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Amikacin Pharmacokinetics in Patients Receiving High-Dose Cancer Chemotherapy

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We retrospectively analyzed amikacin pharmacokinetics in 28 patients (mean age, 47.4 ± 13.6 years) who received high-dose chemotherapy during a neutropenic febrile episode. Patients received an experimental protocol of high-dose anticancer chemotherapy. Amikacin pharmacokinetic parameters were calculated from two or more concentrations in serum around a single dose by the method of Sawchuck and Zaske (J. Pharmacokinet. Biopharm. 4:183–195, 1976). Predicted parameters were calculated by using standard methods. The observed amikacin volume of distribution and clearance were significantly greater and the elimination half-life was longer than predicted (0.38 ± 0.13 versus 0.25 liter/kg [$P = 0.0001$], 1.51 ± 0.92 versus 1.17 ± 0.38 liters/h/kg [$P = 0.012$], and 3.8 ± 2.4 versus 2.9 ± 1.1 h [$P = 0.011$], respectively). Multivariate analysis revealed that albumin correlated negatively and creatinine correlated positively with the volume of distribution and the elimination half-life. Creatinine and the percentage below the ideal body weight correlated negatively and hematocrit correlated positively with clearance. Administration of dosage regimens based on predicted pharmacokinetic parameters yielded subtherapeutic amikacin concentrations in serum in our patients. Because of the increased dosage requirements and the need for adequate antibiotic treatment in this population, we suggest guidelines for empiric dosing for patients with advanced cancer receiving intensive chemotherapy.

The use of aminoglycoside antibiotics in many situations has largely been supplanted by newer agents which have a more favorable therapeutic-to-toxic effect ratio. However, aminoglycosides in combination with beta-lactam antibiotics continue to be the standard for empiric therapy of granulocytopenic patients with cancer at onset of fever (11). Elevations in the aminoglycoside distribution volume (V) and clearance (CL) have been noted in adult patients with a variety of solid and hematologic malignancies (5–7, 10). Increases in V and CL cause subtherapeutic serum aminoglycoside concentrations if dosage adjustments are not made. However, these kinetic alterations are not uniform in all subgroups of cancer patients. Furthermore, no combination of factors has been described to predict accurately which patients will require larger aminoglycoside doses.

There is evidence that therapeutic peak concentrations of aminoglycosides achieved within the first 24 to 48 h of therapy improve survival in patients with gram-negative bacteremia (6). In a study of patients with gram-negative bacteremia, death occurred in 1 of 41 patients who achieved therapeutic aminoglycoside concentrations within the first 48 h of therapy, compared with 9 of 43 patients with subtherapeutic concentrations (8). Administration of subtherapeutic doses of bactericidal antibiotics to patients with malignancies who develop granulocytopenia and fever could therefore result in increased mortality.

We studied the disposition of amikacin in patients with refractory solid tumors and lymphomas receiving a phase I protocol of the chemotherapeutic agents cisplatin, etoposide, and cyclophosphamide in doses three- to sevenfold higher than usual and attempted to identify variables in this population which could predict the need for higher dosages of aminoglycoside antibiotics. The pharmacokinetics of aminoglycosides in this subset of patients have not been previously reported.

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MATERIALS AND METHODS

Patients. Records of patients admitted to our university hospital for high-dose chemotherapy of advanced malignancies resistant to conventional therapy between January 1987 and June 1988 were reviewed. All patients received a chemotherapy regimen consisting of cyclophosphamide at 2.5 g/m^2/day for 2 days (days 1 and 2) and etoposide at 500 mg/m^2/day and cisplatin at 50 mg/m^2/day for 3 days (days 1 to 3). Febrile episodes while patients were granulocytopenic were treated empirically with vancomycin, ceftazidime, and amikacin, with appropriate adjustments for culture-proven infections.

