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Pharmacokinetics of Intramuscularly Administered Aminosidine in Healthy Subjects

THOMAS P. KANYOK,[1] AARON D. KILLIAN,[1] KEITH A. RODVOLD,[1,2]* AND LARRY H. DANZIGER[1,2]

Colleges of Pharmacy[1] and Medicine,[2] University of Illinois at Chicago, Chicago, Illinois

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Aminosidine is an older, broad-spectrum aminoglycoside antibiotic that has been shown to be effective in in vitro and animal models against multiple-drug-resistant tuberculosis and the *Mycobacterium avium* complex. The objective of this randomized, parallel trial was to characterize the single-dose pharmacokinetics of aminosidine sulfate in healthy subjects (eight males, eight females). Sixteen adults (mean [± standard deviation] age, 27.6 ± 5.6 years) were randomly allocated to receive a single, intramuscular aminosidine sulfate injection at a dose of 12 or 15 mg/kg of body weight. Serial plasma and urine samples were collected over a 24-h period and used to determine aminosidine concentrations by high-performance liquid chromatographic assay. A one-compartment model with first-order input, first-order output, and a lag time (T_{lag}) and with a weighting factor of $1/y^2$ best described the data. Compartmental and noncompartmental pharmacokinetic parameters were estimated with the microcomputer program WinNonlin. One subject was not included (15-mg/kg group) because of the lack of sampling time data. On average, subjects attained peak concentrations of 22.4 ± 3.2 μg/ml at 1.34 ± 0.45 h. All subjects had plasma aminosidine concentrations below 2 μg/ml at 12 h, and all but two subjects (one in each dosing group) had undetectable plasma aminosidine concentrations at 24 h. The dose-adjusted area under the concentration-time curve from 0 h to infinity of aminosidine was identical for the 12- and 15-mg/kg groups (9.29 ± 1.5 versus 9.29 ± 2.2 μg · h/ml per mg/kg; $P = 0.998$). Similarly, no significant differences ($P > 0.05$) were observed between dosing groups for peak aminosidine concentration in plasma, time to peak aminosidine concentration in plasma, T_{lag}, apparent clearance, renal clearance, elimination rate constant, and elimination half-life. A significant difference was observed for the volume of distribution (0.35 versus 0.41 liters/kg; $P = 0.037$) between the 12 and 15 mg/kg dosing groups. Now that comparable pharmacokinetic profiles between dosing groups have been demonstrated, therapeutic equivalency testing via in vitro pharmacokinetic and pharmacodynamic modelling and randomized clinical trials in humans should be conducted.

The original Strategic Plan proposed by the Advisory Council for the Elimination of Tuberculosis previously set a goal to reduce the incidence of tuberculosis (TB) in the United States to less than 1 case per million by the end of the first decade of the 21st century (4). Unfortunately, North America experienced a resurgence of TB in 1984 which has, in all likelihood, delayed the achievement of this goal (11). However, what concerns public health officials even more is the proportion of TB cases caused by multiple-drug-resistant tuberculosis (MDR-TB). In a recent nationwide survey of MDR-TB in the United States, resistance to isoniazid and/or rifampin was found in 9.5% of the cases (3). Current treatment regimens for MDR-TB have met with discouraging results, including high rates of relapse, morbidity, and mortality (1, 9, 10). However, initial treatment regimens that include two or more drugs with in vitro activity against MDR-TB may result in improved outcomes (27, 29).

Aminosidine, formerly known as paromomycin, is a broad-spectrum aminoglycoside antibiotic first marketed worldwide in 1959 (8, 20) and currently available in the United States only as an oral formulation (20). This entity has been shown to be effective in vitro (12) and in vivo in animal models of MDR-TB and the *Mycobacterium avium* complex (MAC) (13). Aminosidine has been safely administered parenterally for over 30 years in Europe (2, 5, 7, 16, 19, 22, 23, 26, 28). In North American literature, aminosidine has been reported to be both ototoxic and nephrotoxic when given parenterally to animals and humans (15); however, worldwide experience with the injectable compound has not revealed a higher incidence of these adverse effects than incidences of the adverse effects of either gentamicin or kanamycin (2). Before initiating clinical trials for this agent against TB and MDR-TB, we conducted a phase I pharmacokinetic study of healthy subjects to establish the pharmacokinetics of aminosidine in normal individuals.

