacokinetic data from Western populations. Thus, pharmacokinetic and pharmacodynamic studies of amikacin therapy need to be performed among various Korean subpopulations. This study aims to evaluate the pharmacokinetic parameters of a once-daily amikacin regimen in adult Korean patients and compare them according to renal function so as to help design the optimal regimen for individualized once-daily amikacin administration.

METHODS

Study Population

This retrospective study was undertaken for patients receiving amikacin once daily against gram-negative infection from March 2001 to March 2004 at a tertiary care university hospital in Seoul, Korea. Patients were included for analysis if they were over 18 years of age, have received two or more once-daily doses of amikacin, and have had steady state pre-and post-dose serum concentrations measured. Patients with endocarditis, burns and on hemodialysis were excluded from the evaluation.

Data Collection

Patient characteristics such as gender, age, weight, height, type of infection, underlying disease, baseline biochemical markers, number of treatment days, and dosing information were collected. Biochemical markers [e.g., Scr, blood urea nitrogen (BUN), albumin, serum hemoglobin (Hb), and serum amikacin concentration] were obtained on the day of each amikacin concentration measurement. Other information such as the patients' total daily dose of amikacin, dosing interval, duration of infusion, and duration of therapy were collected.

The exact time of administration of amikacin was acquired from the nursing medication administration record, interviews of the charge nurse, and the data sheet maintained by the pharmacy department. The sampling time of amikacin was obtained from a medical technologist. Each patient's CLcr, ideal body weight, and degree of obesity were calculated.

Drug Administration

A usual dose of 500 mg of amikacin in a 100mL normal saline solution was administered once daily in combination with one or more antibiotics. Clinical pharmacists adjusted the subsequent patients' doses using the software program CAPCIL® (Simkin Inc., FL, USA).

Drug Concentration Analysis

Two amikacin plasma samples at steady state were drawn from each of the patients who were receiving once-daily doses of amikacin. A post-dose sample was drawn 30-60 minutes after the completion of the 30-minute infusion of amikacin, whereas a pre-dose sample was drawn 60 minutes before the next dose. The serum concentrations of amikacin were determined by

means of fluorescence polarization immunoassay (Cobas Integra 800 analyzer, Roche, Germany). The lowest and highest limits of detection were 0.3 mg/L and 80 mg/L, respectively.

Criteria for Diagnosis of Infection

The diagnosis of infections was based on symptomatic, physical, histological, laboratory and radiological findings as well as bacteriological assessment through the isolation of a pathogen from an appropriate source. The definition of each infection was based on the standard definitions of the Center for Disease Control and Prevention (CDC).[20]

Pharmacokinetic Parameters of Amikacin

A pharmacokinetic analysis was performed for each patient using the CAPCIL[®] program. The pharmacokinetic parameters of amikacin including clearance (CL), half-life ($T_{1/2}$), and volume of distribution (Vd) were calculated using the multiple-point linear method. Individual patient data including serum concentrations, age, weight, height, gender, Scr, dosage history, and indication for therapy were entered into the CAPCIL[®] program. The measured levels that were less than 0.3 mg/L were revised to 0.15 mg/L. The therapeutic plasma concentration range of amikacin for its C_{peak} and C_{trough} were regarded to be between 1 mg/L and 40 mg/L.[3,15]

Comparison of Pharmacokinetic Parameters According to CLcr

To evaluate the difference between the pharmacokinetic parameters (CL, $T_{1/2}$, and Vd) of amikacin according to the renal function, the patients were classified into four subgroups based on their CLcr as follows: CLcr < 40 mL/min; 40 mL/min CLcr 60 mL/min; 60 mL/min < CLcr 90 mL/min; CLcr > 90 mL/min.

Statistical Analyses

ANOVA was used to evaluate the difference between the pharmacokinetic parameters C_{trough} and C_{peak} of amikacin in four subgroups divided by CLcr. Scheffe was used for post hoc analysis. The p-value of < 0.05

was considered statistically significant. Statistical analyses were performed using the SAS computer program (Windows 8.0 version).

RESULTS

Baseline characteristics of the patients

A total of 353 adult in-patients treated with once-daily doses of amikacin were included in the evaluation. Clinical pharmacists monitored these patients' doses. Patient characteristics are shown in Table 1. The patients included in this study had significant variations in age, weight, height, and baseline biochemical markers as shown in Table 1. One hundred sixty-nine (45%)

Table 1. Patient characteristics (n=353)

