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Pharmacokinetics of Amikacin in Hematologic Malignancies

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The pharmacokinetics of amikacin in 10 patients with hematologic malignancies and 1 patient with aplastic anemia were investigated. At an administered dose of 7 mg/kg of body weight, a volume of distribution of 0.4 liters/kg, an elimination half-life of 3.0 h, and a total body clearance of 2.1 ml/min per kg, amikacin achieved a peak level in blood of 21 μg/ml. Results of the study revealed that there was a marked increase in volume of distribution of amikacin in these patients compared with normal.

On the basis of experience with monitoring aminoglycoside levels in serum, we observed that patients with hematologic diseases tended to develop subtherapeutic drug concentrations and therefore required higher doses. Our study was designed to determine the pharmacokinetic parameters of amikacin in immunocompromised patients and to investigate what physiological factors, such as level of hemoglobin and fever, might contribute to such changes.

All patients were admitted because of high fever, and sources of infection were extensively investigated (Table 1). All patients had normal creatinine and liver function tests on admission. All patients initially received the combination of amikacin and a cephalosporin or penicillin. Amikacin dosage was adjusted according to dosing guidelines proposed by Sarubbi and Hull (13). The loading dose was 7 to 7.5 mg/kg of body weight, and the maintenance dose was computed as a percentage of the loading dose, according to the corrected creatinine clearance calculated by using serum creatinine on the basis of the Cockcroft and Gault formula (3). Maintenance doses were administered every 8 h. The drug was diluted to 100 ml and infused slowly over 15 min. Serum samples were collected serially at 0 and 15 min and at 2, 4, and 8 h from the beginning of the infusion. The study began on the day patient was admitted (day 1). Samples were collected after patients received the loading dose (dose 1). The same protocol then was repeated for the maintenance dose on day 3 (dose 6) and on the day the patients attained normal temperatures, usually on days 7 to 10. Concentrations of amikacin in serum were determined by enzyme immunoassay (EMIT-Amikacin assay for in vitro diagnostic use; Syva Co.). Dosage was adjusted to achieve peak concentrations of at least 25 μg/ml.

Pharmacokinetic parameters were derived by conventional calculations based on an intravenous input one-compartment model (4). Volume of distribution and total body clearance were normalized to body weight and body surface area for comparison with previously published values. The data were calculated by using the Abstat program (ABSTAT, dBASE II Statistical Program, release 2.2; Anderson-Bell Co.) and are reported as means ± standard deviations.

Table 2 presents the physiological characteristics of the patients. Table 3 lists the pharmacokinetic parameters of amikacin derived from pooled data in these patients after the loading dose on day 1 and after the maintenance dose on day 3 and the day the infection subsided. Figure 1 is representative of the mean amikacin concentrations in serum versus time during the loading dose and subsequent doses. The kinetics of amikacin appeared similar throughout the course of therapy. The volumes of distribution were 0.39, 0.42, and 0.37 liters/kg, the total body clearance values were 2.14, 2.03, and 2.08 ml/min per kg, and the elimination half-lives computed from the log linear phase for each dose were 3.6, 2.9, and 2.7 h on days 1, 3, and 7, respectively. By using analysis of variance and multiple comparisons, all the physiological and pharmacokinetic parameters on days 1, 3, and 7 were not significantly different except for temperature ($P < 0.001$). After a loading dose of 7.1 mg/kg, peak concentrations in serum of about 21 μg/ml and troughs of 3.5 μg/ml were reached. The subsequent doses of about 7 mg/kg every 8 h achieved similar peaks and troughs of about 23 to 26 μg/ml and 3 μg/ml, respectively.

Multivariate analyses were used to evaluate whether any physiological characteristics of the patients might contribute to the pharmacokinetic parameters. Neither hemoglobin, temperature, nor albumin correlated with volume of distribution or clearance of the drug. However, there was a correlation between hemoglobin and albumin; it is likely that nutritional status affected the hemoglobin and albumin levels similarly. Serum clearance of the drug correlated with area under the curve (as predicted) and trough level, while volume of distribution correlated with area under the curve and peak level of the drug. Amikacin clearance correlated poorly with the creatinine clearance, most likely because the nonrenal function in our patients meant a narrow range of creatinine clearance.

