ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 1997, p. 2597–2601 Vol. 41, No. 12
0066-4804/97/$04.00+0

Administration of Aminoglycosides to Hemodialysis Patients Immediately before Dialysis: a New Dosing Modality

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Received 12 November 1996/Returned for modification 1 July 1997/Accepted 30 August 1997

We describe a new modality for administering aminoglycosides to hemodialysis (HD) patients, namely, a modification of the once-daily regimen which consists of administering the aminoglycosides over 60 min by drip infusion just before each HD session, with a preplanned peak concentration being reached at the beginning of the session and then with a rapidly decreasing concentration being achieved by the start of HD. The area under the concentration-time curve (AUC), i.e., the accumulation of the drug in the body, is thus minimized by this modality. Arbekacin (ABK) was given at a dose of 2 mg/kg of body weight to 10 HD patients infected with methicillin-resistant *Staphylococcus aureus* (MRSA) for 2 weeks (six sessions in total), resulting in the complete disappearance of MRSA in 5 patients. A high rate of elimination of ABK was attained for each patient while the patient was on HD (range, 0.20 to 0.42 h^{-1}; mean 0.28 ± 0.08 h^{-1}) by using high-performance dialyzers provided with membranes made of either polymethylmethacrylate, cellulose triacetate (CTA), or ethylene vinyl alcohol. The best results were obtained with the CTA membrane, as revealed by the overall mass transfer coefficient (K_o). The AUC in the simulation model for the variation in the serum ABK concentration in this modality was calculated to be 40% of that of the conventional post-HD dosing modality, suggesting that a much higher dose could be administered to HD patients who receive HD thrice weekly (4 h per session), giving, e.g., 4 mg/kg initially and before the HD sessions, when there is an interval of 68 h from HD session to HD session, and giving 2 mg/kg before the other sessions.

The concept of once-daily aminoglycoside dosing is based mainly on the short time- and concentration-dependent bactericidal activity of this drug. As for variations in the concentration of the drug in blood during treatment, it is advisable to attain a high peak level of short duration and a possibly low or undetectable trough level once daily (or once every other day). The higher the peak of the serum aminoglycoside concentration, the greater the antibacterial efficacy will be and the larger the area under the serum time-concentration curve (AUC) will be. The greater the AUC, the greater the accumulation of the drug in the body and the more severe the adverse effects of these drugs may be. Therefore, keeping the trough level in serum as low as possible, even undetectable, is crucial, because this translates into a reduced AUC (6, 10, 14). Due to marked accumulation of the drug, the AUC tends to be large in hemodialysis (HD) patients.

Our aim was to obtain the highest possible peak concentration and thereby reduce the AUC (to minimize systemic accumulation of the drug) by administering the aminoglycoside just before HD, based on the fact that aminoglycosides are well dialyzed because they are readily soluble in water, have a molecular mass of 700 Da or less, and show a low level of protein binding.

MATERIALS AND METHODS

The subjects in the study were 10 patients (5 men and 5 women) with chronic renal failure whose ages ranged from 49 to 79 years (mean, 69 ± 8 years) and whose dry weights ranged from 35 to 57 kg (mean, 44 ± 7 kg). Dry weight is an important concept in HD treatment and is defined as the weight at which the patient is normotensive and free of edema and is the target goal that determines the amount of fluid to be removed during the dialysis session (4). In this study, patients with massive fluid retention or sepsis were excluded. All patients were anuric, were undergoing HD three times a week, and had developed bronchitis and/or pneumonia as the first or second complication in the course of treatment. Methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated from sputum specimens from all 10 patients (Table 1).

Written informed consent was obtained from all patients or from their closest relatives, and the study protocol was approved by the Ethical Committee of Hidaka Hospital.

