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Clinical Pharmacokinetics of Sisomicin: Dosage Schedules in Renal-Impaired Patients

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The pharmacokinetics of intravenously administered sisomicin were studied in 33 patients with normal renal function and different degrees of renal impairment. In all patients, the serum disappearance of sisomicin, once distribution equilibrium had been achieved, followed first-order kinetics and percentage of hourly loss from serum decreased proportionally with decreasing renal function. Half-lives averaged 2.06 h in normal subjects (endogenous creatinine clearance greater than 80 ml/min per 1.73 m^2) and reached 35.3 h in a virtually anephric subject. Linear relationships were defined between sisomicin serum half-life and the reciprocal of the endogenous creatinine clearance and serum creatinine concentration. The latter relationship indicates that the half-life of sisomicin may be approximated as twice the serum creatinine concentration and may be used for dosage adjustment in renal-impaired patients. Prediction of the extent of sisomicin removal by hemodialysis may be made from the relationship between the dialyzate of sisomicin and that of creatinine and blood urea nitrogen. Dosage schedules and methods of administration compatible with the pharmacokinetic properties of the antibiotic are finally proposed.

Sisomicin is a new single component aminoglycoside antibiotic isolated from *Micromonospora inyosensis*. The antibiotic, which is structurally related to gentamicin C_{1a}, has an in vitro antimicrobial spectrum similar to that of gentamicin and tobramycin (4, 6, 7, 11). Since its in vitro activity against certain bacterial species is greater than gentamicin or tobramycin and because gram-negative bacilli resistant to either gentamicin or tobramycin or to both are not necessarily resistant to sisomicin (3), this drug may have potentially useful clinical applications.

Due to its structural and pharmacological similarities with gentamicin, the rational use of sisomicin in therapy may be assumed to be dependent on the design of dosage regimens adapted to individual clinical situations. The relatively narrow therapeutic index of aminoglycoside antibiotics, their serum concentration-related toxicity, and the influence of renal function status on their elimination rate are among the factors that have, in recent years, demonstrated the need for precise dosage schedules, particularly in patients with different degrees of renal impairment.

The present study was therefore undertaken to define the pharmacokinetic profile of sisomicin after a single intravenous 1 mg/kg dose in normal, renal-impaired, and hemodialyzed patients (1), to establish clinically useful relationships between simple pharmacokinetic parameters and easily measured indexes of the degree of renal impairment (2), to compare the dialyzate of sisomicin to that of creatinine and blood urea nitrogen (BUN), to predict the extent of sisomicin removal by hemodialysis (3), and to propose safe dosage schedules allowing constant therapeutic serum levels of the drug (4).

MATERIALS AND METHODS

Patients. Thirty-three volunteers (26 males and 7 females), ranging in age from 21 to 72 years and weighing between 48 and 94 kg, were divided into three groups according to their renal function status as determined by the endogenous creatinine clearance (V_{cr}). Group 1 consisted of 18 subjects with V_{cr} > 80 ml/min per 1.73 m^2; group 2, 10 subjects with 4 < V_{cr} < 80 ml/min per 1.73 m^2; and group 3, five patients submitted to chronic hemodialysis. The volunteers were all free from infection at the time of the study and had not received any antibiotic for at least 2 weeks before its initiation. All subjects fully understood the investigational status of sisomicin and informed written consent was obtained.

Human studies. In groups 1 and 2, in order to facilitate blood sampling, to maintain body volumes, and to prevent clotting, physiological serum was infused at the rate of 1 ml/min through an infusion set placed in an arm vein. Patients were maintained

in a supine position for the duration of the experiment. Two-milliliter blood samples were drawn from the catheter immediately before administration of a 1 mg/kg intravenous sisomicin dose given as a bolus over a period of 1 min and at 60, 90, 120, 150, 180, 210, and 240 min after the injection for the patients of group 1. In group 2, blood withdrawals were made for up to 24 h after administration of the dose so as to adequately delineate the elimination phase. In the five patients of group 3, an intravenous dose (1 mg/kg) was administered at the beginning of a dialysis and blood samples were obtained at various times during the procedure. The blood was allowed to clot at room temperature and then was centrifuged. The serum was harvested and stored at −20 C until assayed within the next 3 days. In most patients of groups 1 and 2, complete 24-h urine collections were made. Urine samples were deep frozen at −20 C until assayed.

