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Pharmacokinetics of Amikacin in Serum and in Tissue Contiguous with Pressure Sores in Humans with Spinal Cord Injury

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Pressure sores are a common occurrence in immobilized patients. They increase morbidity and mortality and impede rehabilitation. Antibiotics are routinely used to assist in effecting a cure when infection is present. Nevertheless, for patients with spinal cord injuries (SCI), strategies for effective therapy with antibiotics based on measurement of concentrations in tissue and pharmacokinetic behavior in extravascular spaces do not exist. By analyzing the concentration-time profile and protein binding of amikacin in the interstitial fluid (IF) in contact with pressure sores, we found that the disposition of amikacin in the tissue contiguous with pressure sores appears to be governed by simultaneous first-order and capacity-limited pharmacokinetic behavior. Amikacin disposition in IF proceeded without a simple relationship to amikacin concentrations in serum, and the time course in IF was not accurately simulated by linear models of amikacin pharmacokinetic behavior. Total amikacin clearance estimated from a pharmacokinetic model using simultaneous first-order and nonlinear intercompartmental transfer of amikacin was not significantly different from clearance calculated by us in a prior study of amikacin pharmacokinetic behavior in patients with SCI. In patients with SCI, optimal use of amikacin in the treatment of infected pressure sores is contingent upon accurate characterization of the pharmacokinetic behavior of this aminoglycoside in serum and in the IF in contact with these lesions. Only methods which quantitate amikacin concentration and protein binding in IF and incorporate a model that can simultaneously simulate nonlinear and linear disposition processes should be relied upon to influence therapeutic decision making.

Pressure sores (decubitus ulcers) develop because of tissue death due to ischemia and are one of the most common problems encountered following traumatic spinal myelopathy (35, 45). These lesions are frequently multiple and can vary in severity from mild erythema of the skin to huge necrotic excavations with extensive destruction of underlying connective tissue and bone. Pressure sores impede rehabilitation and have major socioeconomic consequences (7, 35, 45). They are recurrent and often serve as foci of local and systemic sepsis. The devitalized, ischemic tissue adjoining pressure sores invites the growth of microorganisms, and the gram-negative infections which frequently complicate these wounds are often caused by organisms susceptible to aminoglycoside antibiotics (17). Bacteremia can be anticipated to accompany debridement of pressure sores, and the septicemia or cellulitis associated with pressure sores is a significant cause of morbidity and mortality in patients with spinal cord injuries (SCI) (5, 15, 17, 20).

Most bacterial infections are localized in tissue. The interstitial fluid (IF) in tissue contiguous with a pressure sore serves as a medium for propagation of infection and is also the primary path by which antibiotics are transported to a site of infection. Hence, a major determinant of the efficacy of antimicrobial therapy is thought to be the amount of antibiotic available in the IF (2, 6). The concentration of a drug in the IF that is free (unbound to proteins) and generally considered to be biologically active is of greater therapeutic significance than the corresponding total concentration.

Although penetration of antibiotics into living tissue has been extensively studied (3, 4, 18), measurement of antibiotic concentrations in viable tissue surrounding pressure sores in patients with SCI has not been described. Nevertheless, strategies for the use of antimicrobial agents in preoperative prophylaxis or in the treatment of infected pressure sores have evolved in the absence of information about the concentrations in tissue and pharmacokinetic behavior of antibiotics at the precise location where infection originates and is propagated. A dearth of information concerning the concentration and disposition of antibiotics in tissue adjoining pressure sores led us to implement a study of amikacin, an aminoglycoside antibiotic of proven efficacy in the treatment of gram-negative infections, in a population of patients who are highly susceptible to both pressure sores and gram-negative bacterial sepsis.

