

Pharmacokinetics of amikacin and effect of ascites in Korean patients

HO-SOON KIM, IN-JA SOHN, AND DAVID I. MIN

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Amikacin is an aminoglycoside widely used to treat gram-negative bacterial infections.¹ Aerobic gram-negative bacteria that are resistant to one or more aminoglycosides are frequently susceptible to amikacin.² The pharmacokinetics of amikacin have been well characterized. Amikacin is mainly eliminated by the kidneys as unchanged drug, and a patient's renal function generally determines the rate of clearance.³ Large intersubject and intrasubject variations in the pharmacokinetics of amikacin result in substantial fluctuations in the serum concentration and may affect treatment outcomes.^{4,5}

The efficacy and toxicity of amikacin are related to its peak and trough concentrations. Amikacin's toxicity is associated with a high trough serum concentration.⁶ The volume of distribution of amikacin—a highly water-soluble compound—is approximately equal to the extracellular fluid volume. Therefore, the volume of distribution may be influenced by several pathophysiologic factors that alter the amount of body fluid, such as hydration status, congestive heart failure, peritonitis, and renal failure.^{7,8}

The purpose of this study was to characterize the pharmacokinetics of amikacin in Korean patients and investigate the effect of ascites on this drug's pharmacokinetics.

Methods. Data on patients who received amikacin for the treatment of infection at Seoul National University Hospital from January 1995 to December 1996 were retrospectively reviewed. Excluded were patients with incomplete data, patients who received amikacin for less than three days, patients with no record of the exact time of blood sampling, patients not at steady state, patients whose peak serum amikacin concentration was measured before completion of the distribution phase after amikacin was infused (i.e., within 30 minutes), patients whose calculated creatinine clearance (determined by the method of Cockcroft and Gault⁹) was less than 40 mL/min, and patients whose diseases, other than cirrhosis of the liver, might affect amikacin's pharmacokinetics, including burn patients and patients with extensive edema or pleural effusion. Steady state was assumed after amikacin had been given for at least 72

hours without a change in the dosage and with stable renal function during therapy (a change in serum creatinine concentration of <10%). Patients with severe renal dysfunction were excluded from the study because renal dysfunction affects amikacin's pharmacokinetics.

The patients were divided into those with and without ascites. The presence of ascites was confirmed by the patients' medical charts. The following information was obtained from the records: age, sex, body weight, height, serum creatinine concentration, amikacin dosage, amikacin administration history, serum amikacin concentration, and sampling time. Creatinine clearance was calculated on the basis of the Cockcroft and Gault method, serum creatinine concentration, and actual body weight (no patients were obese).⁹

All patients received amikacin by intermittent intravenous infusion over 30 minutes. Blood samples for measuring serum amikacin trough and peak concentrations were taken 30 minutes before the start of each infusion and 30 minutes after its completion. The samples were analyzed by fluorescence polarization immunassay (TDx, Abbott Labora-

HO-SOON KIM, PH.D., is Instructor, College of Pharmacy, Chungnam National University, Daejeon, Republic of Korea. IN-JA SOHN, PH.D., is Director, Department of Pharmacy, Seoul National University Hospital, Seoul, Republic of Korea. DAVID I. MIN, PHARM.D., FCCP, is Associate Professor, Division of Clinical and Administrative Pharmacy, College of Pharmacy, The University of Iowa, Iowa City.

Address correspondence to Dr. Min at the

Division of Clinical and Administrative Pharmacy, College of Pharmacy, The University of Iowa, 118 Pharmacy Building, Iowa City, IA 52242 (david-min@uiowa.edu).

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tories, North Chicago, IL). The inter-day and intraday variabilities of the assay were less than 10%.

The volume of distribution (V), clearance (CL), and half-life ($t_{1/2}$) of amikacin were calculated by Sawchuk-Zaske methods with a one-compartment open model, as follows¹⁰:

$$k = \ln(C_{\text{peak}}/C_{\text{trough}})/t$$

$$V_{(L/kg)} = [\text{dose}(1 - e^{-kt_i})e^{-kT}] / [(C_{\text{peak}}/kt_i)(1 - e^{-k\tau})] / \text{wt}$$

$$CL_{(L/hr/kg)} = (kV) / \text{wt}$$

$$t_{1/2} = 0.693/k$$

where t_i = infusion time (0.5 hour), T = time after completion of the infusion when C_{peak} was measured (0.5 hour), C_{peak} = measured peak concentration (the concentration measured 30 minutes after the completion of each infusion), C_{trough} = measured trough concentration (the concentration scheduled to be measured 30 minutes before start of next dose infusion), t = time between the measured peak and trough concentrations ($t = \tau - t_i - T - 0.5$), τ = dosage interval, and wt = actual body weight.

Student's t test was used to com-

pare the pharmacokinetic values and patient demographics between patients with and without ascites. The a priori level of significance was 0.05.