MATERIALS AND METHODS

Subjects. Sixteen healthy, adult subjects were enrolled into the protocol after informed, written consent was obtained. The protocol had been approved by the Investigational Review Board at the University of Illinois at Chicago. All male and female subjects between 20 and 45 years of age without any evidence of organ dysfunction or laboratory abnormalities were eligible for inclusion in the study. Subjects were required to have a baseline medication history, physical exam, and laboratory evaluation (complete chemistry profile, complete blood cell count with differential, urinalysis, and audiometry testing). Metropolitan Life Insurance tables (18) were used to ensure that all subjects were within 20% of their ideal body weight. Additionally, only subjects with a stable creatinine clearance (CL_{CR}), estimated by the Cockcroft-Gault equation (6) and for which stability was defined as CL_{CR} values which varied by <20% on two consecutive occasions within 1 week prior to the study, were eligible.

Females were excluded if they had a positive serum pregnancy test at baseline. Any subject was excluded if he or she had an absolute neutrophil count that was <1,000/mm^3, a CD4 count that was ≤200/mm^3, a history of allergy, intolerance,

* Corresponding author. Mailing address: m/c 886, Pharmacy Practice, College of Pharmacy, Room # 164, University of Illinois at Chicago, 833 South Wood St., Chicago, Illinois 60612. Phone: (312) 996-3341. Fax: (312) 413-1797. E-mail: kar@uic.edu.

or hypersensitivity to aminoglycosides, a previous history of treatment or prophylaxis for TB in the last two years, clinical evidence of TB or MAC infection, any other serious, acute, or chronic infection, or a previous history of any chronic illness. Subjects were also excluded if they had received any anti-TB agents (including all standard first- and second-line therapies for TB plus agents such as clofazimine, rifabutin, quinolones, or aminoglycosides), corticosteroids, pentoxifylline, or immune modulators (including colony stimulating factors, interferons, interleukins, and levamisole) within 3 months of study initiation. Subjects were required to abstain from alcohol, caffeine, and any other medications during the study period and for 48 hours prior to study enrollment.

Design. The study was designed as a randomized, parallel trial involving sixteen subjects (eight males, eight females). Subjects were admitted to the Clinical Research Center at the University of Illinois at Chicago's College of Pharmacy on the morning of the study day and immediately had their heights and weights recorded. A heparin lock was placed in a peripheral arm vein for pharmacokinetic blood sampling. Subjects were randomly allocated to receive a single, intramuscular (i.m.) aminosidine sulfate (Gabbromicina; Farmitalia Carlo-Erba, Milan, Italy) injection at a dose of 12 mg/kg of body weight ($n = 8$) or 15 mg/kg ($n = 8$). Eight subjects (four in the 12-mg/kg group and four in the 15-mg/kg group) were studied on week 1, and the remainder were examined the following week. Single-dose vials of aminosidine sulfate were reconstituted with 0.75 ml of sterile water, and the total amount of drug to be administered was further diluted to exactly 2 ml with sterile water. Each dose was administered into the gluteal muscle via a 3-ml syringe with a 19-gauge needle.

Two 7-ml tubes containing the anticoagulant edetate disodium tetraacetate were used to collect venous blood samples at 0, 0.33, 0.67, 1, 1.5, 2, 4, 6, 8, 12, and 24 h after administration of aminosidine. Heparin locks were removed after the 12-h sample, and subjects were instructed to return to the Clinical Research Center the following morning for the final 24-h blood collection by separate venipuncture. Blood samples were centrifuged at $1,000 \times g$ for 10 min within 1 h of collection, and plasma was harvested into polypropylene tubes and stored at −70°C until bioanalysis. Urine was also collected during the following intervals: 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, and 12 to 24 h. The total urine volume for each interval was recorded, and a 10-ml aliquot was also stored in polypropylene tubes at −70°C until assay. Baseline laboratory and audiometry testing was repeated at the end of the 24-h observation period.