Arbekacin (ABK) [1-*N*-(*S*)-4 amino-2-hydroxybutyryl dibekacin] is a new semisynthetic aminoglycoside obtained by acylation of dibekacin (11), which is readily soluble in water, has a molecular mass of 552.624 Da, and shows a low protein-bound ratio (3 to 12%). In patients with normal renal function, the half-life ($t_{1/2}$) of ABK is 2.1 h and the volume of distribution (V) is 0.25 to 0.38 liters/kg (5).

ABK is effective against both gram-positive and gram-negative bacteria, as well as against almost all MRSA isolates (2, 8, 9). In Japan, the maximal approved dosage of ABK for an adult patient is 200 mg per day, which corresponds to 4 mg/kg of body weight.

Administration of ABK and HD prescription. All 10 patients were administered ABK just before HD six times in 2 weeks. Because the elimination rate of ABK during HD was an unknown factor, we aimed for a peak level of 6 to 10 μg/ml and the lowest trough level that could possibly be attained, as suggested by previous reports on HD patients receiving other aminoglycosides (3, 7). Consequently, the dose of ABK chosen was 2 mg per kg of body weight (dry weight) on the basis of the data of Fillastre et al. (5) (V = 0.32 liters/kg).

ABK sulfate was dissolved in 100 ml of saline and was administered by means of an infusion pump within exactly 60 min; the amount remaining in the infusion line was measured to calculate the actual dose.

We did not change the basic dialysis regimen prescribed for each patient; i.e., the dialyzer, blood flow rate (QB), ultrafiltration rate, the amount of dialysate delivered by a single pass of the system at a flow rate of 500 ml/min, and the time per session (4 h) were the same as usual. Three types of membrane materials, all of which were high-flux and/or high-efficiency dialyzers, were used, namely, polymethylmethacrylate (PMMA; BK0.8U and BK1.2U; Toray Industries Inc., Tokyo, Japan), cellulose triacetate (CTA; FB70U, FB90U, and FB130U; Nissho

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Corporation, Osaka, Japan), and ethylene vinyl alcohol (EVAL; KF201C800 and KF201C1200; Kawasumi Laboratories Inc., Tokyo, Japan) (Table 2).

Sputum specimens were examined for MRSA once a week from the beginning of treatment for 6 weeks.

Pharmacokinetic studies. The pharmacokinetic parameters of ABK during HD were determined at the time of the first dialysis session for all patients. The pharmacokinetic parameters of ABK while the patients were not on HD were determined before the start of this study on interdialysis days 2 weeks before the start of treatment with ABK for five patients (patients 1, 3, 4, 8, and 10) who were administered the same dose used in the study of pharmacokinetic parameters during HD. One patient (patient 6) agreed to monitoring of the drug concentration in serum throughout the course of treatment.

Collection of samples. At the time of the first dialysis session, blood samples were drawn at the beginning of drug administration (time, −1 h) and at the end of drug administration, when dialysis began (time zero). At 3 to 5 min after the start of dialysis, samples were drawn from the arterial and venous ends of the dialyzer; thereafter, samples were drawn at 1, 2, 3, and 4 h. During this process, the hematocrit was also determined each time by using the blood sample from the arterial end of the dialyzer.

On the interdialysis days, that is, between two sessions, with a 72-h interval from session to session, blood samples were drawn before drug administration and then at 30 min and 1, 2, 3, 4, 8, 12, 24, 48, and 72 h after the beginning of the infusion.

In the patient in whom the levels of the drug in plasma were being monitored throughout the course of treatment, samples were drawn at the beginning of each dosing, at the end of dosing, and at the end of the dialysis session from the second until the last dialysis sessions. Sera were separated by centrifugation and were stored at −20°C until they were assayed.

Determination of serum ABK concentrations. The serum ABK concentration was determined by high-performance liquid chromatography (HPLC) with an LC-10A system analyzer (Shimadzu, Kyoto Japan) and an Inertsil ODS-2,5 μ column (4.6 by 150 mm; GL Science, Osaka) by the postlabeling method.

