Pharmacokinetics of Gentamicin and Kanamycin During Hemodialysis

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The pharmacokinetics of gentamicin, kanamycin, and creatinine were studied in patients undergoing hemodialysis. After intravenous injection of single doses of the drugs, 50 to 60% of the doses of both antibiotics were cleared from the body during a 6-h period; this occurred almost entirely by the hemodialysis process. No correlation was found between the dialysance of the aminoglycosides and creatinine. The pharmacokinetic data were used to make dosage regimen recommendations for treatment of hemodialysis patients with these antibiotics.

Dosage regimens of antibiotics which are eliminated primarily by the kidney must be adjusted in patients with renal failure to prevent accumulation of the drug to toxic body levels. Aids such as nomograms and computer programs are presently available for dosage adjustments of the aminoglycosides in relation to renal function (5, 6, 8, 9, 13, 18, 20). These methods are usually based on relating the half-life of the drug to the serum creatinine concentrations or clearances of patients. However, patients who are undergoing intermittent hemodialysis represent a unique problem in drug therapy. The drug dosage regimen must be adjusted for intermittent periods of time when drug removal may occur by dialysis, in addition to other possible nonrenal mechanisms of drug elimination from the body.

One purpose of this study was to examine the pharmacokinetics of gentamicin and kanamycin in patients undergoing hemodialysis with two types of disposable artificial kidneys, by which the dialysis of these antibiotics has not been studied in detail. The major purpose, however, was to assess whether the elimination rate of the two drugs can be related to the dialysance of creatinine. Such a relationship, if existent, could provide a method for adjusting antibiotic dosage regimens in situations where the plasma concentration of antibiotic cannot be measured directly.

MATERIALS AND METHODS

Patient studies. Eight patients who were undergoing routine, intermittent hemodialysis participated in the study. The glomerular filtration rates of these patients were less than 5 ml/min. Six patients were studied with each antibiotic. The diagnosis, studies performed, drug doses, and other relevant information

concerning each patient are listed in Table 1. None of the patients received any other antibiotics during the study and the usual activities and food intake of the patients were allowed. Informed written consent to participate in the study was obtained from each patient.

Two types of dialyzers were employed: the Cordis Dow Artificial Kidney (Cordis Corp., Miami, Fla.), utilizing a single pass technique with regenerated cellulose hollow fibers; and two brands of single path coil dialyzers with Cuprophan membranes (manufactured by Extracoporeal Medical Specialties, King of Prussia, Pa., and Travenol Labs, Morton Grove, Ill.). Dialysis fluid flow varied between 300 and 500 ml/min. Blood flow through the hemodialyzer was at a normal rate and was measured by the air bubble transfer time.

A single intravenous dose of one of the antibiotics (0.5 mg of gentamicin per kg or 3 mg of kanamycin per kg) was infused (over 1 min) into the venous return of the artificial kidney at approximately 30 min after the start of dialysis. Blood samples were collected from the blood inlet and outlet of the artificial kidney at 0, 0.5, 1, 2, and 4 h after injection of the drug and at the termination of the dialysis procedure. Samples of dialysate fluid were also obtained at 0, 1, and 2 h and at termination of dialysis. Six of the patients had slight renal function. In these, the total urine output during the dialysis period was collected and assayed for drug. At least 1 week was allowed between studies for those patients who received both antibiotics.

Assays. The antibiotic concentrations in plasma, dialysis fluid, and urine were determined microbiologically by the method of Bennett et al. (5). Known concentrations of antibiotic were added to each patient's blank plasma which served as the standard curve for assaying plasma concentration of the antibiotics in the individual patients. The concentration of creatinine was measured in the first and last plasma samples and in the urine and dialysis fluid, by the direct colorimetric method described by Heinegard and Tiderstrom (12).