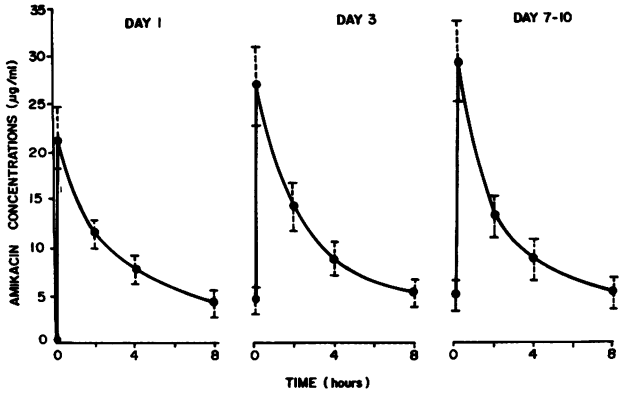

FIG. 1. Time-concentration relationship of amikacin during days 1, 3, and 7 through 10 of treatment.

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TABLE 1. Patient characteristics[a]

Patient no.	Underlying disease	Age (yr)	No. of granulocytes/mm^3	Cause of fever	Organism
1	ANLL	31	7,350	UTI	*Escherichia coli*
2	ANLL	53	516	Pneumonia	*Klebsiella pneumoniae*
				Anal abscess	*Pseudomonas aeruginosa*
3	ANLL	30	700		
4	ANLL	53	380	Oral ulcer	*Pseudomonas aeruginosa*
5	ANLL	30	825	Sepsis	No growth
6	ALL	40	130	Sepsis	No growth
7	ALL	43	<100	Dental root abscess	*Pseudomonas aeruginosa*
8	Aplastic anemia	26	253	Gingivitis	*Pseudomonas aeruginosa*
9	Lymphoma	43	1,400	Cellulitis	*Staphylococcus aureus*
				Infected hemorrhoid	
10	Lymphoma	30	9,000	Gingivitis	
11	CML	28	>20,000	Aspiration pneumonia	

[a] Abbreviations: ANLL, acute nonlymphocytic leukemia; ALL, acute lymphocyte leukemia; CML, chronic myelocytic leukemia; UTI, urinary tract infection.

All 10 patients who were diagnosed as having infections in this study improved with antibiotic therapy. Three patients, two with acute lymphocytic leukemia and one with aplastic anemia, showed signs of response to the therapy only when adequate peak levels of amikacin were attained. In these patients, the peak amikacin concentrations were initially in the subtherapeutic range. When the dose was increased to achieve a concentration of 30 μg/ml, the patients clinically improved and became afebrile. The median times to reach normal temperatures was 5 to 7 days after antibiotics were started. Of our 29 specimens taken at peak level, only 4 had concentrations of less than 15 μg/ml, and these were adjusted to achieve adequate levels in blood of about 25 to 30 μg/ml within 24 h. The patients had no significant changes in neutrophil counts during the course of treatment. None of our patients had breakthrough bacteremia. In this study, none of our patients developed nephrotoxicity or ototoxicity.

The pharmacokinetic parameters obtained with these patients with hematologic diseases were compared with data from other groups of patients reported in the literature (Table 4). The volume of distribution reported previously for adults varied from approximately 0.17 ± 0.06 liters/kg (5) to 0.29 ± 0.058 liters/kg (2) and is considerably less than the volume of distribution of 0.39 ± 0.16 liters/kg obtained in this study. The total body clearance in our study of 2.08 ml/min per kg, or 121.59 ml/min per 1.73 m^2, is within the range of 78.6 to 129.7 ml/min per 1.73 m^2 reported by others (12). The half-life of 3.0 h is slightly longer than half-lives in previous reports, which are consistent with the larger volume of distribution. The amikacin clearance (107 ml/min) in our patients was almost equal to corrected creatinine clearance estimated from creatinine concentrations in serum (110 ml/min). In contrast, the amikacin clearance in other studies was considerably less than creatinine clearance, ranging from 70% (12) to 83% (2) of creatinine clearance. We conclude that the pharmacokinetics of amikacin in patients with hematologic malignancies (including one with aplastic anemia) are different from previous reports for healthy adults. Pharmacokinetic studies of amikacin have also been performed with eight pediatric oncology patients who received 5 mg of the drug per kg every 6 to 8 h. The elimination half-life averaged 1.2 h, volume of distribution averaged 0.24 liters/kg, and total body clearance averaged 2.51 ml/min per kg. The volume of distribution and the clearance are greater than values reported for other pediatric groups and probably account for the larger dose (per kilogram) needed to achieve and maintain therapeutic levels in these patients (7). In another retrospective review of pharmacokinetic data obtained from 35 aminoglycoside regimens given to 32 hospitalized oncology-hematology patients, the volume of distribution (mean ± standard deviation) for all aminoglycosides was 0.41 ± 0.31 liters/kg, with a range of 0.20 to 0.65 liters/kg, values much larger than previously reported for nononcology patients (9). The need to increase the dose of amikacin in patients with hematologic-oncologic conditions was emphasized in both these studies. Overall, our data for adults are consistent with results of previous studies in pediatric patients.