The coefficient of variation for HPLC in the determination of ABK levels in human serum were found to be 2.7 to 3.8%. The limit of sensitivity of HPLC with serum was 0.2 μg/ml. A good linear relationship was found between HPLC and the microbiological assay when *Bacillus subtilis* ATCC 6633 was used as the test strain, as follows: concentration of HPLC = 0.995 × (concentration of microbiological assay) 0.8 ($n = 55$; $r = 0.956$; $P < 0.001$).

None of the antibiotic agents coadministered to our patients was labeled; therefore, none of them interfered with the determination of serum ABK concentrations (Table 1).

The pharmacokinetic analysis was described by the standard one-compartment model. The parameters theoretical peak serum level of the drug in serum (C_{max}), elimination rate constant (K_d while on HD; K_i while off HD), elimination $t_{1/2}$ ($t_{1/2}$ while on HD and off HD), apparent V, and total body clearance (CL) while on HD were calculated by the semilogarithmic plot method and the least-squares regression technique. AUC was calculated by the trapezoidal method (in simulation and in continuous monitoring). The clearance of ABK from the dialyzer was calculated by the standard blood side determination formula: ABK clearance of the dialyzer = $[A(\text{ABK}) - V(\text{ABK})/A(\text{ABK})] \times \text{QB}(1 - \text{Hct} \times 1/100)$, where A(ABK) and V(ABK) are the concentrations of ABK at the inlet and outlet, respectively; QB is the blood flow rate of the blood pump; and Hct is the hematocrit reading (in percent) obtained at the inlet of the dialyzer. In order to assess the clearance of the dialyzers by the same standards, the overall mass transfer coefficient (K_o), which represents the efficacy of solute transport by diffusion and which is specific to the membrane material, was calculated by a simulation analysis for each of the three types of dialyzer membrane materials (12, 13) (see the Appendix).

Simulations. By using the mean values of V, K_d, and K_i, obtained in the process described above, the patterns of variations in the serum ABK level when the drug is administered either just before the HD session or after the HD session was simulated. An ABK treatment schedule for HD patients who receive HD thrice weekly at 4 h per HD session was simulated on the basis of the overlying principle from the graph, assuming that the duration of treatment is 4 weeks and that ABK is administered to them three times a week, wherein each parameter described above was assumed to be constant and the targeting AUC method of Begg et al. (3) was taken into consideration.

RESULTS

In five patients (patients 1, 2, 6, 7, and 8) sputum cultures became negative within the second week of treatment and remained negative during the follow-up period. In patients 4, 9, and 10, a second course of treatment at a dose of 3 mg/kg was attempted, wherein the cultures of sputum from one patient (patient 9) became negative in the second week of treatment, but one patient (patient 4) died of aspiration pneumonia and another patient (patient 10) died due to sepsis; bacterial eradication could not be determined in these patients. In pa-

TABLE 1. Background, treatment, and outcomes for all patients who participated in this study

Patient no.	Sex[a]	Age (yr)	Body wt (kg)[b]	Underlying disease	Complications	Other antibiotic(s)	Bacterial eradication	Outcome
1	M	73	55	Nephrosclerosis	Acute cholecystitis pneumonia	Piperacillin, sulfamethoxazole trimethoprim	Successful	Alive
2	F	75	40	Nephrosclerosis	Bronchitis		Successful	Alive
3	M	49	45	Diabetic nephropathy	Myocardial infarction, pneumonia	Minocycline		Died due to a second acute myocardial infarction (dropout)
4	M	68	40	Diabetic nephropathy	Intracerebral hemorrhage, bronchitis	Lomefloxacin, aztreonam		Increased the dose to 3 mg/kg; died of aspiration pneumonia
5	F	79	38	Diabetic nephropathy	Intracerebral hemorrhage, bronchitis	Ceftazidime, clindamycin		Changed drug to vancomycin and fosfomycin; died of aspiration pneumonia
6	M	65	57	Multiple myeloma	Bronchitis		Successful	Alive
7	M	68	46	Diabetic nephropathy	Bronchitis		Successful	Alive
8	F	73	35	Glomerulonephritis	Acute cholecystitis, bronchitis	Piperacillin, ceftazidime	Successful	Alive
9	F	63	48	Glomerulonephritis	Intracerebral hemorrhage, bronchitis	Minocycline		Increased the dose to 3 mg/kg; sputum cultures became negative; alive
10	F	73	40	Nephrosclerosis	Acute cholangitis bronchitis	Piperacillin		Increased the dose to 3 mg/kg; died due to sepsis
Mean ± SD		69 ± 8	44 ± 7					