MATERIALS AND METHODS

Volunteer selection. Twelve nonobese male volunteers (five tetraplegic, seven paraplegic) between 26 and 66 (mean, 44 ± 12) years of age were consecutively entered into the study. All had traumatic spinal myelopathy of greater than 1 year duration (chronic SCI) and were deemed to have neurologically complete injuries as defined by complete absence of sensation and total loss of voluntary muscle control below the zone of SCI at the primary injury site (Frankel Grade A) (14). Volunteers with acute febrile illness, a hematocrit of less than 35 vol%, impaired creatinine clearance (below 75 ml/min per 1.73 m^2), obesity, cachexia, or hepatic or cardiac disease were excluded from study. None of the men had received aminoglycoside antibiotics during the month before they entered the study. All patients with SCI were studied at 12 to 18 h before surgical or laser (12) debridement of pressure sores so that administration of amikacin was considered to be part of a clinically indicated preoperative regimen of antibiotic prophylaxis. Written in-

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formed consent was obtained from each volunteer by an institutionally approved protocol.

Study protocol. Each subject received amikacin sulfate by intravenous infusion (7.5 mg/kg) over a 30-min period (Amikin, lot G4J08; Bristol Laboratories, Syracuse, N.Y.) through a constant-flow syringe pump. Each study was begun at 13.30 ± 1.5 h of the study day. During the first 45 min, whole-blood samples were obtained from an extremity contralateral to the infusion site. Thereafter, blood was obtained from the indwelling heparinized catheter used for the amikacin infusion. Samples (5 ml) were collected at 10, 20, 30 (end of infusion), 45, 60, 90, 120, and 150 min and thereafter at 2-h intervals for up to 8.5 h. A two-syringe technique was used, and the blood withdrawn into the first syringe (1.5 ml) was discarded.

Amikacin concentrations in IF. A modified version of the methods used by Hoffstedt et al. (24) and Ryan (37) was used to quantitate concentrations of amikacin in IF. By an aseptic technique, a no. 4, 3/8-in. (1 in. = 2.54 cm) curved cutting needle attached to one end of a continuous, sterilized, prepackaged cotton tape (umbilical tape, no. 10-A, 1/8 in. wide; Ethicon Inc., Somerville, N.J.) marked with indelible ink at 5-cm intervals was threaded subcutaneously. All tapes were cut from the same lot. The absence of sensation associated with complete SCI obviated the need for local anesthesia. Four tapes were implanted into each subject. Two tapes were placed in viable tissue within 2.5 cm of the pressure sore margin; two tapes (control tapes) were implanted in normal tissue not less than 10 cm from the ulcer margin. All pressure sores were grade III or greater, over bony prominences, and well below the level of myelopathy.

Concurrent with the acquisition of whole-blood samples, a fresh 5-cm length of tape was aseptically advanced and allowed to equilibrate for 5 to 8 min. After equilibration, the portion of implanted tape impregnated with IF (always >2.5 cm long) was immediately cut off and placed into a sterile container before being processed. Lengths (2.5 ± 0.1 cm) of the tape visibly impregnated with fluid were eluted in 750 μl of buffer for 30 min in a shaker bath at 37°C and assayed for amikacin.

A correction for blood contamination was made by using a spectrophotometric analysis of a sample of the tape eluate to be assayed for amikacin and comparing the percent absorbance of the tape eluate with a standard dilution curve calibrated to read hemoglobin concentration. Correction for the hematocrit of each subject was incorporated into each calculation. The concentration of amikacin measured in each tape and attributable to blood (serum) contamination was then subtracted from the total concentration of amikacin measured (33). Tapes containing greater than 33% whole blood were discarded from further consideration. Amikacin recovery from tape was essentially complete (>95%) and did not increase measurably with prolonged elution.

Assay of amikacin. Absence of amikacin in the systemic circulation was confirmed by analysis of a blood sample drawn before administration of the test drug. Sera were separated at bedside and frozen until assayed. Amikacin concentrations in serum, in IF deemed uninvolved with the pressure sore (control tapes >10 cm from the ulcer margin), and in IF within 2.5 cm of the ulcer margin were determined in duplicate by using a fluorescence polarization immunoassay (TD_x; Abbott Laboratories, North Chicago, Ill.). The TD_x dilution protocol was used to quantitate amikacin in the 12.5 ± 3.9-μl volume of IF that was absorbed into each 2.5-cm length of umbilical tape. In serum, the TD_x assay sensitivity for amikacin is 0.2 μg/ml. The interassay coefficients of variation for TD_x control samples of 5.0, 15.0, and 30.0 μg/ml were 4.44, 4.50, and 5.50%, respectively. Amikacin absorbed into tape and eluted into 750 μl of TD_x buffer showed a reproducible linear correlation with an amikacin standard curve prepared by using 12.5-μl samples of amikacin in serum at concentrations of 7.5 to 60.0 μg/ml and diluted with TD_x buffer to give a final volume of 750 μl. Modification of the assay for amikacin in IF was validated as sensitive to a minimum concentration of 10 μg/ml per 2.5 cm of tape. The intra-assay coefficients of variation for the spiked IF standard curve at concentrations of 20.0, 30.0, 40.0, and 60.0 μg/ml were 21.1, 9.5, 9.1, and 13.6%, respectively.