Assay. The analysis of plasma and urine samples was performed with a high-performance liquid chromatographic (HPLC) assay developed at the University of Illinois at Chicago. After a 10- or 100-fold dilution with water, 30 μl of a 0.1-mg/ml solution of kanamycin B sulfate was added as an internal standard to 300 μl of urine. Phosphate buffer (0.1 M, pH 7.8) containing 1% Trizma-8.5 [tris(hydroxymethyl)aminoethane and hydrochloride], 400 μl of dimethyl sulfoxide, and 100 μl of 2% (vol/vol) 2,4-dinitrofluorobenzene in ethanol (EtOH) was added for derivatization at 64°C for 30 min. The samples were washed with 3 ml of toluene, and the derivatized compounds were extracted from the remaining aqueous layer with 3 ml of acetonitrile-toluene (1:1 [vol/vol]). After evaporation to dryness under a stream of nitrogen at 30 to 40°C, the residue was reconstituted with 1 ml of acetonitrile-water (1:1 [vol/vol]). Ten microliters of the extract was injected onto a ZORBAX SB C-18 reversed-phase HPLC column (4.6 by 250 mm) at 50°C with a mobile phase of methanol-water (64:36 [vol/vol]) adjusted to pH 3.0 with phosphoric acid. The pump was set at a flow rate of 2 ml/min, and the UV detector was set at a wavelength of 350 nm with a sensitivity of 0.02 absorbance units full scale. The ratio of the drug peak area to that of the internal standard was plotted to construct a linear standard curve over the range of 0.5 to 50 μg/ml against which the study samples were evaluated. The limits of detection and quantitation were 0.2 and 0.5 μg/ml, respectively. Intra- and interday coefficients of variation for the quality control samples ($n = 6$) at 36.9, 11.0, and 2.21 μg of aminosidine per ml in plasma were 2.8 and 2.9%, 3.8 and 3.1%, and 5.7 and 3.1%, respectively.

For the analysis of plasma samples, proteins were precipitated with 100 μl of 2 M perchloric acid and were centrifuged at $1,500 \times g$ for 5 min. The supernatant was neutralized with 80 μl of 1.5 M NaOH. After derivatization as described above, 20 μl of the reconstituted sample was injected onto the same HPLC apparatus. The standard curve for aminosidine in urine was linear over the range of 1.0 to 50 μg/ml. The limits of detection and quantitation were 0.5 and 1.0 μg/ml, respectively. Intra- and interday coefficients of variation for the quality control samples ($n = 7$) at 36.6, 14.6, and 2.92 μg of aminosidine per ml in urine were 1.5 and 3.4%, 0.9 and 2.1%, and 2.3 and 2.3%, respectively.

Pharmacokinetic evaluation. Pharmacokinetic analysis was performed on plasma and urine concentration-time data collected over 24 h following aminosidine sulfate administration. Compartmental and noncompartmental pharmacokinetic parameters were estimated with the microcomputer program WinNonlin (version 1.0; Scientific Consulting, Inc., Apex, N.C.).

Initial estimates of pharmacokinetic parameters were obtained by stripping the plasma concentration-time data with the microcomputer program RSTRIP (version 5.0; Micromath Inc., Salt Lake City, Utah). These initial estimates were then used to generate a best fit of the data by using nonlinear least-squares regression within WinNonlin. Analysis of residuals, parameter standard errors, a correlation matrix, and the Akaike information criteria (30) were used for model discrimination. A one-compartment model with first-order input, first-order output, and a lag time (T_{lag}) (WinNonlin library model 4) was chosen as the most appropriate pharmacokinetic model. The data were best described by using a weighting factor of $1/y^2$.

TABLE 1. Demographic data and dosing information for subjects enrolled in aminosidine pharmacokinetic study

Subject	Age (yr)	Wt (kg)	Ht (cm)	BSA[a] (m^2)	Aminosidine sulfate dose in:		Aminosidine dose (mg)
					mg	mg/kg	
12-mg/kg group							
1	28	80.0	172.7	1.94	1,000	12.5	782.0
3	28	77.2	189.2	2.04	900	11.7	703.8
7	26	52.3	162.6	1.55	600	11.5	469.2
9	25	62.9	162.6	1.67	800	12.7	625.6
11	23	69.5	174.0	1.83	800	11.5	625.6
6	23	52.7	166.1	1.58	600	11.4	469.2
8	29	59.5	168.4	1.68	700	11.8	547.4
14	29	91.8	188.0	2.18	1,100	12.0	860.2
Mean	26.4	68.2	172.9	1.81	812.5	11.9	635.4
SD	2.5	14.0	10.5	0.23	181.0	0.48	141.0
15-mg/kg group							
2	25	48.1	154.4	1.44	700	14.6	547.4
5	29	69.5	173.0	1.83	1,000	14.4	782.0
4	24	62.7	162.6	1.67	900	14.4	703.8
10	42	73.6	178.1	1.91	1,100	14.9	860.2
12	20	77.7	166.1	1.86	1,000	12.9	782.0
13	37	87.7	179.1	2.07	1,300	14.8	1,016.6
15	26	75.5	110.9	1.97	1,100	14.6	860.2
Mean	29.0	70.7	170.9	1.82	1,014	14.4	793.2
SD	7.8	13.0	10.2	0.21	186	0.68	146.0

[a] BSA, body surface area.