[a] M, male; F, female.
[b] Corresponds to dry weight (see text).

TABLE 2. Dialysis prescription and pharmacokinetic data

Patient no.	Dialysis prescription				Pharmacokinetic data								
	Dialyzer		QB (ml/min)	Water removed (kg)	Dose per kg[a]	C_{max} (μg/ml)	Elimination rate constant (h^{-1})		$t_{1/2}$ (h)		V (liter/kg)	CL on HD (ml/min)	CL of ABK by dialyzer (ml/min)
	Membrane material	Surface area (m^2)					On HD (K_d)	Off HD (K_i)	On HD	Off HD			
1	PMMA	1.2	160	0.5	1.47	5.1	0.30	0.015	2.3	47	0.29	80	60
2	PMMA	0.8	150	1.7	1.92	5.2	0.24		2.9		0.37	59	41
3	CTA	0.9	130	2.2	1.60	5.3	0.32	0.020	2.2	34	0.30	72	53
4	CTA	0.9	150	1.0	1.85	6.4	0.42	0.014	1.7	51	0.29	80	68
5	CTA	0.7	100	2.0	1.96	5.2	0.23		3.0		0.38	55	47
6	CTA	1.3	150	3.2	1.64	5.8	0.35		2.0		0.28	93	83
7	EVAL	1.2	185	3.0	1.91	6.2	0.26		2.7		0.31	61	55
8	EVAL	0.8	120	1.6	1.80	5.5	0.23	0.020	3.0	34	0.32	44	41
9	EVAL	0.8	155	0.3	1.92	7.4	0.22		3.2		0.26	46	44
10	EVAL	0.8	90	1.2	1.96	6.0	0.20	0.016	3.5	43	0.32	43	34
Mean		0.9	139	1.7	1.80	5.8	0.28	0.017	2.6	42	0.31	63	52
SD		0.2	29	1.0	0.17	0.7	0.07	0.003	0.6	8	0.04	17	15

[a] Refers to dry weight.

tient 5, the drug was changed from ABK to vancomycin (10 mg/kg thrice weekly) with concomitant use of fosfomycin (10 mg/kg thrice weekly); however, the patient died of aspiration pneumonia in the third week of treatment and bacterial eradication could not be accurately assessed. Another patient (patient 3) died of a second acute myocardial infarction during treatment with ABK (Table 1).

The values of the pharmacokinetic parameters and the CL of ABK by the dialyzers are given in Table 2. For the dosage actually given (mean, 1.8 ± 0.17 mg/kg; range 1.47 to 1.96 mg/kg), the value of each parameter was averaged, as follows: C_{max}, 5.8 ± 0.7 μg/ml; K_d, 0.28 ± 0.07 h^{-1}; K_i, 0.017 ± 0.003 h^{-1}; $t_{1/2}$ on HD, 2.6 ± 0.6 h; $t_{1/2}$ off HD, 42 ± 8 h; V, 0.31 ± 0.04 liters/kg; CL while on HD, 63 ± 17 ml/min; and CL of ABK by the dialyzer, 52 ± 15 ml/min. The CL of ABK by the dialyzer tended to be dependent on the blood flow rate and the surface area of the dialyzer. Of the three types of dialyzers used, those that used a CTA membrane appeared to be the