Characteristics	
Gender	
Male, n (%)	213 (60)
Female, n (%)	140 (40)
Age (years)	60.9±17.0 (18.0-91.0)
Weight (kg)	
Total body weight	58.6± 12.2 (26.7-120.0)
Ideal body weight	58.7± 9.4 (36.0-79.5)
Degree of obesity (%)	100.9± 18.5 (49.9-157.4)
Height (cm)	163.7± 9.1 (131.0-185.0)
Indication for therapy, n (%)	
Pneumonia	131 (37.1)
Urinary tract infection	51 (14.5)
Sepsis	29 (8.2)
Cholecystitis	22 (6.2)
Others	120 (34.0)
Underlying diseases, n (%)	
Cancer	75 (21.2)
Hypertension	67 (19.0)
Diabetes mellitus	61 (17.3)
Liver cirrhosis	15 (4.2)
Chronic renal failure	13 (3.7)
Congestive heart failure	6 (1.7)
None	116 (32.9)
Baseline biochemical markers	
Serum BUN (mg/dL)	16.1±13.1 (1.6-112.1)
Serum creatinine (mg/dL)	1.0±0.5 (0.2-7.6)
Creatinine clearance (mL/min)	63.9±35.3 (8.9-300.0)
Serum albumin (g/dL)	3.1± 0.5 (1.5-4.4)
Serum Hemoglobin (g/dL)	10.8±2.0 (6.8-15.9)
Administration of amikacin	
Dose (mg/day)	467.4±138.6 (100-1000)
Dose (mg/kg/day)	8.3 2.9 (1.5-19.2)
Duration (days)	11.9 7.9 (3-105)

Values are presented by mean ± SD (range).
SD, standard deviation; BUN, blood urea nitrogen

Table 2. Pharmacokinetic parameters of amikacin

Parameters	Mean±SD	Range
Clearance (mL/hr/kg)	55.4±23.7	7.2-152.3
Volume of distribution (L/kg)	0.35±0.12	0.12-0.80
Half life (hr)	5.22±3.34	1.88-29.30
C_{peak} (mg/L)	26.35±9.28	9.50-61.00
C_{trough} (mg/L)	1.14±1.95	0.01-14.94

C_{peak}, predicted serum peak concentration of amikacin; C_{trough}, predicted serum trough concentration of amikacin; SD, standard deviation

patients were 65 years of age or older. 194 (55%) patients had CLcr that was lower than 60 mL/min. 67 out of 353 total patients were admitted in the intensive care unit and CLcr was lower than 60 mL/min in 61% of them (n=41).

Most patients received amikacin once daily except for seventeen patients (4.8%) who received amikacin every other day. Seventy percent of the patients received 500 mg of amikacin once a day. Frequently administered concomitant antibiotics were penicillins (n = 47), third-generation cephalosporins (n = 258), macrolides (n = 42), and glycopeptides (n = 26).

Pharmacokinetic Parameters of Amikacin

The estimated values of CL, Vd, $T_{1/2}$, C_{peak}, and C_{trough} of amikacin are shown in Table 2. The number of patients with C_{trough} level between 1 and 5 mg/L or above 5 mg/L was 93 and 18, respectively. The ICU patients were noted to have higher C_{trough} levels than general ward patients, as 14.9% of ICU patients, compared to the 2.8% of general ward patients, had C_{trough} above 5 mg/L, as well as 44.8% of ICU patient, compared to the 22.0% of general ward patient, had C_{trough} between 1 and 5 mg/L. 40.3% of ICU patient and 75.2% of general ward patient had C_{trough} below 1 mg/L. The number of patients with C_{peak} levels between 40 and 50 was 35 and that with above 50 mg/L was 6.