Serum protein binding. Total amikacin and unbound (free) amikacin were determined for each study subject over a range of amikacin concentrations in serum. Unbound amikacin was obtained from 500-μl samples of serum placed in a disposable membrane filter system (Centrifree; Amicon) and centrifuged at 1,000 × *g* in a fixed-angle (45°) rotor for 10 min at ambient room temperature. Each ultrafiltrate and the parent serum were assayed for amikacin in duplicate by fluorescence polarization immunoassay.

IF binding. Artificial IF was prepared by diluting pooled plasma with an ultrafiltrate of plasma. The ultrafiltrate contained no proteins with molecular weights of ≥30,000. A dilution in the ratio of 1 volume of pooled plasma to 2 volumes of plasma ultrafiltrate was performed to achieve a 66% reduction in the concentration of total plasma proteins without a significant alteration of plasma ionic content. The concentrations of sodium, potassium, magnesium, total protein, albumin, and calcium in the artificial IF prepared in this manner were 138, 3.6, and 1.4 meq/liter, 2.6 and 1.4 g/dl, and 5.5 mg/dl, respectively. This solution was designed to closely approximate, in vitro, previously described estimates of the protein and electrolyte composition of human IF (10, 23). Artificial IF was used as a substrate for binding studies, because we were unable to recover adequate volumes of true IF from implanted tapes. The artificial IF (pH 7.4) was then spiked with a stock solution of amikacin in high-pressure liquid chromatography-grade water (5 mg/ml) to provide target concentrations of 7.5, 12, 15, and 20 μg/ml. Following 60 min of incubation at 37°C, total and unbound amikacin were quantitated in duplicate at each concentration by using the previously described ultrafiltration technique and TD_x assay.

Estimation of individual IF volumes. The volume of the IF (V_{IF}) or second compartment for each man was calculated by using a modification of the linear relationship developed by Gibaldi et al. (19) and Faed (13) to relate the apparent volume of distribution of a poorly protein-bound drug to its binding in plasma and IF:

$$V_{IF} = [(f_p \times CL' \times f_{IF}/\beta \times f_p) - (V_p \times f_{IF}/f_p)] \times 1.3 \quad (1)$$

where V_P is the plasma volume, V_{IF} is the volume of the IF compartment (V_{ECF} [extracellular fluid volume] − V_p), f_p is the fraction of the total amount of the drug unbound in plasma, f_{IF} is the fraction of the total amount of the drug unbound in artificial IF, β is the individual apparent terminal elimination rate constant, and CL′ is the individual intrinsic clearance. V_p is not significantly influenced by the pathophysiology of SCI and was estimated with a nomogram (11). The factor 1.3 represents an experimentally derived multiplier used by us to correct for the increase in the apparent volume of distribution of aminoglycoside antibiotics (amikacin and gentamicin) attributable to the influence of chronic SCI on expansion of the extracellular fluid volume (41–43). It

represents a conservative estimate of this increase. The fractions of free amikacin in serum and in artificial IF (plasma ultrafiltrate) were experimentally determined to be 0.83 and 0.95, respectively.

Analysis of data. Visual inspection of plots of the time courses of amikacin concentrations in IF for individuals and for mean concentrations in all of the subjects suggested that a capacity-limited process governed amikacin disposition. We subsequently chose to simulate and compare the simultaneous dispositions of amikacin in serum and in IF by using compartmental models which incorporate first-order or simultaneous first-order and capacity-limited disposition kinetics.