Pharmacokinetic calculations. The drug and cre-

TABLE 1. *Pathophysiological characteristics and drug studies performed in the hemodialysis patients*

Subject	Diagnosis	Sex	Age (year)	Weight (kg)[a]	Predialysis serum creatinine (mg%)	Hct (%)[a]	Study and dose (mg)	
							Gen-tamicin	Kana-mycin
GC	Polycystic kidneys	M	49	69.0	12.0	37.3	36	
KE	Chronic glomerulone-phritis	F	26	54.0	17.3	11(19.6)	28	150
DG	Chronic glomerulone-phritis	F	43	61.8	17.0	21.5	32	175
BH	Alport's syndrome	M	19	95(97.3)	17.6	17.5	52	300
RH	Chronic glomerulone-phritis	M	26	63.6	16.2	23.1		200
AL	CHF and chronic glo-merulonephritis	M	69	70.5	4.6	27.5	36	
RR	Chronic pyelonephritis	M	47	83.6	13.0	27.7		250
IW	Polycystic kidneys	F	43	61.8	12.7	23.8	32	175

[a] Second number refers to the kanamycin study. The increase in Hct (hematocrit) in patient KE was caused by a blood transfusion.

atinine concentrations were used to determine the respective dialysances of (Cl_D) by using a modified form of the dialysance equation proposed by Wolf et al. (23):

$$Cl_D = [Q_E(C_i - C_o)]/(C_i - C_d) \qquad (1)$$

where C is the drug or creatinine concentration, with the subscripts indicating i for plasma inlet to the artificial kidney, o for plasma outlet from artificial kidney, and d for dialysis fluid. Q_E is the effective plasma flow rate as defined by Jusko et al. (14) as

$$Q_E = Q \cdot (1\text{-Hct}) \cdot (1\text{-}F_b) \qquad (2)$$

where Q is the total blood flow, Hct is the hematocrit, and F_b is the fractional protein binding of the drugs.

For all the patients studied, the drug concentration in the dialysis fluid was negligible and the C_o/C_i ratio appeared to be constant. Equation 1 thus reduces to

$$Cl_D = Q_E \cdot F_E \qquad (3)$$

where F_E is the extraction fraction which is the ratio

$$F_E = (C_i - C_o)/C_i \qquad (4)$$

The pharmacokinetics of both gentamicin and kanamycin can be described with a one-compartment model. The apparent volume of distribution (V_D) was determined from the extrapolated zero-time plasma concentration ($C_p{}^o$) using the equation:

$$V_D = \text{Dose}/C_p{}^o \qquad (5)$$

The half-life ($t\frac{1}{2}$) can be obtained from graphical data which also yields the elimination constant (k_{el}) and the body clearance (Cl_B) from

$$k_{el} = 0.693/t_{\frac{1}{2}} \qquad (6)$$

and

$$Cl_B = k_{el} \cdot V_D \qquad (7)$$

The renal clearance of the drugs (Cl_R), when existent,

was calculated from the 6-h urinary recovery of the drug (X_u) and the 0- to 6-h area under the plasma concentration versus time curve:

$$Cl_R = X_u/\int_0^6 C_p \cdot dt \qquad (8)$$

The latter can be obtained using trapezoidal areas.

These pharmacokinetic parameters were initially estimated graphically as described above. Subsequently, the values of V_D, k_{el}, and Cl_D were obtained more objectively by nonlinear least-square regression using the NONLIN computer program of Metzler (19). This involved simultaneous characterization of the plasma inlet (C_i) and outlet (C_o) concentrations of the antibiotics using the relationships

$$C_i = (\text{Dose}/V_D) \cdot e^{-k_{el} \cdot t} \qquad (9)$$

and

$$C_o = [Cl_D/(1\text{-}Q_E)] \cdot (\text{Dose}/V_D) \cdot e^{-k_{el} \cdot t} \qquad (10)$$

where equation 2 was used to obtain Q_E. In the latter case, experimental patient values of Hct and Q and literature values of F_b (0.25 for gentamicin and 0 for kanamycin) were included in the computer iterations.