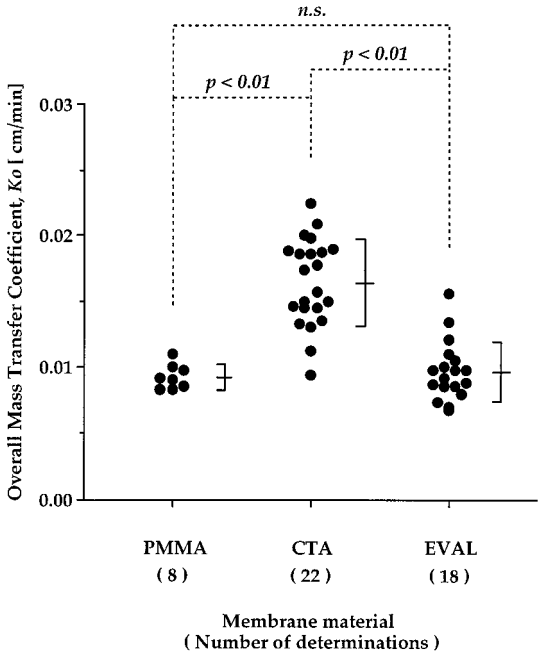

FIG. 1. The K_o for each of the three types of dialyzer membrane materials calculated as follows: for PMMA, $9.3 \times 10^{-3} \pm 0.96 \times 10^{-3}$ cm/min (range, 8.3×10^{-3} to 1.1×10^{-2} cm/min; $n = 8$); for CTA, $1.6 \times 10^{-2} \pm 0.33 \times 10^{-2}$ cm/min (range, 9.4×10^{-3} to 2.2×10^{-2} cm/min; $n = 22$); for EVAL, $9.7 \times 10^{-3} \pm 2.2 \times 10^{-3}$ cm/min (range, 6.8×10^{-3} to 1.6×10^{-2} cm/min; $n = 18$). The K_o for CTA was greater than the K_o for PMMA and the K_o for EVAL. *, $P < 0.01$ (Student's t test); n.s., not significant.

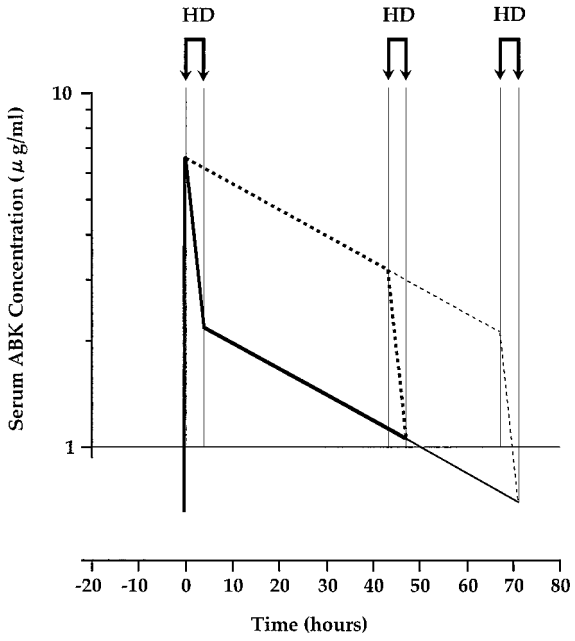

FIG. 2. Patterns of variation in serum ABK concentrations when administered according to two different modalities, modality I (——) and modality II (– – –; conventional modality). The pharmacokinetic parameters used here are the mean values given in Table 2.