To determine sisomicin and endogenous creatinine clearances over a 2-h period in groups 1 and 2, the volunteers voided before administration of the dose, and urine was collected from 0 to 120 min and from 120 to 240 min after injection of the dose. Clearances were calculated from the results of the second aliquot in the usual way and corrected for a body surface area of 1.73 m^2. BUN and creatinine concentrations were determined on an aliquot of the same samples used for the antibiotic assay.

Assay. Serum and urine samples were assayed by the large plate, well-agar diffusion method of Bennett et al. (1) using *Bacillus subtilis* ATCC 6633 as the test organism. Five individual assays of unknown samples were performed and averaged. The measured antibacterial activity was assumed to be related to unchanged sisomicin. Standard curves for serum and urine were constructed using pooled fresh human serum and phosphate buffer (pH = 8), respectively, and were in the range of 0.62 to 10 μg/ml. Phosphate buffer was used to dilute urine samples 10- or 20-fold.

Pharmacokinetic analysis. All intravenous data were interpreted according to one-compartment, open-model kinetics. First-order elimination rate constants (k_e) were derived from the regression analysis of the logarithms of terminal serum concentrations versus time plots. The apparent volume of distribution (V_d) was estimated by dividing the dose by the extrapolated concentration at zero time. Sisomicin, BUN, and creatinine dialyzates (DIA) were calculated from the following equation (i): DIA $= C_i - C_f/C_i$ where C_i and C_f, respectively, represent the initial and final concentrations over 3 or 6 h during a 6-h dialysis procedure.

Constant infusion rate dosage regimens were derived using a pharmacokinetic model allowing determination of zero-order infusion rate from elimination data and desirable steady-state concentration (9).

RESULTS

After rapid intravenous infusion and once distribution equilibrium had been achieved, sisomicin disappeared from serum according to first-order kinetics in both normal subjects and renal-impaired patients. High coefficients of correlation ($r < -0.98$; $P < 0.01$) were obtained in all individual cases for the regression analysis of log terminal serum concentration versus time plots.

Mean serum concentrations (±95% confidence intervals [C.I.]) are illustrated in Fig. 1 for the subjects of group 1.

Renal function data, pharmacokinetic parameters, and the percentage of dose eliminated in 24 h are shown in Table 1 for the subjects of groups 1 and 2. In patients with V_{cr} > 80 ml/min per 1.73 m^2, half-lives were in the range 72.16 to 151 min (mean ± 95% C.I.:123.75 ± 7.7 min). These values are similar to those found by Rodriguez et al. (9). Sisomicin half-life increases with the severity of renal impairment to reach 35.3 h in a virtually anephric ($V_{cr} < 2$ ml/min per 1.73 m^2) patient. Several attempts were made to quantitatively relate pharmacokinetic parameters to renal function data. Excellent fits were particularly obtained between sisomicin elimination rate constant (expressed as percentage of hourly loss) and endogenous creatinine clearance (Fig. 2) and between sisomicin half-life and serum creatinine concentration (Fig. 3). The latter relationship reveals that the half-life, expressed in hours, may be approximated as twice the serum creatinine concentration. Although the relation between the two parameters is undoubtedly more complex, the simple $y = 2x$ identity may serve as a useful approximation for dosage adjustment until creatinine urinary clearance may be determined.