Peak concentration in plasma (C_{max}) and the time of C_{max} (T_{max}) were determined directly by a visual analysis of the individual observed aminosidine concentration-time data. The area under the concentration-time curve from 0 to 24 h (AUC_{0-24}) was determined by concentration of the areas obtained with the linear trapezoidal method (ascending portion of curve up to T_{max}) and the log trapezoidal method (descending portion of the curve). The area term was extrapolated to infinity ($AUC_{0-\infty}$) by adding AUC_{0-24} to the portion of area obtained by dividing the final measured plasma concentration by the elimination rate constant (β). β and the absorption rate constant (k_a) were determined by nonlinear least-squares regression. To compare aminosidine sulfate dosing groups, $AUC_{0-\infty}$ was normalized for the amount of drug administered per kilogram of total body weight.

The elimination half-life ($t_{1/2}$) was calculated by dividing β into the natural logarithm of two. The apparent clearance (CL/F) and volume of distribution (V_β/F) were calculated with the following equations: $CL/F = \text{dose} \cdot S/AUC_{0-\infty}$ and $V_\beta/F = \text{dose} \cdot S/AUC_{0-\infty} \cdot \beta$, where F is the fraction of bioavailability and was assumed to equal a value of 1 (100%). A salt factor (S) of 0.782 was used to correct the dose of aminosidine sulfate.

Renal clearance (CL_R) of aminosidine was determined by dividing the amount of drug excreted in the urine for the 24-h period after drug administration by AUC_{0-24}. Both CL/F and CL_R were standardized to a body surface area of 1.73 m^2, and V_β/F was standardized to total body weight.

Evaluation of ototoxicity. A complete history of familial and acquired hearing impairment and vestibular disorders was conducted for each subject prior to admission into the study. Air conduction audiometry (Grason-Stadler 16 audiometer; Littleton, Mass.) was performed within 7 days before and after the administration of aminosidine. The range of test frequencies was 250 to 12,000 Hz. Hearing loss was defined as a perception loss at at least two frequencies of ≥15 dB in the same ear or ≥10 dB in both ears.

Statistical analysis. An unpaired, two-tailed Student t test was used to compare the pharmacokinetic parameters of the 12- and 15-mg/kg dosing groups. An a posteriori value of less than 0.05 was considered significant. Data are presented as means ± one standard deviation.

RESULTS

Subjects ranged in age from 20 to 42 years (mean, 27.6 years) and in weight from 48.1 to 91.8 kg (mean, 69.4 kg). The mean calculated CL_{CR} was 101.0 ± 16.5 ml/min/1.73 m^2 (range: 75.2 to 132.8 ml/min/1.73 m^2) at baseline and 97.2 ± 18 ml/min/1.73 m^2 (range: 54.9 to 128.9 ml/min/1.73 m^2) at the end of the

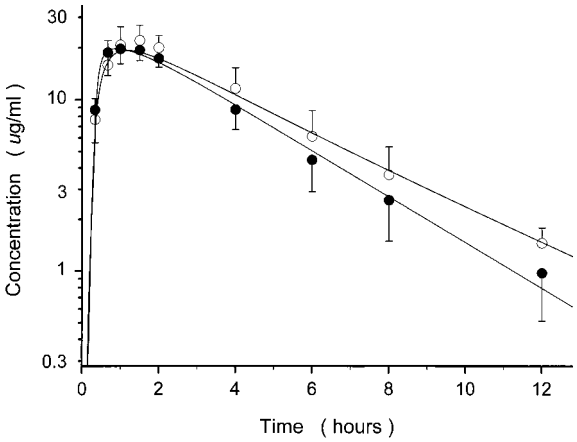

FIG. 1. Curves of mean concentration in plasma versus time for patients receiving aminosidine sulfate. ●, 12-mg/kg group; ○, 15-mg/kg group. Error bars represent one standard deviation. The solid lines represent the computer-fitted nonlinear least-squares regression analysis of plasma concentration-time data.

study. Demographic data and dosing information are presented in Table 1. One subject was not included (15-mg/kg group) because her actual sampling times were not available for the pharmacokinetic analysis.