Patients were included in the study if their records showed two or more aminoglycoside concentrations around a single dose. The following data were retrieved from each patient's medical record: cancer type (solid tumor or lymphoma), age, sex, height, weight, pretreatment body surface area, ethnic background, blood urea nitrogen (BUN), creatinine, albumin, hematocrit, bilirubin, and serum glutamic pyruvic transaminase. Weights and laboratory tests were retrieved from the day the amikacin concentrations were obtained whenever possible or within 48 h.

Assays. Amikacin concentrations were analyzed by using a COBAS BIO centrifugal analyzer and EMIT assays (Syva, Palo Alto, Calif.). The lower limit of detection of the assay was 2.5 μg/ml, with intra- and interday coefficients of variation of 2.6 and 3.9%, respectively, at 15.0 μg/ml.

Pharmacokinetics. Pharmacokinetic parameters were calculated from measured concentrations in serum by using the Sawchuck-Zaske method (16). Predicted population estimates for pharmacokinetic parameters were calculated as follows (3, 14):

TABLE 1. Patient characteristics

Value	Age	Body wt (kg)		Body surface area (m^2)	Albumin (g/liter)	BUN (mg/dl)	Creatinine (mg/dl)	CL_{CR} (ml/min)[a]	Hematocrit (%)	Bilirubin (mg/dl)	SGPT[b] (mg/dl)
		Actual	Ideal								
Mean ± SD	47.4 ± 13.6	63.9 ± 14.4	64.8 ± 9.0	1.72 ± 0.23	2.7 ± 0.5	14 ± 11	1.0 ± 0.4	86 ± 30	28 ± 4	1.4 ± 1.5	41 ± 59
Range	17–7	42.0–98.0	45.1–84.0	1.35–2.29	1.9–4.0	2–41	0.5–2.1	32–146	20–34	0.4–6.1	10–232

[a] Calculated.
[b] Serum glutamic pyruvic transaminase.

$$V = 0.25 \text{ liter/kg}$$

$$CL_{CR\ male} = (140 - \text{age}) \times \text{kg}/(72 \times \text{SCr})$$

$$CL_{CR\ female} = CL_{CR\ male} \times 0.85$$

$$k_{el} = 0.00293\ (CL_{CR}) - 0.014$$

$$CL = k_{el} \times V$$

where CL_{CR} is creatinine clearance, SCr is serum creatinine, and k_{el} is the elimination rate constant.

Statistical analysis. Predicted and observed amikacin pharmacokinetic parameters were compared by using the Wilcoxon signed-rank test (19). Univariate and stepwise forward linear regressions (SAS Institute, Inc.) were used to analyze associations between amikacin pharmacokinetic parameters and other patient factors (9).

RESULTS

Demographic characteristics are listed in Table 1. Records from 28 patients (20 male and 8 female) were evaluable. Eight patients had lymphomas. The other 20 had a variety of solid tumors. Patients ranged from 17 to 67 years of age. Of the patients studied, 18 were non-Hispanic Caucasian, 7 were Hispanic, 2 were Native American, and 1 was Asian. Mean body weight was 62.4 ± 13.4 kg. Ten patients' body weights were at or above the ideal (range, 100 to 131%); those of the other 18 were below the ideal (range, 70 to 95%). All but one of the patients were hypoalbuminemic (albumin concentration below 3.5 g/dl). All patients were anemic. All but six patients had normal liver function tests.

The predicted and observed amikacin pharmacokinetic parameters are listed in Table 2. CL, V, and elimination half-life ($t_{1/2}$) were significantly greater than predicted, with V most significant. The V of 0.38 liter/kg calculated from the serum amikacin concentrations was significantly greater than that predicted by population estimates ($P = 0.001$). Of the 28 patients, 11 had Vs that exceeded 0.4 liter/kg. Four patients had Vs below the predicted 0.25 liter/kg, two of which were below 0.2 liter/kg (0.16 and 0.19 liter/kg). The mean observed amikacin CL was 23.5 ± 51% greater than predicted. Nine of the 28 patients had observed CLs below those predicted (range predicted, 42 to 98%). The other 19 patients' CLs ranged from 101 to 306% of those predicted, with 8 exceeding 150%. The $t_{1/2}$s averaged 132 ± 187% of the predicted values, being longer than predicted in 19 of the 28 patients (range, 101 to 534%).