Curve fitting and estimation of pharmacokinetic parameters were accomplished by using the ADAPT-PC program package (9) modified to support pharmacokinetic parameter estimation from compartmental models incorporating simultaneous linear and capacity-limited disposition processes. The functions incorporated into the computational algorithm are as follows:

$$\dot{x}_1 = R(1) - X(1) \times k_{el} - X(1) \times \frac{V_{max} \times V_{IF}}{K_m \times V_{IF} + X(1)} + X(2) \times k_{21}$$

$$\dot{x}_2 = X(1) \times \frac{V_{max} \times V_{IF}}{K_m \times V_{IF} + X(1)} - X(2) \times k_{21}$$

where $R(1)$ is the rate input, $X(1)$ is the amount in the central compartment, $X(2)$ is the amount in the interstitial compartment, V_{IF} is the volume of the IF compartment, V_{max} is the maximum central compartment-interstitial compartment transfer rate constant, K_m is the IF concentration at which one-half of the V_{max} is observed, k_{el} is the overall elimination rate constant, and k_{21} is the IF compartment-central compartment transfer rate constant.

Model parameters were simultaneously fitted to serum and averaged IF data by minimizing a conventional nonlinear, ordinary least-squares objective criterion by using the following model output equations: $Y(1) = X(1)/V_1$ and $Y(2) = X(2)/V_{IF}$. $Y(1)$ and $Y(2)$ represent amikacin concentrations from serum and IF (average measured values for two control and two wound tapes), respectively, and V_1 is the volume of the central compartment. V_{IF} was not fitted but was calculated by using equation 1 and held constant to allow estimation of the other model parameters. Plots of residuals versus estimated concentrations or time supported the use of ordinary least-squares analysis and a unity weighting scheme.

The best simulation of the time course of amikacin in serum and in IF following a single intravenous dose was achieved by using a two-compartment open model with elimination from the central compartment. This model incorporated simultaneous first-order and capacity-limited kinetics to describe the transfer of amikacin between a central compartment (V_1) and a peripheral compartment (V_{IF}). Identification of the simplest treatment (smallest number of exponentials) to describe the data was obtained from application of the Akaike information criterion (AIC) (50). The area under the time-concentration curve (AUC) of amikacin in tissue or serum was calculated by using a noncompartmental method that used the Lagrange method of polynomial approximation (LAGRAN) (36).

The significance of the difference between means or medians was tested by using an appropriate parametric or nonparametric analysis of variance (Kruskal-Wallis). The method of Scheffé was used for multiple comparisons between group means; multiple comparisons between medians were performed with the ARCSINE transformation (28). The strength of association of variables was tested by using linear regression analysis. A probability of less than or equal to 0.05 was considered statistically significant. All data are expressed as means ± standard deviations, unless otherwise indicated. The adequacy and appropriateness of the size of the study population needed to support statistical inference were determined by using the method of Stolley and Strom (44).

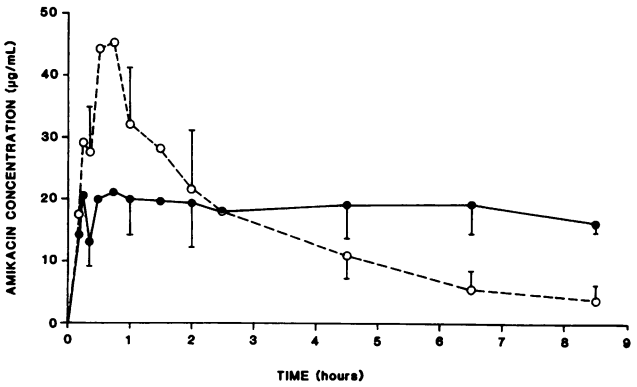

FIG. 1. Concentrations of amikacin (mean ± standard deviation) after a single intravenous dose in the serum (○) and IF (●) of 12 patients with SCI. Amikacin concentrations in IF at a pressure sore margin and those in the IF of uninvolved tissue at a distance of 10 cm or more did not differ significantly. An average of the combined IF data was plotted. The time-course profile of the combined tissue IF data suggests capacity-limited disposition of amikacin.