The ratio of sisomicin renal clearance to siso-

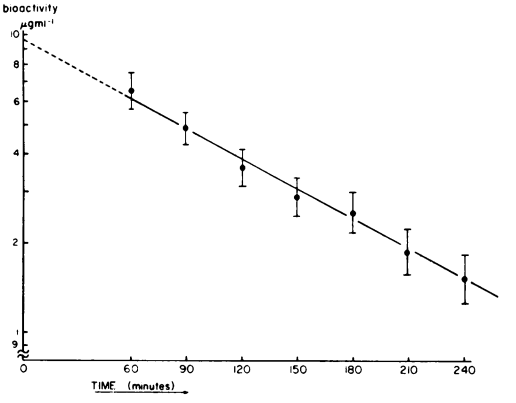

FIG. 1. *Mean serum concentrations of sisomicin as a function of time after a single intravenous dose of 1 mg/kg in the 18 subjects of group 1. Bars indicate 95% confidence intervals. The line through the points has a correlation coefficient of −0.99.*

TABLE 1. *Pharmacokinetic and renal function data for the patients of groups 1 and 2*[a]

Group and patient	$\dot{V}_{cr}$	CR_s	$\dot{V}_{si}$	$t^1/_2$	$(\%D_u)24$
Group 1					
1	152.97	0.8	47.70	81.76	ND
2	131.10	0.9	89.74	97.79	ND
3	106.13	1.1	61.85	72.16	ND
4	108.60	0.9	43.01	127.60	ND
5	125.60	1.0	59.83	108.57	82
6	147.25	1.0	72.14	108.05	98
7	181.55	0.8	126.26	78.00	91
8	133.85	0.9	40.42	105.74	83
9	136.79	0.8	26.00	85.60	92
10	113.82	0.9	51.36	77.15	98
11	116.58	0.9	68.17	77.08	99
12	141.92	1.0	41.25	92.74	78
13	104.51	1.0	23.14	138.10	100
14	175.99	0.9	57.39	86.03	90
15	81.29	1.3	47.32	151.01	92
16	111.41	0.8	74.74	72.69	65
17	89.51	1.0	33.00	105.57	85
18	131.54	0.7	73.00	100.98	89
Group 2					
1	30.00	3.3	9.26	350.50	52
2	20.77	4.4	9.64	957.60	41
3	4.42	7.5	1.05	1609.50	42
4	15.71	7.3	2.65	795.23	21
5	63.02	2.0	19.90	179.19	42
6	7.56	12.6	4.26	1178.30	ND
7	12.49	6.6	4.36	1184.90	15
8	67.36	1.2	25.74	130.68	30
9	7.41	10.9	1.98	1347.70	25
10	6.64	17.7	1.81	2226.10	17

[a] Abbreviations: $\dot{V}_{cr}$, endogenous creatinine clearance (ml/min); CR_s, serum creatinine concentration (mg/100 ml); $\dot{V}_{si}$, sisomicin renal clearance (ml/min); $t^1/_2$, sisomicin biological half-life (minutes); $(\%D_u)24$, percentage of administered dose excreted in urine in the first 24 h; ND, not determined.

micin body clearance ($\dot{V}_{si}/k_eV_d$) in the subjects of group 1 was 0.88 ± 0.16 (mean ± 95% C.I.), indicating that nonrenal contributions to the total elimination profile account for approximately 10%. This is confirmed by the fact that, in anephric patients, the percentage of hourly loss is of the order of 3.2%, whereas, in patients with V_{cr} = 100 ml/min per 1.73 m^2, this value is about 34%. Furthermore, 89% ± 5% (mean ± C.I.) of the administered dose was recovered in urine after 24 h (i.e., 12 half-lives), indicating again that the major process for clearing sisomicin from serum appears to be renal excretion.

The extent to which a drug is removed by hemodialysis depends on many variables, particularly the duration of the procedure, the blood flow through the artifical kidney, the size and quality of the filter, and the composition of the dialysis bath. This makes the utilization of the usual concept of dialysis difficult, especially when dosage adjustments have to be made in clinics where antibiotic assays may not be available. It therefore appeared useful to attempt to relate the dialyzate of sisomicin to the dialyzate of an easily and rapidly assayed natural substance. Table 2 shows that sisomicin is removed from the blood as rapidly as BUN and faster than creatinine. Similar results have also been reported for tobramycin (J. C. Pechère, B. Roy, and R. Dugal, 9th Int. Congr. Chemother., London, U.K., Abst. M544, 1975). The relative dialyzates vary very little between patients and may be used to predict the extent to which sisomicin is removed from the blood during hemodialysis.