Figure 1 shows the actual and computer-predicted mean plasma aminosidine concentration-time profiles obtained with the 12- and 15-mg/kg doses. A one-compartment model with first-order input, first-order output, and T_{lag} adequately described the data.

Mean pharmacokinetic parameters for aminosidine after a single 12- or 15-mg/kg i.m. dose are reported in Tables 2 and 3, respectively. On average, subjects attained peak concentrations of 22.4 ± 3.2 μg/ml at 1.34 ± 0.45 h. All subjects had plasma aminosidine concentrations below 2 μg/ml at 12 h, and all but two subjects (one in each dosing group) had undetectable plasma aminosidine concentrations at 24 h. The dose-adjusted $AUC_{0-\infty}$ of aminosidine was identical for the 12- and 15-mg/kg groups (9.29 ± 1.5 versus 9.29 ± 2.2 μg · h/ml per mg/kg; $P = 0.998$). Similarly, no significant differences ($P > 0.05$) were observed between dosing groups for C_{max}, T_{max}, T_{lag}, CL/F, CL_R, β, and $t_{1/2}$. A significant difference was observed for V_β/F (0.35 versus 0.41 liters/kg; $P = 0.037$) between the 12- and 15-mg/kg dosing groups. In addition, the k_a between groups demonstrated a trend towards a significant difference (6.27 versus 2.65 h^{-1}; $P = 0.057$).

The amounts and percentages of the aminosidine doses excreted in the urine during each collection period are presented in Fig. 2. For most subjects, the majority of the dose was excreted in the urine within the first 6 h, with about 50% of the dose being detectable in the urine within the first 4 h. The mean amount of aminosidine recovered in the 24-h urine collection was 430.6 mg (67.8%) for the 12-mg/kg dose and 485.6 mg (60.1%) for the 15-mg/kg dose. The mean CL_R was 79.6 ± 15 and 76.1 ± 12 ml/min/1.73 m^2 for the 12- and 15-mg/kg groups, respectively. These rates were not significantly different.

Safety. Aminosidine was generally well tolerated after i.m. administration. Subject 2 (15 mg/kg) complained of minor pain at the injection site that persisted for the duration of the study. No clinically significant changes were observed in individual laboratory values except for subject 9 (12 mg/kg) who had baseline and poststudy calculated CL_{CR}s of 109.9 and 54.9 ml/min/1.73 m^2, respectively, representing a 50% decline in calculated renal function. No subject demonstrated evidence of hearing loss on audiometric testing.

DISCUSSION

The pharmacokinetic parameters for aminosidine in the present study are in agreement with those obtained by investigators in Europe. Novarini and colleagues (19) found that in subjects with CL_{CR}s greater than 80 ml/min, serum aminosidine concentrations were also nearly undetectable at 12 h after single i.m. doses of 500 mg. They noted peak serum aminosidine concentrations between 15 and 20 μg/ml in subjects with CL_{CR}s above 100 ml/min. Our peak serum aminosidine concentrations were higher, most likely as a result of the milligram-per-kilogram dosing schedule used in our study. No subject in our protocol received a total dose of less than 600 mg (range, 600 to 1,300 mg). Also, the peak serum aminosidine concentrations of the two groups were not significantly different. This may reflect a delayed i.m. absorption and/or limitations on the amount of drug that gets absorbed via this route. Similarly, this may offer an explanation for the prolonged $t_{1/2}$ in the group that received the 15-mg/kg dose.