SCI levels were assigned values based on a method previously described by us that arbitrarily assigns a numeric value to each of 30 anatomic spinal cord levels (first cervical [C_1] through fifth sacral [S_5]) represented as points along a sine curve (40). By using this paradigm, we have been able to demonstrate a statistically significant inverse linear relationship between the magnitude of the amikacin volume of distribution at steady state and the level of injury (41).

RESULTS

Amikacin levels in IF were attained rapidly and declined slowly. Peak amikacin concentrations in IF were observed in less than 20 min at both the control and ulcer sites in all patients. There was little fluctuation in the concentrations thereafter. Sustained amikacin concentrations in tissue were observed during the terminal elimination phase of amikacin from serum (Fig. 1). Following correction for blood contamination, significant differences could not be demonstrated between mean amikacin concentrations in tissue more than 10 cm from the pressure sore margin (control tapes) and amikacin concentrations measured in IF within 2.5 cm of the ulcer margin. Hence, all tape data were combined. Tapes implanted adjacent to the pressure sore margin, where hyperemia secondary to inflammation was postulated, were more likely to exhibit blood contamination than were control tapes.

The pharmacokinetic behavior of amikacin in IF and serum was best simulated with a two-compartment open model using simultaneous first-order and capacity-limited

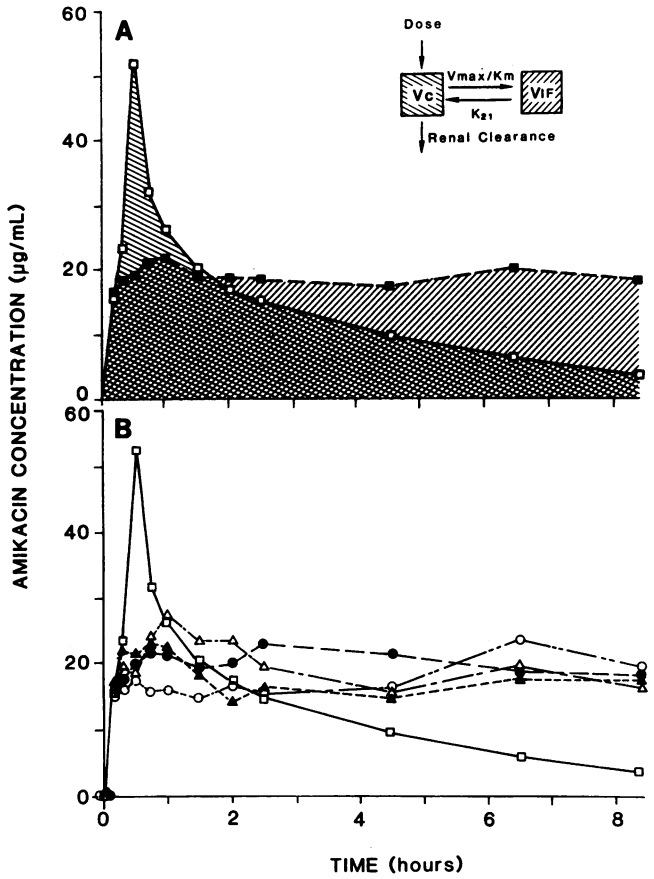

FIG. 2. (A) Amikacin time-concentration data for the serum (□) and IF (■) of a representative patient with SCI. Vc, Volume in the central compartment. (B) No statistically significant difference exists between amikacin concentrations measured in IF at a pressure sore margin and those in the IF of uninvolved healthy adjacent tissue. Symbols: △ and ▲, amikacin concentrations measured in paired tapes implanted in the pressure sore margin; ○ and ●, measurements of amikacin concentrations in paired tapes in healthy tissue at a distance of not less than 10 cm from the wound margin.

disposition kinetics (Fig. 2). The best fit of serum and IF data was achieved when the intercompartmental transfer of amikacin from serum to IF was expressed in terms of a capacity-limited process. The superiority of this model in simulating amikacin pharmacokinetics in serum and IF in our patient population was established heuristically and by comparing the AICs (statistical analysis) generated by two- and three-compartment models which incorporated either first-order kinetics or simultaneous first-order and capacity-limited disposition processes (Table 1).