RESULTS

The maximal plasma concentration of gentamicin (obtained from arterial blood at 0.5 h after intravenous injection) averaged 2.8 [standard deviation (SD) 0.6] μg/ml, whereas that for kanamycin averaged 14.7 (SD 3.2) μg/ ml. None of the patients demonstrated any adverse effects from the low concentrations of the antibiotics during or after the study period.

Plasma concentrations at various times after intravenous injection of gentamicin and kanamycin in two typical hemodialysis patients are shown in Fig. 1. The data usually showed a monoexponential pattern indicative of first-

order elimination of the antibiotics (equation 9). The plasma concentrations of antibiotic in the artificial kidney outflow were usually about 70 to 80% of the inflow concentrations for both drugs, an extraction fraction of 0.2 to 0.3. The extraction fraction did not appear to change with time which, along with the monoexponential behavior of the elimination curve, allowed characterization of the data using a one-compartment open model.

The pharmacokinetic parameters calculated from the gentamicin and kanamycin data using equations 9 and 10 are presented in Table 2. The apparent volume of distribution for both drugs was approximately 20% of body weight. This agrees well with values obtained previously in studies of patients with normal renal function (8, 16, 20). The clearance values and elimination rate constants were similar for both drugs and for all of the patients studied regardless of other variables present in the system (e.g., type of dialyzers, blood flow rate, pressure). The elimination constant (k_{el}) for gentamicin averaged 0.129 per h and the mean half-life ($t_{1/2}$) was 5.7 h, whereas for kanamycin, similar k_{el} and $t_{1/2}$ values of 0.152 per h and 4.9 h, respectively, were found. The renal clearance of both drugs, when kidney function was present, was usually less than 2 ml/min and did not contribute significantly to the total body clearance of the drugs in these patients.

The total body clearance of gentamicin was similar to the dialysance value. This suggests that gentamicin is eliminated almost entirely by dialysis (except for the slight amount excreted by the kidneys in some patients), with little or no metabolism occurring in these patients. The total body clearance of kanamycin appeared to be slightly greater than the dialysance of the drug. This may be due to either a metabolic-biliary mechanism of elimination of a small part of the dose or may reflect experimental variability in the data.

The dialysis data for the individual patients are summarized in Table 3. The dialysance values for both kanamycin and gentamicin were relatively uniform, as expected from the similarity in chemical nature of the two aminoglycoside antibiotics. However, there was appreciable variability in the dialysance of creatinine. The dialysances of the aminoglycosides are shown in Fig. 2 in relation to the creatinine dialysances in these patients. No correlation was found between the dialysance of creatinine and the antibiotics (r = 0.14 and $P \simeq$ 0.5 for gentamicin; r = 0.30 and $P \simeq$ 0.6 for kanamycin).
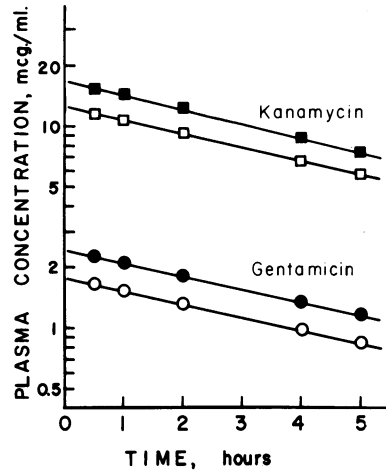

FIG. 1. *Plasma concentrations of gentamicin (circles) and kanamycin (squares) as a function of time after an intravenous injection of 0.5 mg of gentamicin per kg was given to patient IW and 3 mg of kanamycin per kg to patient RH. Closed and open symbols represent arterial (dialysis inlet) and venous (dialysis outlet) plasma concentrations, respectively. All lines were fitted to equations 9 and 10 by computer least-squares regression.*

The calculations of the dialysance of the two drugs are based on literature values for the degree of plasma protein binding. It was assumed that gentamicin was 25% protein bound (8, 21), whereas kanamycin was 0% bound (20). It was recently reported that gentamicin is not bound at all to plasma proteins (11). However, our attempts to measure the binding of gentamicin either by ultrafiltration or dialysis using cellophane membranes were unsuccessful because of the rapid loss or degradation of the antibiotic in the presence of the membrane.