The mechanism of increase of volume of distribution and total body clearance of amikacin in hematologic patients is unclear. We attempted to correlate physiological characteristics of the patients such as creatinine clearance, hemoglobin, temperature, and serum albumin to pharmacokinetic parameters such as volume of distribution and total body clearance. However, multiple stepwise regression analyses did not reveal any significant relationship. This may be because the data were insufficient to establish significant

TABLE 2. Physiologic parameters[a]

Parameter	Day 1	Day 3	Days 7–10
CL_{CR}[b] (ml/min)	100.0 ± 26.0	108.0 ± 38.5	122.0 ± 34.0
Hemoglobin (g%)	10.0 ± 1.9	9.7 ± 1.3	10.2 ± 1.2
Temp (°C)	38.8 ± 0.4	38.1 ± 1.0	36.9 ± 0.2
Albumin (g/liter)	35.3 ± 5.6	32.5 ± 7.9	34.6 ± 3.1

[a] Values are means ± standard deviations.
[b] CL_{CR}, Creatinine clearance.

TABLE 3. Pharmacokinetic parameters[a]

Parameter[b]	Day 1	Day 3	Days 7–10
Dose (mg/kg)	7.2 ± 0.9	6.8 ± 1.0	7.3 ± 1.3
C_{max} (μg/ml)	21.6 ± 5.2	27.0 ± 14.4	23.4 ± 9.4
C_{min} (μg/ml)	4.0 ± 3.3	3.4 ± 3.2	3.0 ± 2.3
V (liters/kg)	0.4 ± 0.2	0.4 ± 0.2	0.4 ± 0.1
CL_{amk} (ml/min per kg)	2.14 ± 1.60	2.03 ± 1.07	2.08 ± 0.80
Half-life (h)	3.6 ± 2.2	2.9 ± 0.9	2.7 ± 1.1
AUC (μg · h/ml)	100.6 ± 56.3	83.7 ± 49.2	70.1 ± 24.1

[a] Values are means ± standard deviations.
[b] Abbreviations: C_{max}, maximum concentration; C_{min}, minimum concentration; V, volume of distribution; CL_{amk}, amikacin clearance; AUC, area under the curve.

TABLE 4. Comparison of amikacin kinetics in various studies[a]

Patient type and source of data (reference)	V (liters/kg)	$t_{1/2}$ (h)	CL_{amk}	
			ml/min per kg	ml/min per 1.73 m^2
Healthy				
Clarke et al. (2)	0.29 ± 0.60	2.3 ± 0.4	2.30 ± 0.19	99.9 ± 8.6
Plantier et al. (12)	0.21 ± 0.08	1.4 ± 0.4	1.20 ± 0.00	78.6 ± 12.1
Hoffler et al. (5)	0.17 ± 10.0	1.4 ± 0.0		
Lode et al. (8)	0.18 ± 0.20	1.9 ± 0.3		129.7 ± 0.0
Kirby et al. (6)	0.30 ± 0.58	2.2 ± 0.4		100.0 ± 8.6
Pediatric, Vogelstein et al. (14)	0.27 ± 0.05	1.6 ± 0.4	1.97 ± 0.41	
Pediatric oncology, Kramer et al. (7)	0.24 ± 0.04	1.2 ± 0.4	2.51 ± 0.86	109.0 ± 37.5
Adult oncology				
Manny and Hutson (9)[b]	0.41 ± 0.13			
Ramathibodi Hospital	0.39 ± 0.16	3.1 ± 1.4	2.08 ± 1.15	121.6 ± 74.2

[a] Abbreviations: V, volume of distribution; $t_{1/2}$, elimination half-life; CL_{amk}, amikacin clearance. Values are means ± standard deviations.
[b] Study included other aminoglycosides.

correlations or because the physiological parameters studied are, in fact, independent of the pharmacokinetic variables.

The efficacies and toxicities of aminoglycosides correlate with concentrations in serum (1, 10, 11). As the patients become immunocompromised and infections become more exotic, patients require adequate concentrations and combinations of antibiotics to assure optimal activity to combat the infections effectively. In addition, since these patients often require prolonged and multiple courses of antibiotics, the potential for serious side effects such as nephrotoxicity is of concern. Thus, knowledge of the pharmacokinetics of amikacin in such patients is important for optimizing the dosing regimen in terms of efficacy and at the same time minimizing the risk of unnecessary adverse drug reactions.

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