Patient factors found to correlate significantly with amikacin pharmacokinetic parameters by univariate analysis are shown in Table 3. No association with sex or type of malignancy was found. Lower body weight, smaller body surface area, and lower serum albumin concentration correlated with increased amikacin V ($P < 0.05$). Ethnicity was also associated with V but not with the other pharmacokinetic parameters. Non-Hispanic Caucasians had smaller weight-normalized Vs than the other ethnic groups considered together (0.34 versus 0.45 liter/kg, respectively). The relationships between V and age, sex, percentage below the ideal body weight, BUN, BUN-creatinine ratio, hematocrit, bilirubin, and type of malignancy (lymphoma versus solid tumor) were not statistically significant.

Age, weight, percentage below the ideal body weight, BUN, and creatinine correlated negatively with the amikacin k_{el} ($P < 0.05$). Weight, percentage below the ideal body weight, body surface area, BUN, and creatinine clearance correlated with amikacin CL ($P < 0.05$). There was a positive correlation between creatinine and amikacin CLs and k_{el} ($P < 0.05$). The relationship between these parameters and albumin, the BUN-creatinine ratio, hematocrit, and bilirubin was not statistically significant.

We used stepwise linear regression to examine further the association between the factors analyzed by univariate analysis and the measured amikacin pharmacokinetic parameters. As shown in Table 4, an increase in creatinine was associated with a larger V, a longer $t_{1/2}$, and a smaller k_{el} and CL. A decrease in albumin or an increase in the BUN-creatinine ratio was associated with a larger V and a longer $t_{1/2}$. A higher hematocrit or a weight closer to the ideal was associated with an increase in CL.

The relationships between weight and amikacin V and between CL_{CR} and k_{el} are shown in Fig. 1 and 2. We suggest that an empiric regimen be used initially on the basis of the relationships derived from our study. Loading doses of 12 mg/kg should be given. Maintenance doses should be based

TABLE 2. Amikacin pharmacokinetic parameters

Value	Mean ± SD (range)			
	V (liter/kg)	CL (liters/h/kg)	$t_{1/2}$ (h)	k_{el} (h^{-1})
Predicted	0.25	1.17 ± 0.38 (0.67–1.98)	2.9 ± 1.1 (1.5–6.2)	0.27 ± 0.09 (0.11–0.46)
Measured	0.38 ± 0.13 (0.16–0.66)[a]	1.51 ± 0.92 (0.34–3.79)[b]	3.8 ± 2.4 (1.4–11.0)[c]	0.25 ± 0.12 (0.063–0.51)[d]

[a] $P = 0.0001$.
[b] $P = 0.012$.
[c] $P = 0.011$.
[d] $P = 0.10$.

TABLE 3. Univariate associations between host factors and amikacin pharmacokinetic parameters

Factor	Correlation coefficient			
	V (liter/kg)	CL (liter/h/kg)	k_{el} (h^{-1})	$t_{1/2}$ (h)
Age	−0.0015	−0.36[a]	−0.46[b]	0.29
Body wt	−0.40[b]	−0.60[c]	−0.39[b]	0.36[a]
Percentage below ideal body wt	−0.21[d]	−0.58[d]	−0.51[d]	0.54[d]
Body surface area	−0.40[b]	−0.57[d]	−0.34[a]	0.33[a]
Percentage below initial body surface area	0.03	−0.43[b]	−0.54[d]	0.64[c]
Albumin	−0.53[d]	−0.0088	0.35	−0.44[b]
Creatinine	−0.37[a]	−0.64[c]	−0.57[d]	0.46[b]
CL_{CR}	0.31[b]	0.74[c]	0.46[c]	−0.48[d]
BUN	−0.15	−0.51[d]	−0.28[b]	0.60[c]
BUN-creatinine ratio	0.11	−0.29	−0.28	0.56[d]
Hematocrit	0.19	0.30	−0.23	−0.15
Bilirubin	0.23	−0.15	−0.25	−0.45[b]

[a] $0.05 < P \leq 0.10$.
[b] $0.01 < P < 0.05$.
[c] $0.001 \leq P < 0.001$.
[d] $0.001 < P < 0.01$.