A tissue penetration index (TPI) for total amikacin was defined in terms of the ratio of the area under the amikacin IF time-concentration curve (AUC_{IF}) to the area under the serum time-concentration curve (AUC_s) over sampling periods of up to 8.5 h (Table 1). The mean TPI for amikacin was 1.20. An inverse association between amikacin AUC_{IF} and AUC_s was demonstrated by using linear regression and could be represented by the equation $AUC_{IF} = 209.40 - 0.56(AUC_s)$, with a correlation coefficient of 0.68 ($P \leq 0.03$). The nonlinear processes affecting amikacin disposition prevented extrapolation of the time-course profile of amikacin in tissue to infinity; hence, an accurate estimate of the terminal elimination rate constant was unobtainable. The

TABLE 1. Pharmacokinetic parameters estimated by using simultaneous linear and capacity-limited disposition kinetics and model output statistical summary

Patient no.	V_1 (liters)	V_{IF} (liters)	Total clearance (ml/min per kg)	CL′ (ml/min per kg)	k_{e1} (h^{-1})	k_{21} (h^{-1})	V_{max} (mg/h per liter)	K_m (mg/liter)	TPI	Model A[a]			Model B[b]		
										AIC	r		AIC	r	
											Serum	IF		Serum	IF
1	5.8	9.9	0.61	0.74	0.387	2.95	59.89	3.37	0.83	75.2	0.98	0.81	79.7	0.98	0.66
2	6.3	7.5	0.79	0.95	0.481	24.25	401.50	0.07	1.31	67.4	0.98	0.94	92.9	0.92	0.44
3	2.3	6.2	0.54	0.65	0.685	4.63	114.00	0.61	1.49	70.9	0.98	0.78	87.4	0.93	0.75
4	5.9	2.0	0.34	0.41	0.250	4.13	122.90	0.05	1.60	54.1	0.99	0.94	62.0	0.88	0.95
5	7.3	5.9	0.54	0.65	0.300	3.57	69.99	0.79	0.80	38.7	0.94	0.79	33.9	0.98	0.93
6	3.4	1.2	0.29	0.35	0.327	3.35	85.28	0.05	2.07	72.7	0.97	0.72	73.8	0.89	0.88
7	4.4	5.9	0.59	0.71	0.471	2.41	51.37	0.45	1.91	65.2	0.97	0.80	68.6	0.95	0.74
8	3.9	9.1	0.65	0.78	0.837	1.91	52.37	2.00	0.77	54.8	0.98	0.90	56.3	0.98	0.83
9	6.0	10.0	0.55	0.66	0.403	2.73	60.50	1.27	1.10	80.6	0.97	0.78	86.4	0.96	0.60
10	8.2	14.2	0.42	0.51	0.333	2.14	47.11	2.51	0.72	63.0	0.99	0.80	65.5	0.99	0.69
11	2.0	17.0	0.66	0.80	1.910	6.46	653.60	9.24	1.13	67.8	0.98	0.89	66.9	0.98	0.87
12	9.9	12.4	0.44	0.53	0.210	4.92	64.45	0.01	0.67	72.7	0.98	0.74	74.4	0.96	0.45
Mean ± SD	5.4 ± 2.4	8.4 ± 4.7	0.54 ± 0.14	0.65 ± 0.17					1.20 ± 0.50						

[a] Model A, Hybrid two-compartment open model, simultaneous linear and capacity-limited disposition kinetics.
[b] Model B, Two-compartment open model, linear disposition kinetics.

TABLE 2. Characteristics of volunteers

Patient no.	Age (yr)	Wt (kg)	Ht (cm)	Serum albumin (g/dl)	Dose (mg)	Injury duration (yr)	Injury level
1	45	61.4	180.3	3.9	450	20	T_2
2	26	63.6	180.3	4.2	475	2	C_5
3	52	48.7	175.3	3.5	375	32	T_{12}
4	44	71.8	172.7	3.1	550	18	C_6
5	35	68.2	182.9	3.4	500	4	C_6
6	38	63.6	188.0	3.4	475	15	T_{12}
7	27	61.1	175.3	3.3	450	3	T_{12}
8	60	84.8	180.3	4.0	650	18	T_9
9	53	72.6	182.9	3.8	550	23	T_2
10	45	98.2	177.8	3.8	750	22	C_4
11	66	95.5	188.0	2.8	725	38	T_{10}
12	41	78.7	182.9	3.7	600	16	C_5
Mean ± SD	44 ± 12	72.4 ± 14.7	180.6 ± 4.8	3.6 ± 0.4	508 ± 184	18 ± 11	

ratio of AUC_{IF} to AUC_s (TPI), as we have defined it, is therefore an unreliable index of amikacin penetration into tissue.