In Novarini's study, the C_{max} was observed to be inversely correlated to CL_{CR}, indicating that renal dysfunction may influence the C_{max} of the drug with a given dose. Unfortunately, all subjects received a dose of 500 mg regardless of body weight, making it difficult to discern whether the subjects with diminished renal function achieved higher C_{max} values solely as a result of a higher milligram-per-kilogram dose, solely as a

TABLE 2. Single-dose pharmacokinetic parameters for 12-mg/kg aminosidine sulfate dose

Subject	C_{max} (μg/ml)	T_{max} (h)	k_a (h^{-1})	T_{lag} (h)	$AUC_{0-\infty}$ (μg · h/ml)	CL/F (ml/min/1.73 m^2)	CL_R (ml/min/1.73 m^2)	V_β/F (l/kg)	β (h^{-1})	$t_{1/2}$ (h)
1	23.4	1.52	1.64	0.12	103.1	112.7	87.5	0.32	0.297	2.34
3	17.2	2.02	1.08	0.10	84.7	117.4	80.5	0.38	0.285	2.43
7	20.8	0.98	6.23	0.23	70.5	123.8	81.6	0.36	0.357	1.94
9	22.2	1.13	7.56	0.35	74.6	144.8	112.0	0.39	0.344	2.01
11	25.0	0.67	12.19	0.30	87.5	112.6	66.5	0.32	0.322	2.15
6	21.4	0.67	10.58	0.29	76.9	111.3	67.1	0.37	0.316	2.20
8	22.2	1.10	9.39	0.32	79.0	118.9	75.1	0.37	0.314	2.21
14	20.2	1.47	1.50	0.16	114.1	99.7	66.3	0.28	0.290	2.39
Mean	21.6	1.19	6.27	0.23	86.3	117.7	79.6	0.35	0.32	2.21
SD	2.3	0.46	4.41	0.10	15.0	13.0	15.0	0.04	0.03	0.17
CV (%)[a]	10.7	38.4	70.3	41.6	17.4	11.1	19.2	10.4	8.1	7.9

[a] CV, coefficient of variation.

TABLE 3. Single-dose pharmacokinetic parameters for 15-mg/kg aminosidine sulfate dose

Subject	C_{max} (μg/ml)	T_{max} (h)	k_a (h^{-1})	T_{lag} (h)	$AUC_{0-\infty}$ (μg · h/ml)	CL/F (ml/min/1.73 m^2)	CL_R (ml/min/1.73 m^2)	V_β/F (l/kg)	β (h^{-1})	$t_{1/2}$ (h)
2	19.9	1.00	3.08	0.20	56.4	194.3	101.6	0.39	0.512	1.35
5	17.3	2.00	0.87	0.06	92.2	133.7	77.4	0.42	0.289	2.40
4	29.3	1.05	4.27	0.29	110.0	110.5	66.0	0.31	0.325	2.13
10	23.5	1.50	2.45	0.18	122.2	106.3	75.4	0.41	0.234	2.96
12	24.2	2.02	1.21	0.20	94.1	128.8	69.9	0.37	0.288	2.41
13	23.6	1.50	2.66	0.23	135.8	104.2	67.9	0.42	0.203	3.41
15	26.1	1.50	4.02	0.23	120.6	104.4	74.4	0.52	0.183	3.78
Mean	23.4	1.51	2.65	0.20	104.5	126.0	76.1	0.41	0.29	2.64
SD	3.9	0.40	1.29	0.07	26.3	32.4	12.0	0.06	0.11	0.82
CV (%)[a]	16.7	26.6	48.6	36.2	25.2	25.7	15.8	15.0	37.8	31.1

[a] CV, coefficient of variation.

result of a lower CL_{CR}, or both. However, it is likely that diminished elimination of aminosidine occurs during the absorptive phase following i.m. injection, allowing aminosidine to accumulate to a greater extent in individuals with significant renal dysfunction (CL_{CR} = 10 to 30 ml/min).

Rimoldi and coworkers (22) also studied the impact of renal disease on the pharmacokinetics of aminosidine. They found that $t_{1/2}$ averaged between 2 and 3 h for subjects with normal renal function (CL_{CR} > 60 ml/min) but could increase to up to 40 h for subjects with varying degrees of renal impairment. Similarly, in our subset of healthy subjects for whom the estimated CL_{CR}s were greater than 75 ml/min/1.73 m^2, $t_{1/2}$ averaged 2 to 3 h (range: 1.3 to 3.8 h). Since aminoglycoside antibiotics are eliminated primarily unchanged by the kidney via glomerular filtration (14), renal elimination usually accounts for 85 to 95% of the administered dose. The average percentage of aminosidine excreted in the urine in this study (61%) is less than most values previously reported. Moreover, renal clearance was also less than that estimated by other investigators (24, 25) and probably reflects a lower urinary recovery of aminosidine.