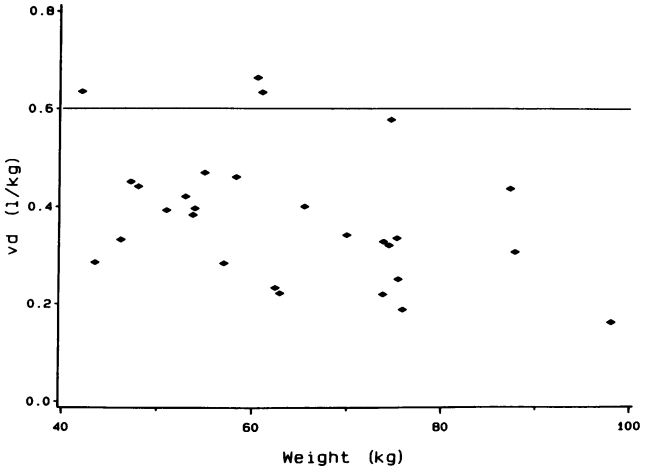

FIG. 1. Relationship between amikacin V (vd) and body weight. After receiving a standard loading dose of 12 mg/kg, patients below the line would be expected to have a peak concentration in serum of ≥20 μg/ml.

on the relationships $V = 0.38$ liter/kg and $k_{el} = (0.00287 \cdot CL_{CR}) - 0.0000581$.

DISCUSSION

Our findings of a significantly larger than predicted amikacin V and CL and a longer $t_{1/2}$ in patients with a variety of refractory malignancies are consistent with previous reports (5–7, 10). However, the finding of a significant correlation between increases in the V and hypoalbuminemia has not been noted previously in febrile patients with cancer.

Manny and Hutson (7) found a mean aminoglycoside V of 0.41 liter/kg in 32 hematology-oncology patients. No attempt was made to identify patient-specific factors associated with the increased V. Also, no analysis of CL was undertaken. Phillips et al. (10) retrospectively analyzed 24 patients with hematologic malignancies. The mean V in those patients was 0.425 liter/kg. This study did not investigate CL. No correlation was found between V and age, sex, albumin, hematocrit, platelet count, absolute neutrophil count, and disease type. Patients who had received combination chemotherapy treatment with doxorubicin or mitoxantrone had larger Vs than patients who received other agents ($P = 0.05$). Higa and Murray (5) prospectively analyzed 35 patients with malignancy and correlated aminoglycoside V and CL with age, sex, cancer type, leukocyte count, and albumin. No correlation was found with any of the patient parameters examined, although both V and CL were significantly elevated above the accepted normal values. No multivariate analyses of patient-specific variables were undertaken in either of these reports. Kaojarern et al. (6) prospectively analyzed 10 patients with hematologic malignancies. They found that both the V and CL were elevated. Multivariate analysis was performed on hemoglobin, temperature, and albumin to correlate these parameters with V and CL. No significant correlations were found.