DISCUSSION

Kanamycin and gentamicin are potentially toxic drugs which have proven to be extremely valuable in the treatment of pseudomonas infections. Since these antibiotics are eliminated almost entirely in the urine and there is a high risk of toxicity in patients with renal impairment (2, 22), it would be useful to be able to accurately predict therapeutic plasma concentrations and half-lives of the aminoglycosides in patients with impaired renal function who are undergoing hemodialysis. Knowledge of the dialysance properties is also needed for consideration of hemodialysis in treatment of aminoglycoside overdosages.

The half-lives of gentamicin (5.7 ± 1.0 h) and kanamycin (4.9 ± 1.2 h) found in this study

TABLE 2. *Pharmacokinetic parameters of gentamicin and kanamycin in hemodialysis patients*

Patient	$V_D{}^a$ (liters)	V_D (% body wt)	$k_{el}{}^a$ (per h)	$t_{1/2}$ (h)	Cl_B (ml/min)	Cl_D (ml/min)^a	Cl_R (ml/min)
Gentamicin							
GC	13.2 (0.1)	19.0	0.124 (0.06)	5.6	27.1	30.8 (1.2)	2.0
KE	8.8 (0.6)	16.0	0.125 (0.05)	5.3	35.5	35.5 (3.0)	0
DG	11.0 (0.5)	18.0	0.116 (0.04)	6.0	21.3	31.5 (2.3)	0
BH	14.9 (0.5)	15.6	0.093 (0.05)	7.5	23.0	31.6 (2.0)	0.2
AL	16.8 (0.7)	23.8	0.146 (0.14)	4.8	40.8	29.5 (3.4)	1.1
IW	13.0 (0.7)	21.0	0.147 (0.07)	4.7	31.8	27.8 (2.9)	0.6
Mean		18.9	0.129	5.7	27.1	31.1	
SD		3.1	0.022	1.0	8.2	2.6	
Kanamycin							
KE	11.2 (0.3)	21.1	0.160 (0.05)	4.3	29.8	29.6 (0.0)	0
DG	13.7 (1.8)	22.5	0.236 (0.14)	2.9	53.8	28.1 (8.2)	0
BH	17.8 (0.7)	18.3	0.120 (0.08)	5.8	35.6	24.0 (3.5)	0.39
RH	12.1 (0.7)	19.0	0.155 (0.06)	4.5	31.2	26.2 (3.1)	0.33
RR	18.8 (1.1)	22.5	0.108 (0.14)	6.4	33.8	26.7 (5.3)	1.6
IW	17.2 (0.3)	28.5	0.133 (0.03)	5.2	38.2	30.6 (1.4)	0.7
Mean		22.0	0.152	4.9	37.0	27.5	
SD		3.6	0.046	1.2	8.7	2.4	

^{a} Values in parentheses are the standard deviations of the least-square fitted parameters.

TABLE 3. *Dialysance properties of gentamicin and kanamycin*

Patient	Type of dialyzer	Pressure applied^a	Dialytic blood flow (ml/min)	Extraction fraction	Dialysance (ml/min) Drug (Cl_D)	Creatinine (Cl_c)	Ratio of Cl_D:Cl_c
Gentamicin							
GC	Dow	yes (+)	150	0.44	30.8	53.7	0.56
KE	Coil	no	170	0.31	35.5	55.9	0.63
DG	Dow	yes (−)	190	0.28	31.5	88.7	0.36
BH	Dow	yes (−)	175	0.29	31.6	99.6	0.32
AL	Coil	no	140	0.39	29.5	44.0	0.67
IW	Coil	no	170	0.29	27.8	85.4	0.33
Mean				0.33	31.1	71.2	0.48
SD				0.07	2.6	22.8	0.16
Kanamycin							
KE	Coil	no	140	0.26	29.6	74.5	0.40
DG	Dow	yes (−)	180	0.22	28.1	86.7	0.32
BH	Coil	no	150	0.20	24.0	55.4	0.43
RH	Coil	no	140	0.25	26.2	85.2	0.30
RR	Dow	yes (−)	170	0.22	26.6	109.2	0.24
IW	Coil	no	170	0.23	30.6	85.8	0.35
Mean				0.23	27.5	82.8	0.34
SD				0.02	2.4	17.6	0.07