TABLE 3. Simulations of the variations (predictable range) of C_{max}, trough level, and AUC when ABK is administered either just before the HD session (modality I) or after the HD session (modality II)[a]

Dose (mg/kg)	C_{max} range (μg/ml)	Trough level range (μg/ml)		AUC range (μg · h/ml)			
				Modality I		Modality II	
		48 h	72 h	48 h	72 h	48 h	72 h
2[b]	8.9–13.1 (6.6)	1.4–2.1 (1.1)	1.1–1.4 (0.7)	117–165 (86)	165–216 (107)	288–404 (213)	417–545 (272)
4, 2, 4[c]	11.2–20.4	1.8–2.2	1.4–2.2	148–183	214–334	363–450	545–846

[a] Duration of treatment, 4 weeks.
[b] 2 mg/kg was given every time. Values in parentheses correspond to the values obtained after single (initial) dosing.
[c] The values 4, 2, 4 mg/kg correspond to giving 4 mg/kg initially and before the HD sessions when there is a 3-day (68 h in reality) interval from HD session to HD session and giving 2 mg/kg before the other sessions.

best (Table 2). The K_o of CTA was the highest among the three types of dialyzers (CTA > PMMA, EVAL; $P < 0.01$) (Fig. 1).

In the simulation of single dosing by converting the given dose to 2 mg/kg, the patterns of variations in the serum ABK level after administration according to two modalities were drawn as semilogarithmic graphs: modality I was when ABK was administered just before HD session, and modality II was when ABK was administered just after the HD session (the conventional modality for HD patients) (Fig. 2).

The value for each parameter was calculated, and the values were as follows: C_{max}, 6.6 μg/ml; trough level, 1.1 μg/ml (at 48 h) or 0.7 μg/ml (at 72 h); AUC, 86 μg · h/ml (at 48 h) or 107 μg · h/ml (at 72 h). Thus, the AUC in the case of modality I was 40% of that of the AUC by the conventional modality, modality II, which was calculated to be 213 μg · h/ml (at 48 h) or 272 μg · h/ml (at 72 h).

In clinical practice, when ABK is administered to HD patients three times a week, accumulation of drug occurs after the initial dosing; therefore, the value of each parameter becomes higher after the subsequent dosings. When drug is administered, for example, for 4 weeks, the values of the pharmacokinetic parameters after the second administration were estimated to be as follows: peak levels, mean, 11.8 ± 1.1 μg/ml (range, 8.9 to 13.1 μg/ml); trough levels at 47 h, mean 1.8 ± 0.2 μg/ml (range, 1.4 to 2.1 μg/ml; trough levels at 71 h, mean, 1.3 ± 0.1 μg/ml (range, 1.1 to 1.4 μg/ml); AUC over 0 to 47 h, mean, 151 ± 13 μg · h/ml (range, 117 to 165 μg · h/ml); AUC over 0 to 71 h, mean, 207 ± 16 μg · h/ml (range, 165 to 216) μg · h/ml. The AUCs in case of modality II were estimated to be 370 ± 31 μg · h/ml (range, 288 to 404 μg · h/ml) at 47 h and 524 ± 39 μg · h/ml (range 417 to 545 μg · h/ml) at 71 h. The ratios of the AUCs in modality I/AUCs in modality II were constantly about 40% (Table 3). For the continuously monitored patient, patient 6, the peak and trough levels and AUCs yielded almost the same results (Fig. 3). Likewise, a treatment schedule of 4 weeks at the maximum doses was also simulated, which satisfied the proposal of Begg et al. (3) (AUC at 24 h, 101 μg · h/ml), e.g., administering doses of 4, 2, and 4 mg/kg, i.e., giving 4 mg/kg initially and before the HD sessions when there is 3-day (68 h, in reality) interval from HD session to HD session and giving 2 mg/kg before the other sessions. The values of the parameters in this simulation were estimated to be as follows: peak levels, mean, 15.0 ± 3.2 μg/ml (range, 11.2 to 20.4 μg/ml); trough levels at 47 h, mean, 2.1 ± 0.1 μg/ml (range, 1.8 to 2.2 μg/ml); trough levels at 71 h, mean, 2.0 ± 0.4 μg/ml (range, 1.4 to 2.2 μg/ml); AUC at 47 h, mean, 174 ± 12.1 μg · h/ml (range, 148 to 183 μg · h/ml); AUC at 71 h 301 ± 58 μg · h/ml (range, 214 to 334 μg · h/ml). In the case of modality II, the AUCs become extremely large when drug was administered as doses of 4, 2, and 4 mg/kg as well as 2 mg/kg.