DISCUSSION

The present study suggests that the elimination kinetics of sisomicin bear some similarities to those of other aminoglycoside antibiotics. In subjects with normal renal function, the half-life of sisomicin is in the same range as that reported for tobramycin (Pechère et al., 9th Int. Congr. Chemother., Abstr. M544, 1975) and gentamicin (4). Volumes of distribution are also in the same range of values and indicate that sisomicin diffusion is apparently limited to extracellular space. Finally, the main route of elimination of sisomicin, as that of tobramycin and gentamicin, is essentially renal excretion: the present results indicate that metabolism and other nonrenal contributions to excretion are less than 10%. Consequently, renal impairment affects the elimination rate constant, and therefore the half-life, which necessitates a

TABLE 2. *Dialyzate of sisomicin relative to BUN and creatinine dialyzate*[a]

Patient	DIA_{SI}	DIA_{BUN}	DIA_{CR}	DIA_{SI}/DIA_{BUN}	DIA_{SI}/DIA_{CR}
1	0.29	0.26	0.26	1.12	1.12
	0.49	0.41	0.39	1.20	1.26
	0.28	0.20	0.18	1.40	1.56
2	0.30	0.38	0.35	0.79	0.86
	0.35	0.37	0.29	0.95	1.21
	0.55	0.61	0.54	0.90	1.02
	0.40	0.36	0.28	1.11	1.43
4	0.21	0.39	0.30	0.62	0.70
	0.54	0.58	0.49	0.93	1.10
	0.41	0.37	0.27	1.11	1.52
	0.44	0.60	0.52	0.73	0.85
	0.28	0.32	0.26	0.96	1.08
Mean 95% confidence interval:				0.97/0.14	1.17/0.19

[a] DIA, Dialyzate; SI, sisomicin; BUN, blood urea nitrogen; CR, creatinine.

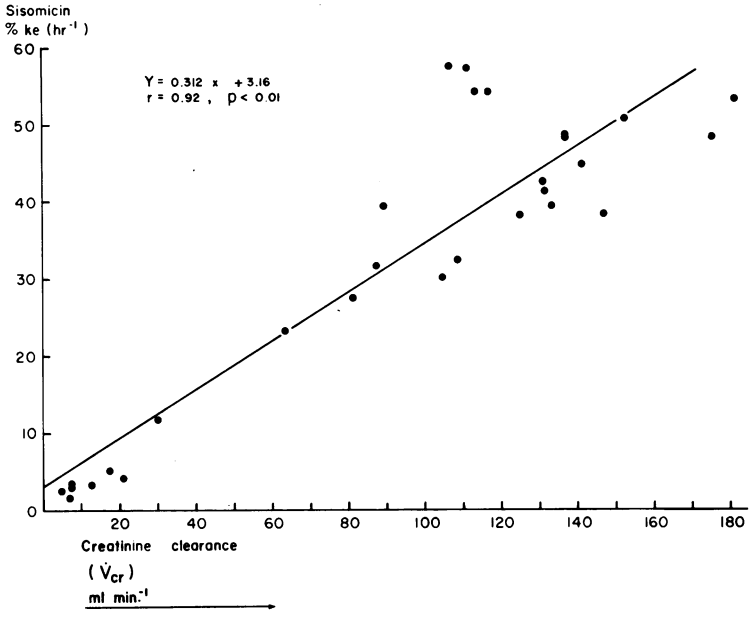

FIG. 2. *Relationship between sisomicin percentage of hourly loss (%k_e) and the endogenous creatinine clearance in the patients of groups 1 and 2.*

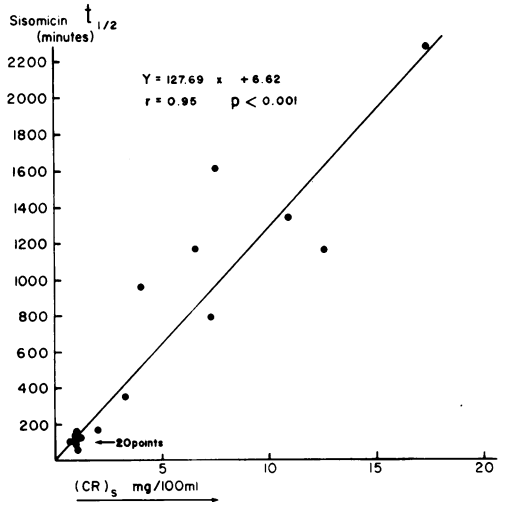

FIG. 3. *Relationship between sisomicin half-life and serum creatinine concentration in the patients of groups 1 and 2.*

modification of dosage regimens to prevent accumulation and toxicity.