Comparison of Pharmacokinetic Parameters According to Creatinine Clearance

CL, Vd, and $T_{1/2}$ of amikacin stratified by CLcr were compared as shown in Figure 1. There were significant differences in the mean values of the CL, $T_{1/2}$, and Vd
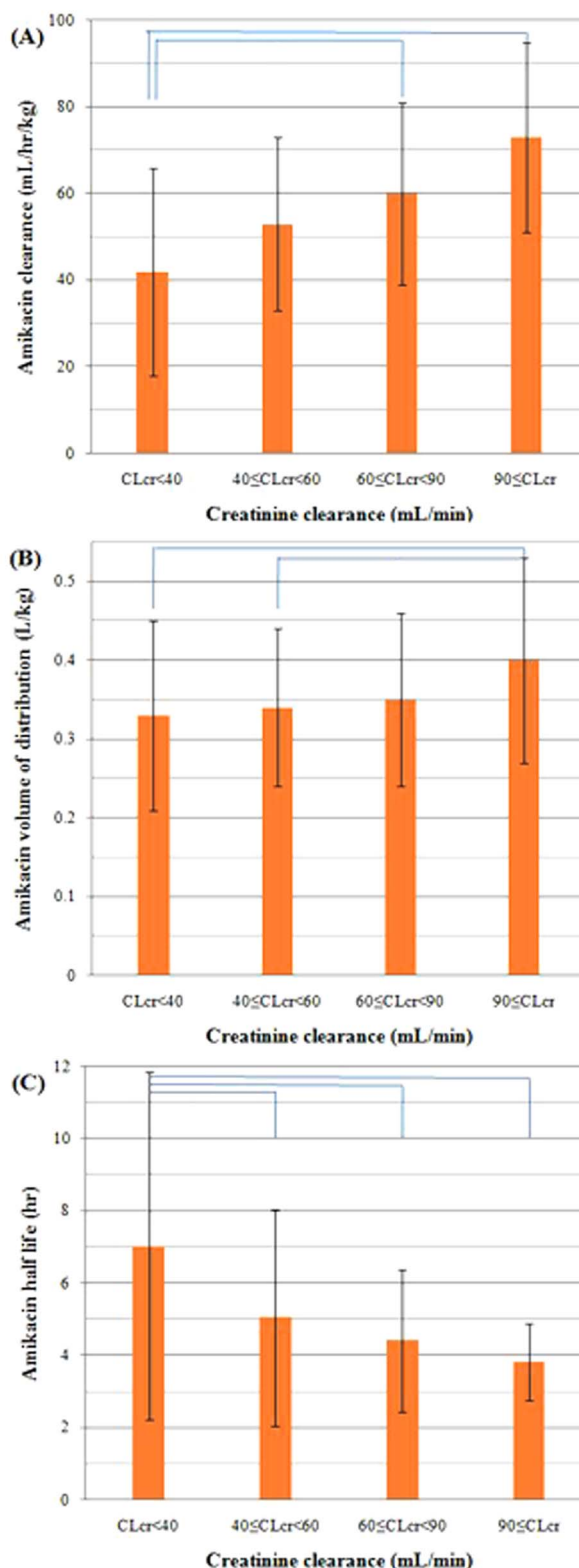

Fig. 1. Comparison of (A) clearance, (B) volume of distribution, and (C) half life of amikacin by creatinince clearance of patient.
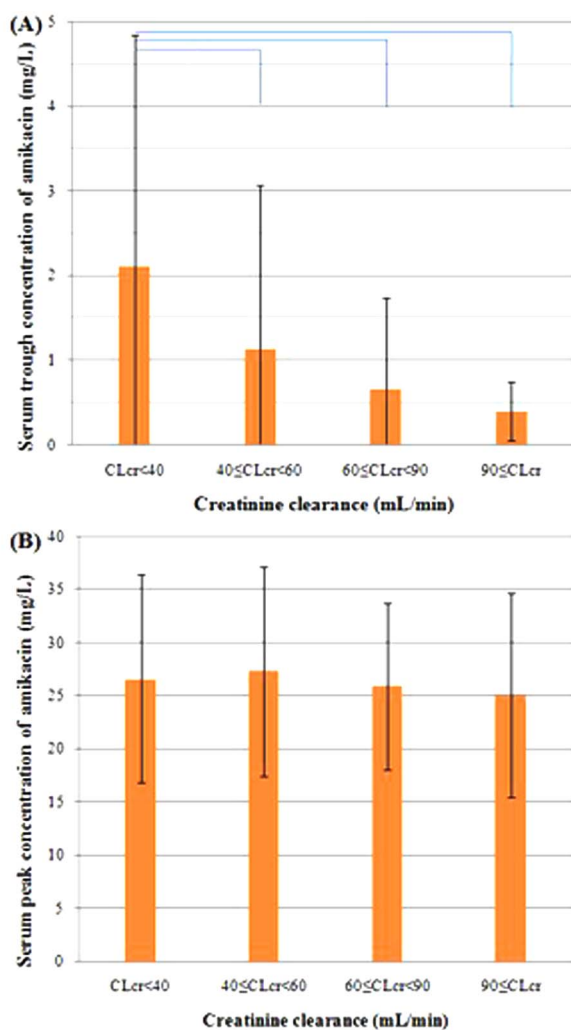
Fig. 2. Comparison of (A) predicted serum trough concentration, and (B) predicted serum peak concentration of amikacin by creatinince clearance of patient.

among 4 groups stratified by CLcr (p<0.001 for all). Generally, CL and Vd of amikacin decreased whereas $T_{1/2}$ increased when CLcr diminished. Post hoc analysis showed (1) clearance of amikacin with CLcr lower than 40 mL/min decreased significantly compared to CLcr higher than 60 mL/min, (2) volume of distribution with CLcr lower than 60 mL/min decreased significantly compared to CLcr higher than 90mL/min, and (3) half life with CLcr lower than 40 mL/min increased significantly compared to CLcr higher than 40mL/min. The estimated C_{trough} compared by CLcr had differences as shown in Figure 2. No difference was observed in the mean C_{peak} values of the patients with different states of renal function (p=0.4471).