Although recovery of the total dose of an aminoglycoside may require urine collection for 10 to 20 days, it is unlikely that more than an additional 5 to 10% of the total administered dose would have been recovered had we collected urine for a longer duration. Possible explanations for this include reduced tissue accumulation relative to those of other aminoglycosides (24), incomplete bioavailability or delayed absorption from the i.m. route, and/or decreased tubular reabsorption of aminosidine. It has been reported that aminoglycoside CL averages 50% of CL_{CR}, but reported CLs can decrease sharply after urinary concentrations of the drug decline and tubular reabsorption becomes pronounced (25). It is also possible that aminosidine exhibits enhanced biliary elimination relative to other aminoglycosides (17, 21). In our opinion, the higher CL values were likely reflective of incomplete bioavailability and/or the limited observation period inherent to the study design rather than an excretion profile which is unique within its class.

An explanation for the difference in mean V_β/F values between groups was not found. It is possible that such a parameter may be influenced by the chosen model, subject sex, and/or the choice of weight used to normalize pharmacokinetic parameters. Retrospective analyses of our data suggest that the latter two do not influence the results. That is, there were no apparent differences between male and female subjects, which might have been postulated to be due to variations in bodily composition. Similarly, there were no significant changes when

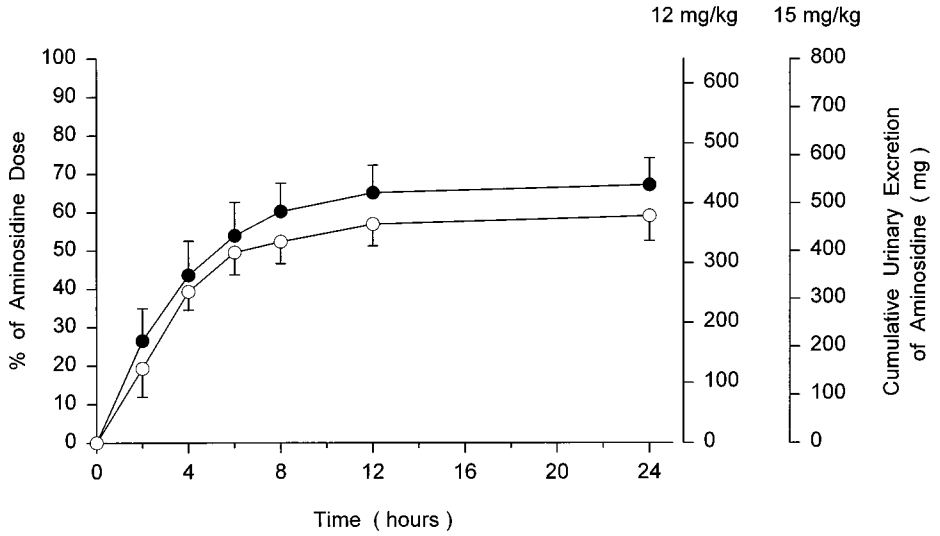

FIG. 2. Mean percentages and amounts of aminosidine excreted in the urine during each collection period. ●, 12-mg/kg group; ○, 15-mg/kg group. Error bars represent one standard deviation.

pharmacokinetic parameters were normalized to ideal body weight as opposed to total body weight. Thus, the observed findings may be attributable to our choice of pharmacokinetic model or to some other unknown factor.

Of the 16 subjects who were given i.m. aminosidine in this study, only one subject complained of pain at the site of injection which lasted for more than a few minutes. Although the pain was noted to persist for the duration of the study, this adverse effect was considered to be mild in nature and did not require any special treatment. One subject also experienced an asymptomatic decline in renal function which could potentially be attributable to aminosidine. Since this study was not designed to evaluate the safety profile of aminosidine, further clinical trials will be required to determine whether the incidence of nephrotoxicity is different from those observed with other aminoglycoside antibiotics.

Now that comparable pharmacokinetic profiles between dosing groups have been demonstrated, the next step will be to conduct therapeutic equivalency testing via in vitro pharmacokinetic and pharmacodynamic modelling and randomized clinical trials in humans. As streptomycin, amikacin, and kanamycin have been used in daily and intermittent regimens to treat TB infections, it is likely that aminosidine will also be effective when administered in such a manner. However, since the potencies of the aminoglycoside antibiotics may differ with respect to bactericidal activity against *Mycobacterium tuberculosis*, future dose optimization studies must address this issue carefully.

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