The ratio of sisomicin clearance to creatinine clearance ($\dot{V}_{si}/\dot{V}_{cr}$) was found to be (mean ± 95% C.I.) 0.43 ± 0.08 in the subjects of group 1 and 0.33 ± 0.08 in the subjects of group 2. Sisomicin clearances less than half that of creatinine have been recently reported (12) and would suggest that the antibiotic undergoes some tubular reabsorption. The same hypothesis has also been discussed for tobramycin (Pechère et al., 9th Int. Congr. Chemother., Abstr. M544, 1975) and for gentamicin in patients with pyelonephritis (2).

In the early stages after administration of a single 1-mg/kg intravenous dose, serum levels in moderately and severely renal-impaired patients are comparable to those obtained in normal volunteers. This would suggest that concern over the influence of renal impairment of sisomicin parmacokinetics may be limited to modifications in elimination. Thus, in a renal-impaired subject, the usual loading dose could be administered and the maintenance dose and/or the dosage interval adjusted according to the elimination rate in this patient.

In practice, aminoglycoside antibiotics are usually administered intramuscularly at doses varying from 1 to 1.5 mg/kg every 8 h in adults with normal renal function, which means for sisomicin a dose every four half-lives. However, with drugs having short half-lives, discontinuous administration may lead to the antibiotic having a low degree of activity in serum for several hours. To avoid the risk of fluctuating serum levels and to ensure constant levels in severe infections for which sisomicin is most likely to be recommended, it would appear that a continuous intravenous injection might be a desirable method of administration. Some prac-

tical propositions may be deduced from the present data.

Sisomicin has been shown to obey two-compartment open-model kinetics after a bolus intravenous dose (Pechère, Pechère, and Dugal, Eur. J. Clin. Pharmacol, in press). Equilibrium between the central and peripheral compartments is reached within minutes, after which time serum concentration decrease is a function of time, with a half-live averaging 2 h. As a reasonable approximation one can consider that, a few minutes after intravenous rapid dosing, serum levels follow the one-compartment model kinetics. When a drug is administered by constant-rate intravenous infusion, the time *(t)* course of serum concentration *C* during the infusion is described by the following equation (ii) (10): $C = k_o/k_eV_d\ (1 - e^{-k}e^t)$ where k_o is the zero-order infusion rate and other symbols have been defined above. Steady-state concentration C_{ss} is obtained from (iii): $C_{ss} = k_o/k_eV_d$. If one chooses 4 μg/ml as the desirable sisomicin steady-state concentration and uses mean data for normal subjects in the present experiment (k_eV_d = 65 ml/min, k_e = 0.0058/min), it can easily be determined from equations (ii) and (iii) that the initial loading dose should be 45 mg (or 0.65 mg/kg for a man of 70 kg) followed by a constant-rate infusion of 15.6 mg/h as long as the steady state is needed.

However, to start the continuous injection, the pharmacokinetically sound practice of administering a bolus intravenous loading dose may lead to near toxic concentrations when the drug still obeys two-compartment kinetics. Accordingly, the initial loading dose of 45 mg should be administered as a rapid infusion over a period of 10 min, after which a second infusion of 15.6 mg/h may be started. Using equation (ii), it may be shown that the rapid 10-min infusion will yield a concentration of 3.97 μg/ml, which will be maintained as long as the second infusion of 15.6 mg/h is given. This dosage regimen agrees with that derived from a two-compartment model analysis of intravenous data (58.5 mg for 15 min, or 3.9 mg/min followed by 15.6 mg/h as long as the steady state is desired). In a renal-impaired patient, the initial dose may remain the same and the second infusion may be adjusted according to the elimination rate constant for this patient as determined from renal function data according to Fig. 2 or 3.

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