Results. The study included a total of 118 patients, 28 of whom had ascites. The patients' demographic data are summarized in Table 1. There were no significant differences in age, body weight, or calculated creatinine clearance between patients with ascites and patients without ascites. Table 2 presents the pharmacokinetic findings. Overall, there was wide individual variability. The mean \pm S.D. volume of distribution was significantly greater in patients with ascites (0.36 ± 0.11 L/kg) than in patients without ascites (0.28 ± 0.05 L/kg) ($p = 0.0008$), and the mean \pm S.D. half-life was significantly longer (3.81 ± 1.56 versus 2.28 ± 0.58 hours) ($p = 0.0002$). However, the clearance of amikacin did not differ significantly (1.3 ± 0.8 mL/min/kg in the group with ascites and 1.5 ± 0.5 mL/min/kg in the group without ascites).

Discussion. Amikacin is almost completely eliminated by the kidneys as unchanged drug, and kidney function generally determines body clearance.¹ This study found that the mean volume of distribution and clearance of amikacin among Korean patients

were quite variable and that the volume of distribution was larger in patients with ascites than those without it, as might be expected because of expansion of extracellular volume.

Previously, Lanao et al.¹¹ studied 10 patients with cirrhosis of the liver and reported that amikacin was immediately distributed to ascites fluid and appeared to accumulate there. However, Sampliner et al.¹² reported that the clearance and half-life of tobramycin were not significantly influenced by ascites but that its volume of distribution increased proportionally with the volume of ascites fluid.

Amikacin is primarily excreted unchanged in the urine.^{1,2} There was no significant difference in amikacin clearance between Korean patients with ascites and those without it, which is similar to the results for other ethnic groups.¹³ Ascites appeared to increase the half-life of amikacin. This finding might be clinically relevant when estimating amikacin dosages and dosage intervals for patients with this condition.

Conclusion. Ascites due to cirrhosis of the liver significantly affected the pharmacokinetics of amikacin in Korean patients. Patients with abnormal extracellular fluid volume should be monitored frequently.

Table 1. Demographic Characteristics of Study Patients^a

Characteristic	Mean \pm S.D. Value	
	Patients with Ascites (n = 28)	Patients without Ascites (n = 90)
Age (yr)	52 \pm 14	49 \pm 13
Actual body weight (kg)	55 \pm 11	60 \pm 10
Creatinine clearance (mL/min)	78 \pm 33	80 \pm 27

^aNone of the characteristics differed significantly between the groups.

Table 2. Pharmacokinetics of Amikacin in Study Patients

Variable	Mean \pm S.D. Value			p^a
	All Patients (n = 118)	Patients with Ascites (n = 28)	Patients without Ascites (n = 90)	
Clearance (mL/min/kg)	1.5 \pm 0.6	1.3 \pm 0.8	1.5 \pm 0.5	0.0002
Volume of distribution (L/kg)	0.30 \pm 0.08	0.36 \pm 0.11	0.28 \pm 0.05	0.0008
Half-life (hr)	2.70 \pm 1.12	3.81 \pm 1.56	2.28 \pm 0.58	0.0002

^aPatients with ascites compared with patients without ascites.

References

1. Matthews SJ. Aminoglycosides. In: Schumacher JE, ed. Therapeutic drug monitoring. 1st ed. East Norwalk, CT: Appleton & Lange; 1995:237-94.
2. Price KE, DeFuria MD, Pursianno TA. Amikacin, an aminoglycoside with marked activity against antibiotic-resistant clinical isolates. *J Infect Dis.* 1976; 134:S249-61.
3. Clarke JT, Libke RD, Regamey C et al. Comparative pharmacokinetics of amikacin and kanamycin. *Clin Pharmacol Ther.* 1974; 15:610-6.

4. Zaske DE, Strate RG, Kohls PR. Amikacin pharmacokinetics: wide interpatient variation in 98 patients. *J Clin Pharmacol.* 1991; 31:158-63.
5. Pechere JC, Dugal R. Clinical pharmacokinetics of aminoglycoside antibiotics. *Clin Pharmacokinet.* 1979; 4:170-99.
6. Bodey GP, Valdivieso M, Feld R et al. Pharmacology of amikacin in humans. *Antimicrob Agents Chemother.* 1974; 5:508-12.
7. Mann HJ, Fuhs DW, Awang R et al. Altered aminoglycoside pharmacokinetics in critically ill patients with sepsis. *Clin Pharm.* 1987; 6:148-53.
8. Dasta JF, Armstrong DK. Variability in aminoglycoside pharmacokinetics in critically ill surgical patients. *Crit Care Med.* 1988; 16:327-30.
9. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976; 16:31-41.
10. Sawchuk RJ, Zaske DE, Cipolla RJ et al. Kinetic model for gentamicin dosing with the use of individual patient parameters. *Clin Pharmacol Ther.* 1977; 21:362-9.
11. Lanao JM, Dominguez-Gil A, Macias JG. The influence of ascites on the pharmacokinetics of amikacin. *Int J Clin Pharmacol Ther Toxicol.* 1980; 18(2):57-61.
12. Sampliner R, Perrier D, Dowell R. Influence of ascites on tobramycin pharmacokinetics. *J Clin Pharmacol.* 1984; 24(1):43-6.
13. Gill MA, Kern JW. Altered gentamicin distribution in ascites patients. *Am J Hosp Pharm.* 1979; 36:1704-6.