DISCUSSION

The results of treatment were not excellent since MRSA disappeared from only 50% of the patients (55% when the one patient who dropped out is considered). The relatively low disappearance rate might be due in part to a dosing interval that was too long and the use of an antibiotic dose that was probably insufficient.

It may be not practical to reduce the interval between HD sessions by increasing the number of dialysis sessions to more than three times a week for the sake of administering aminoglycosides more frequently, however, it is strongly suggested that a much higher dose be administered to HD patients, because the AUC in the simulation model was calculated to be 40% of that from the conventional post-HD dosing modality.

Our concept involves maximizing the use of HD to control the concentration of aminoglycosides in plasma, thereby attaining high peak levels of short duration and low trough levels, like those observed with the once-daily regimen for patients with creatinine clearances of >20 ml/min (3, 6).

The results obtained in this study and our simulation model

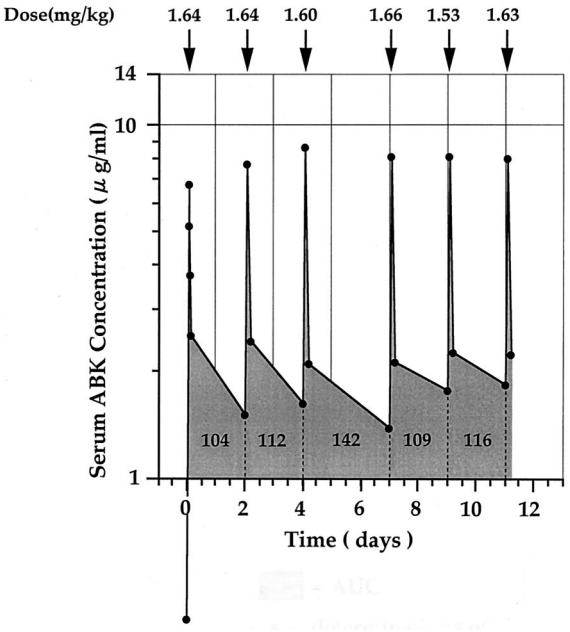

FIG. 3. Results of continuous monitoring of serum ABK concentration in patient 6. The dose actually given and the corresponding dialysis session are indicated on the top of the graph (arrows). Numerals in the shaded area indicate the AUC after each ABK dosing. ●, determinations of serum ABK concentration.

are attributable to improved dialyzers, i.e., high-performance dialyzers. Fillastre et al. (5) reported in 1987 that the $t_{1/2}$ of ABK in serum while patients are on HD was 4.71 h (elimination rate constant, 0.147 h^{-1}). Agarwal and Toto (1) observed that TAF 175 L (a high-efficiency cuprammonium rayon dialyzer) was almost twice as efficient as CD 135 (a conventional saponified cellulose ester dialyzer) at removing gentamicin; the elimination rate constant was 0.263 h^{-1} for TAF 175 L and 0.132 h^{-1} for CD 135.

The aminoglycosides currently available on the market resemble ABK in their pharmacological properties. Our administration modality with high-performance dialyzers will offer several possible future applications for HD patients with the potential for improved efficacy and safety.

ACKNOWLEDGMENTS

We thank H. Nihei and M. Mineshima of the Department of Nephrology of Tokyo Women's Medical College, for useful suggestions and advice; H. Sekiguchi and T. Hoshino, technical staff of the Dialysis Center of Hidaka Hospital; Y. Ogura, chief pharmacist of Hidaka Hospital, for expert assistance; and Johanna Matsuda for correction of the manuscript.

APPENDIX

Estimation of K_o. Solute and fluid transport occurs during a hemodialysis session. When a high-performance dialyzer is used, these factors are expressed, as shown in Fig. A1.