^{a} The Dow Artifical Kidney allows variable water and solute ultrafiltration by application of negative or positive pressure across the dialysis membrane.

correlate well with other reports of half-lives of the aminoglycosides during hemodialysis. In studies which employed the Kiil dialyzer, approximately 70 to 80% of both kanamycin and gentamicin were removed during a 12-h dialysis (1, 16). Cutler et al. (8) also found 50% removal of gentamicin from the body during a 6- to 8-h period of hemodialysis (the type of dialyzer was not specified). The pharmacokinetics of the aminoglycosides during hemodialysis on machines other than the Kiil have not been thoroughly investigated. Because of differences in the structure and mechanism of the various types of artificial kidneys, it is proper and

necessary to check the dialysance of the aminoglycosides and other toxic drugs in each of the various dialyzers which are in clinical use.

No relationship was found between the dialysances of the aminoglycosides and creatinine. This finding differs from the observations of one other study (21), whereas the range of drug-creatinine dialysance ratios (0.3 to 0.6) found in the present study is similar to that obtained in two other investigations. Riff and Jackson (21) found the dialysance of gentamicin to be 60% of that of creatinine in five patients treated with a Kolff-type single coil dialyzer. However, the method used to calculate the dialysance values was not stated. Christopher et al. (7), using a Kiil dialyzer, found gentamicin dialysance of 24 (SD 0.6) ml/min and a creatinine dialysance of 77 (SD 22) ml/min (for a ratio of about 0.31). These values are similar to our average dialysance values (gentamicin = 31.1 ml/min and creatinine = 71.2 ml/min) and their variability is also consistent with our data (Fig. 2).

In comparing literature reports of drug and creatinine dialysance values, the method of calculation which was employed is an important consideration. A proper dialysance equation requires use of an effective blood flow which is corrected for the patient's hematocrit and degree of drug binding to proteins. These factors account for the amount of drug in the blood which is not readily diffusible during hemodialysis. Falsely elevated dialysance values will be obtained if the total blood flow rate is used instead of the effective blood flow (Q_E). For example, if total blood flow had been used in the present study, the dialysance values generated would exceed the body clearance of the drugs, a physiologic and pharmacokinetic impossibility. Some equations in the current literature do not employ this type of correction factor (18; B. A. Halpren, N. S. Coplon, and S. G. Axline, Prog. Abstr. Intersci. Conf. Antimicrob. Ag. Chemother., 13th, Washington D.C., Abstr. 59, 1973) and the dialysance values thus obtained will overestimate the true removal rate of the drug from the body. {If the drug is taken up in appreciable quantities by the erythrocytes and released during hemodialysis, then the dialysance equations should employ the total blood flow to reflect the actual clearance of the drug. However, then the whole blood concentrations must also be used to calculate dialysance: $Cl_D = Q [1 - (C_{Bo}/C_{Bi})]$, where C_{Bi} and C_{Bo} are the inlet and outlet whole blood concentrations. This equation, proposed by Gaylor (10), does not correct for plasma protein binding of the drug, a further complicating factor. In the case of gentamicin, the red cell concentration is only
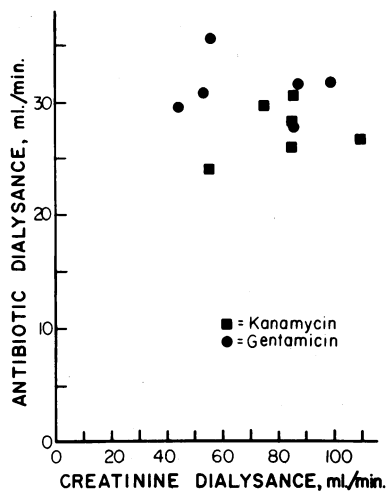