Amikacin binding to serum protein was determined at four concentrations in patients with SCI by using an ultrafiltration technique. The mean and median amikacin binding values were 17.5 ± 8.6 and 17.1%, respectively. These values did not covary with amikacin concentrations in serum ($P > 0.05$). The mean serum albumin concentration in our study population was 3.58 ± 0.40 g/dl (Table 2). The relationship between free and total amikacin concentrations was linear over the range of amikacin concentrations in serum (3.4 to 74.0 μg/ml) and was described by the regression line $y = 0.76x + 0.93$ ($r = 0.98$, $n = 42$), where y is the concentration of free (unbound) amikacin and x is the total concentration of amikacin in serum.

Amikacin protein binding also was studied in artificial IF. Free and total amikacin levels were measured (20 replicates) at each of four amikacin concentrations (7.5, 12.0, 15.0, and 20.0 μg/ml). In the artificial IF formulated by using an ultrafiltrate of plasma as the diluent, the median and mean protein binding values of amikacin were both 4.8% (range, 0 to 12.2%). No statistically significant difference in protein binding was observed between concentrations of amikacin in artificial IF. Values for the fraction of free amikacin in artificial IF (f_{IF}) were then used to calculate (equation 1) the apparent volume of a second compartment (V_{IF}).

Significant correlations between the neurological level of an SCI or the duration of an injury and pharmacokinetic parameters were sought. Only a weak inverse association between the neurological level of injury and TPI ($r = -0.60$, $P = 0.05$) or AUC_{IF} ($r = 0.51$, $P = 0.09$) was demonstrated.

DISCUSSION

A major determinant of in vivo therapeutic response to aminoglycosides in able-bodied patients is the concentration of antibiotic at the site of infection. Presumably, this same determinant of efficacy is operative in patients with SCI, although the literature about this special population offers little to support this inference. Measurements of amikacin concentrations in the IF that transports antibiotics to the site of an infection in humans with SCI have not been reported. Patients with SCI are characterized by an expanded extravascular volume (22, 34) and altered aminoglycoside pharmacokinetics (41–43); hence, characterization of the time courses of amikacin concentrations in extravascular spaces would be particularly valuable in establishing pharmacokinetic criteria for optimizing therapy.

Accumulation and disposition of drugs in extravascular spaces have conventionally been described by using serum time-concentration data and linear compartmental models. This approach can provide an acceptable fit of experimental results. In general, however, such models tend to oversimplify in vivo phenomena (21, 29, 46, 47) and fail to account for nonlinear pharmacokinetic behavior. Our data suggest that the nonlinear processes that influence the disposition of highly protein-bound drugs should also be anticipated for poorly protein-bound antibiotics, such as amikacin (26).

In our patients, measurement of the concentration of amikacin in IF in contact with pressure sores demonstrated that the time course of amikacin concentrations in IF did not parallel amikacin levels in serum and was not accurately described by linear disposition processes (Fig. 2). Hence, we felt justified in proposing a simulation of amikacin pharmacokinetic behavior in serum and tissue that incorporated nonlinear disposition kinetics. Our findings based on this approach suggested that in patients with SCI, population-specific predictions of amikacin pharmacokinetics should not be based on parameters estimated by models which do not account for capacity-limited kinetics or which rely solely upon time-concentration data obtained from levels in serum.