Unlike those researchers, we found a significant relationship among serum albumin concentration, amikacin V, and $t_{1/2}$. This may be due to the lower albumin concentrations found in our patients compared with those in the other reports. Albumin concentrations were not provided by Phil-

TABLE 4. Multivariate analysis of host factors affecting amikacin pharmacokinetic parameters

Parameter	Factor	Slope estimate	P	r^2
V	Albumin	−0.127	0.004	0.53
	Creatinine	−0.108	0.004	
CL	Creatinine	−0.899	0.010	
	Percentage below ideal body wt	−0.032	0.0004	0.68
	Hematocrit	0.085	0.006	
$t_{1/2}$	BUN-creatinine	0.099	0.003	0.51
	Creatinine	2.721	0.007	
k_{el}	BUN-creatinine	−0.003	0.047	0.56
	Creatinine	0.003	0.0001	

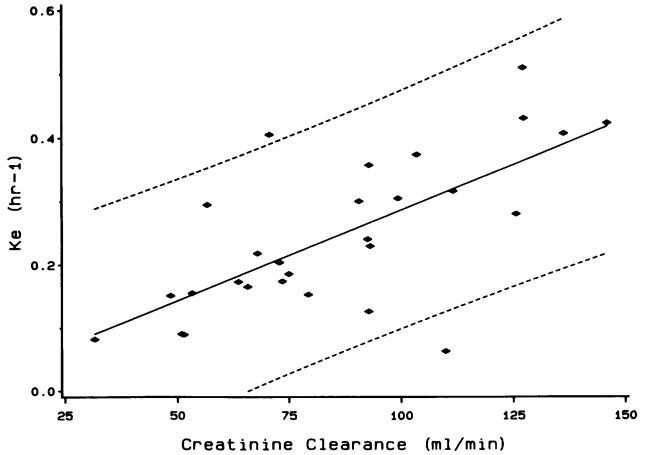

FIG. 2. Relationship between amikacin k_{el} (Ke) and estimated CL_{CR}. The equation for the regression line is $k_{el} = 0.00287$ (CL_{CR}) − 0.0000581 ($r = 0.69$, $P = 0.0001$).

lips et al. or Higa and Murray. It is of note that all of the patients studied by Kaojarern et al. (6) had albumin concentrations in excess of 3.2 g/liter. It has been reported that the aminoglycoside V is elevated in patients with severe hypoalbuminemia (13, 15, 17). The patients described in this report had advanced refractory malignancies and were in a state of cachexia, reflected by a mean serum albumin concentration of 2.7 g/liter. The mechanism by which hypoalbuminemia results in an increased aminoglycoside V is unknown, but it may be due to the low venous oncotic pressure which results in increased extravascular fluid. Since aminoglycosides are distributed readily to that space, the V would be increased in hypoalbuminemia.

Poor nutritional status was also associated with decreased amikacin CL. Percentage below the ideal body weight correlated with decreased amikacin CL. This is similar to results from other investigators. Dickerson et al. observed a significant decrease in gentamicin CL in healthy volunteers after fasting compared with that in a protein-loaded state (4).

Our finding that amikacin CL and $t_{1/2}$ significantly correlated with serum creatinine has been well documented in other patient populations. The direct correlation between serum creatinine and amikacin V was an unexpected finding. Only in severe renal impairment has the V of aminoglycosides been shown to be increased (17, 18). Hematocrit correlated directly with amikacin CL in the multivariate analysis. This relationship has previously been shown to be weakly associated by other investigators (13). An increased BUN-creatinine ratio was associated with a longer amikacin $t_{1/2}$. These patients may have had a smaller intravascular volume, resulting in decreased renal perfusion and prolonged amikacin elimination.

Amikacin dosage regimens derived from other patient populations resulted in subtherapeutic drug concentrations in our patients. Our recommended 12-mg/kg loading dose would result in a mean peak concentration of 30.9 μg/ml and subtherapeutic peak concentrations in only 3 of the 28 patients studied. Toxic concentrations above 40 μg/ml would result in 6 of the 28. However, aminoglycoside toxicity is thought to be caused by prolonged drug exposure (1, 2). The transient exposure to toxic concentrations that would be seen after this loading dose has not been associated with toxicity (12). Because of the wide interpatient variability in these parameters, serum amikacin concentrations should be obtained and the dosing regimen should be individualized for each patient as quickly as possible after initiation of therapy.

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