FIG. 2. Relationship between the dialysance of creatinine and gentamicin (circles) and kanamycin (squares) in the individual patients.

about 10% of that in plasma (21), and thus it is necessary to account only for plasma extraction of the antibiotic.}

In considering the basic physicochemical mechanism of hemodialysis, it is not unexpected that there is little direct correlation between aminoglycoside and creatinine dialysances in individual patients. Both kanamycin (molecular weight 582) and gentamicin (molecular weight 518) fall into the molecular weight classification of middle molecules (compounds with a molecular weight range of 300 to 2,000). It has been found (3) that the dialysance of middle molecules is more dependent upon the membrane surface area rather than dialysate flow (at rates above 200 ml/min) and blood flow, whereas the dialysance of smaller molecules such as creatinine (molecular weight 113) is more directly dependent upon blood and dialysate flow rates. Thus, based on these considerations, it is expected that creatinine removal during hemodialysis will vary according to individual patient parameters and may change during a dialysis period due to alterations in flow rates or applications of negative pressure (as is possible with the Cordis-Dow hollow fiber kidney). However, aminoglycoside dialysance should remain less affected by changes in hemodynamics since middle molecule clearance should be relatively constant in all patients using the same type of dialysis equipment. This behavior appears to account for our experimental findings.

If the membrane surface area differs among the various types of dialysis equipment, there should be a corresponding difference in the

dialysance of the aminoglycosides. Indeed, one study comparing four different types of dialyzers showed an appreciable difference in the dialysance of gentamicin from the various machines (Halpren et al., Prog. Abstr. Intersci. Conf. Antimicrob. Ag. Chemother., 13th, Washington D.C., Abstr. 59, 1973). This was not found in our study where the two types of dialyzers did differ in surface area (Cordis-Dow = 1.2 m², the single-coil dialyzers = 0.7 and 0.84 m²). The lack of difference between machines may be related to the small number of patients studied on each dialyzer.

From the data presented in this study, it appears that measurements of creatinine dialysance cannot be used to accurately estimate the elimination rate of gentamicin and kanamycin. Therefore, general recommendations of dosage schedules of these antibiotics must be made based on the observed half-lives of the drugs. The half-lives of gentamicin and kanamycin were fairly similar in all of the patients of this study which facilitates this estimation.

From previous pharmacokinetic studies of patients with impaired renal function (6, 8, 16), and from the small metabolic clearance values found in the present study, it can be assumed that an essentially anephric patient will have a $t_{1/2}$ of 30 to 60 h for gentamicin during the intervals between hemodialysis periods. From similar studies done with kanamycin, it can be estimated that the $t_{1/2}$ of kanamycin will be 24 to 48 h between dialysis periods (1, 20). It is evident that there is wide variability in the half-lives of the aminoglycosides in functionally anephric patients. Thus, it can be estimated that if a loading dose of kanamycin or gentamicin is given at the end of a dialysis period, approximately three-fourths of that dose would be eliminated by the end of the next 6-h dialysis. Therefore, administering three-fourths of the loading dose after every 6-h dialysis should maintain therapeutic and non-toxic plasma concentrations in patients receiving dialysis 2 or 3 times per week. If dialysis is carried out for longer than 6-h, further dosage adjustments must be made based on the 5- to 6-h half-life.

The potential for ototoxicity from the aminoglycoside antibiotics is greatest upon prolonged treatment (22). Therefore, if the duration of therapy with gentamicin or kanamycin exceeds the usual range of 7 to 10 days, it is recommended that the plasma concentration of these antibiotics be checked to assure the maintenance of therapeutic and nontoxic body levels of the drug.

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