Studies of the time course of antibiotic concentrations in IF have used techniques which several researchers have concluded do not accurately quantitate drug concentrations or correctly simulate disposition kinetics (16, 18, 25, 48). In general, these methods appear to describe pharmacokinetic behavior in inflammatory exudates, tissue homogenates, or unidentifiable deep compartments and probably do not reflect antibiotic disposition in IF. In addition, few studies of antibiotic disposition in IF have incorporated corrections for contamination by blood, although this is a significant source of error that is invariably associated with overestimates of antibiotic concentrations (25, 33, 48). Clinical judgments based on experimental results obtained in this manner can be inaccurate and misleading. By using corrected data, we were unable to demonstrate significant differences between concentrations of amikacin in control tapes and those in tapes adjacent to wounds. Figure 1 displays the time course of combined data on amikacin in serum and in IF (mean concentrations, wound plus control tapes) for all of the subjects studied.

IF may be conceived of as dilute plasma (10, 23) with few

of the physicochemical properties of the protein-rich exudates or of the blood- and protein-rich purees of tissue which many investigators have assayed. Subcutaneous implantation of standardized cotton tapes appears to provide an accurate, interpretable technique for sampling true IF (24, 37) in patients with SCI and avoiding the pitfalls associated with methods using skin windows, suction blisters, implantable capsules, or whole-tissue homogenates.

The persistence of amikacin in tissue has previously been demonstrated in humans and animals. Although delayed aminoglycoside elimination from tissue has been observed by other investigators (6, 8, 31, 38), a direct comparison of results is difficult because of differences in study protocols and extravascular fluid or tissue sampling techniques. The prolonged elimination of amikacin from IF observed in each of our volunteers could not have been demonstrated had we monitored amikacin disposition in IF over truncated study periods (2, 29). A period of 1.5 half-lives is generally considered the minimum interval over which blood should be sampled to describe adequately the pharmacokinetics of a one-compartment model following a single intravenous dose. Most prior studies of amikacin in IF monitored the time-concentration profile over periods which barely approximated two elimination half-lives ($\leq$6 h).

The serum protein binding of amikacin in patients with SCI (17%) did not appear to differ significantly from binding observed in able-bodied populations (range, 3.6 to 21.8%) (27, 49). The maximum concentration of amikacin in IF was attained rapidly, and the configuration of the IF time-concentration curve suggested that a saturable process governed amikacin disposition. Indeed, the linear correlation coefficients were largest and the coefficients of variation of individually estimated pharmacokinetic parameters and model AICs were smallest when capacity-limited disposition was used to describe amikacin transfer between compartments (Table 1). Rapid, extensive tissue binding and sequestration in the expanded extravascular albumin pool characteristic of patients with SCI (32) could partially explain the apparent nonlinear disposition of amikacin.

The absence of a strong association between pharmacokinetic parameters and the neurological level of injury in our study population makes the validity of any inference problematic. Nevertheless, we have previously observed similar trends (41). These trends reflect a probable association between the level of neurological injury and the pharmacokinetic behavior of drugs in a special population in which diminished amikacin efficacy and a potential for toxicity may be anticipated. The validity of these associations, however, must be tested and corroborated in larger populations of patients.

The expanded albumin-rich extravascular fluid space characteristic of patients with SCI (32) can be anticipated to sequester amikacin, thereby significantly increasing the time during which organs particularly susceptible to aminoglycosides are exposed to potentially toxic concentrations (1). Although the persistence of amikacin in tissue may be associated with a therapeutic advantage in terms of an enhanced postantibiotic effect, sustained low concentrations of amikacin may facilitate the emergence of bacterial resistance. Renal impairment and ototoxicity, only poorly predicted by the conventional interpretation of peak and trough amikacin concentrations, can be more effectively detected and prevented when risk is assessed in terms of the magnitude and duration of target organ exposure.

In humans with SCI, accurate characterization of the pharmacokinetic behavior of amikacin in contact with foci of infection requires a method that measures amikacin in IF, estimates amikacin binding in IF, and incorporates a model that has the capacity to simulate nonlinear disposition processes. In conjunction with measurements of the in vivo effectiveness of amikacin, e.g., MIC, the simulation that we have proposed may be useful in developing models which reflect both the pharmacokinetic profile of amikacin in IF and measurements of in vivo effectiveness in patients with SCI. This approach can be applied to the design of individualized dosing regimens which reflect pharmacokinetic behavior and optimally influence the in vivo effectiveness of amikacin at a site of infection (30, 39).

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