When blood passes through a single hollow fiber, solute volume (Q_B) and solute concentration (C_B) change from Q_{Bi} and C_{Bi} at the inlet to Q_{Bo} and C_{Bo} at the outlet, respectively, of the hollow fiber. Likewise, on the dialysate side, water volume (Q_D) and solute concentration on the dialysate side (C_D) change from Q_{Di} and C_{Di} to Q_{Do} and C_{Do}, respectively. Solutes are transferred across the dialysis membrane by diffusion and bulk flow. The solute transfer rate per unit of longitudinal distance of the dialyzer Δz can be expressed as the combination of mass transfer by diffusion, $K_o \cdot A' \cdot [C_B(z) - C_D(z)] \cdot \Delta z$, and mass transfer by bulk flow, $SC \cdot Q_F' \cdot A' \cdot C_B(z) \cdot \Delta z$, which are expressed by the following ordinary differential equations:

$$\frac{d[Q_B(z) \cdot C_B(z)]}{dz} = \frac{d[Q_D(z) \cdot C_D(z)]}{dz} = -K_o \cdot A'[C_B(z) - C_D(z)] - SC \cdot QF' \cdot A' \cdot C_B(z) \quad \text{(A1)}$$

$$\frac{d[Q_B(z)]}{dz} = \frac{d[Q_D(z)]}{dz} = -Q_F' \cdot A'$$

For boundary conditions (BC):

$$\text{for } z = 0,\ C_B(z) = C_{Bi},\ C_D(z) = C_{Do} \text{ and } Q_B(z) = Q_{Bi},\ Q_D(z) = Q_{Do} \quad \text{(A2)}$$

$$\text{for } z = L,\ C_B(z) = C_{Bo},\ C_D(z) = C_{Di} \text{ and } Q_B(z) = Q_{Bo},\ Q_D(z) = Q_{Di}$$

in which the variable and constants are the distance from the dialyzer inlet (z), overall mass transfer coefficient (K_o), ultrafiltration rate per unit of membrane area (QF'), membrane area per unit longitudinal distance (A'), and sieving coefficient [SC; which is equal to $C_D(z)/C_B(z)$].

In the equations described above, the K_o (in centimeters per minute) represents the efficacy of solute transport by diffusion which is specific to the membrane material.

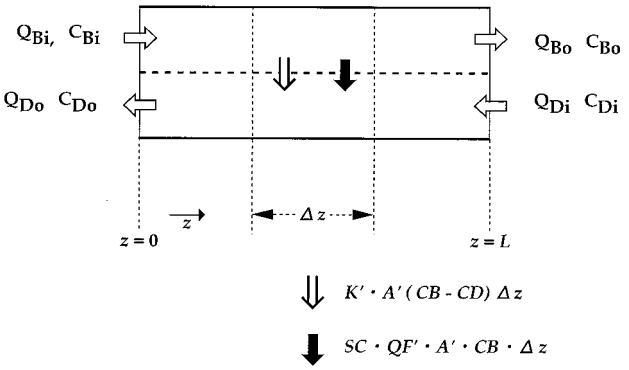

FIG. A1. Model for mass transfer in a high-performance dialyzer. Copied from the work of Sakai and Mineshima (13), with permission of the authors.

Simulation analysis. Because we cannot solve the equations above analytically, they are calculated numerically as a two-point boundary problem by the Runge-Kutta method (for $z = 0$, $C_B = C_{Bi}$; for $z = L$, $C_D = C_{Di}$). If we substitute the appropriate values, such as Q_B, Q_D, ultrafiltration rate, the entire length of dialyzer, and the membrane surface area, which are obtained from individual patients, into equations A1 and A2, the unknown parameter, K_o, can be determined precisely from a simulation analysis on a computer. That is, the input of the postulated value for K_o into the equations is adjusted by an iterative procedure until the best fit for the clinical data is found.

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