DISCUSSION

Several studies have shown variability in the pharmacokinetic parameters of amikacin among patients with different underlying diseases.[1,2,3,15,16,18,19,21,22] However, only limited data is available on the pharmacokinetic or pharmacodynamic variations of once-daily amikacin therapy in Korean adult patients with various underlying diseases and states. This study evaluated the pharmacokinetic parameters of once-daily amikacin doses in adult Korean patients. It is worth noting that most of the patients in the study received an 8.26±2.9 mg/kg dose for the once-daily dose of amikacin, which is lower than what has been recommended by literatures on once-daily amikacin administration.[1,7,12,15,21-23] This may not have been a problem among our study patients, considering that many of them were old and had impaired renal functions. The most frequently administered (70%) dose of amikacin was 500 mg, given once a day. As a result, the mean C_{peak} and C_{trough} of amikacin were lower than what has been reported in other studies.[3,7,15,22,23]

This study also showed that more ICU patients than general ward patients had C_{trough} levels above 1 mg/L, which might have been due to the impaired renal functions of the ICU patients. The amikacin dosage in patients with high C_{trough} levels were adjusted to keep their C_{trough} levels below 1 mg/L. Raveh et al. reported that renal damage is correlated with a high aminoglycoside trough level (> 1.1 mg/L), a low Hb level (< 10 g/dL), a hospital stay longer than 7 days prior to aminoglycoside treatment, and aminoglycoside treatment longer than 11 days.[4] Moreover, several studies report that the nephrotoxicity associated with aminoglycoside treatment is related to the duration of the treatment.[5,6,9] In the study conducted by Bacopoulou et al., there were significant correlations between amikacin's C_{trough} and its elimination rate constant, CL, or $T_{1/2}$.[3]

Clearance of amikiacin has been reported to increase

in young, healthy people and to decrease in critically ill patients or the elderly.[4,16,22] Previous studies showed that CLcr was an important factor in the clearance of amikacin.[1,3,15,19,22] Clearance of amikacin significantly differed according to CLcr. The mean clearance was lowest in patients with the most serious renal impairment (CLcr < 40 mL/min) and highest in patients with the least serious renal impairment (CLcr > 90 mL/min). Diabetes Mellitus (DM) has been shown to be a risk factor for nephrotoxicity.[24,25] Therefore, patients with impaired renal functions or underlying diseases that influence their renal functions such as DM, or who have been admitted in ICU must have their amikacin dose monitored and adjusted according to their renal functions. In patients with severe renal dysfunction, a dose of every 48 hrs or longer is recommended. The mean $T_{1/2}$ of amikacin in the critically ill patients was larger than those found in other studies.[2,3,21,22] Many studies have shown that the $T_{1/2}$ of amikacin increases in the presence of an impaired renal function and DM, and is strongly correlated with the elimination rate constant.[2,3,21,22]

The mean Vd of amikacin in this study was larger than what is reported for healthy volunteers but smaller than that of ICU patients.[2,3,19]

One limitation of this study was that there were significant variations in the characteristics of the study population. Further studies with specific patient groups are needed. As suspected, a lower peak level was observed in the subjects since the dose that was administered was lower than what is traditionally recommended for once-daily doses. However, it is believed that this lower peak level was sufficient for the patient group, as a study by Bacopoulou *et al.*, which included ICU patients, showed that a lower peak level for a once-daily amikacin dose has adequate efficacy with less nephrotoxicity.[3] The optimal once-daily amikacin dosing regimen and the relationship between the C_{peak} and C_{trough} and the efficacy or toxicity of the regimen remain unknown, and there are no clear guidelines for monitoring the once-daily administration of aminoglycosides.[5,26-30] Nevertheless, the results of this study indicate that the pharmacokinetic parameters of amikacin are influenced by CLcr. Therefore, the dose of amikacin should be individualized per patient, considering renal function to achieve its maximal therapeutic efficacy.

CONCLUSION

The mean C_{trough} and C_{peak} obtained from the low-dose, once-daily amikacin samples were 26.35±9.28 mg/L and 1.14±1.95 mg/L, respectively. The mean Vd, CL, and $T_{1/2}$ were 0.35±0.16 L/kg, 55.40±23.72 mL/hr/kg, and 5.22±3.34 hrs, respectively. Clearance of amikacin with CLcr lower than 40 mL/min significantly decreased compared to that of CLcr higher than 60mL/min. Volume of distribution with CLcr lower than 60 mL/min significantly decreased compared with that of CLcr higher than 90mL/min. Half life with CLcr lower than 40 mL/min significantly increased compared with that of CLcr higher than 40mL/min. C_{trough} of patients whose CLcr is lower than 40mL/min were significantly higher than others, whereas C_{peak} in various CLcr were not significantly different. This result indicates that the pharmacokinetic parameters of amikacin are dependent on CLcr, so the dose of amikacin should be individualized per patient for optimal effect.

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