

Pharmacokinetic Parameters of Sisomicin

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Sisomicin in doses of 1 mg/kg was administered intramuscularly to 10 healthy volunteers, and 1 week later the same volunteers received sisomicin at the same dose intravenously. A peak serum concentration of sisomicin of 3.08 $\mu\text{g/ml}$ was obtained 1 h after intramuscular injection, and a peak serum concentration of 7.12 $\mu\text{g/ml}$ was achieved 30 min after a 30-min intravenous infusion. The sisomicin elimination data were analyzed according to a two-compartment model. Pharmacokinetic parameters derived from the intramuscular and intravenous studies were quite similar.

Aminoglycoside antibiotics, such as gentamicin, have become increasingly important in the therapy of infections due to gram-negative bacteria (1, 5). Sisomicin is a new aminoglycoside antibiotic isolated from the fermentation broth of *Micromonospora inyoensis* and closely resembles gentamicin C_{1a}, a component of the gentamicin complex (11). Since aminoglycoside antibiotics can be both nephro- and ototoxic, careful investigation of the pharmacological properties of these antibiotics is mandatory. We report results of pharmacokinetic studies with sisomicin in 10 healthy human volunteers.

MATERIALS AND METHODS

Ten healthy volunteers, aged 19 to 34 years, five male and five female, were the subjects of these studies. The volunteers ranged in weight from 49.9 to 107.3 kg, with a mean weight of 64.92 ± 17 (standard deviation) kg. Informed consent was obtained from all volunteers, in accord with institutional policies.

In the first phase of the study, the 10 volunteers were given 1-mg/kg doses of sisomicin intramuscularly (i.m.). The volunteers voided before injection of the drug, were in the fasting state, and remained sedentary during the study period. Blood samples were obtained just before injection and then at 0.5, 1, 2, 4, 6, 8, and 24 h after injection. Urine was collected for the first 8 h and then during 8 to 24 h after drug administration.

One week later, the same volunteers were used for study with intravenous (i.v.) infusion. Doses of 1 mg of sisomicin per kg were dissolved in 250 ml of 5% dextrose and water and administered i.v. over a 30-min period. Blood samples were collected just before injection and at 0.25, 0.5, 1, 1.5, 2, 4, 6, and 24 h after the end of the infusion. Urine was collected for the first 8 h and then for the following 8 to 24 h.

Serum and urine concentrations of sisomicin were determined by the cup plate assay method, using *Bacillus subtilis* as the test organism by methods previously described (7).

The following laboratory studies were determined before and after administration of both i.m. and i.v. doses of sisomicin: hemogram, urine analysis, blood urea nitrogen, serum creatinine, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, alkaline phosphatase, bilirubin, phosphorus, sodium, potassium, chloride, calcium, albumin, and globulin.

Pharmacokinetic parameters were determined by means of a program written for a Wang 700B programmable calculator. The data were fitted to two regression lines, and the following pharmacokinetic parameters, based on a two-compartment model (2), were calculated: elimination constant, K_e (per hour); transfer rate constants between the central (V_1) and peripheral (V_2) compartments, K_{12} and K_{21} (per hour); "concentration times time" area below the curve, A (micrograms per milliliter per hour); the total apparent volume of distribution (by the area method [2]), V_d (liters per 100 kg); plasma clearance, C (milliliters per minute); and the half-life of the beta elimination phase, $t_{1/2\beta}$ (hours). The corrections developed by Loo and Riegelman (4) were used for the calculation of pharmacokinetic parameters after i.v. infusion.

RESULTS

The average serum concentrations obtained after i.m. injection of sisomicin are listed in Table 1. The highest serum concentration of sisomicin, 3.08 $\mu\text{g/ml}$, was found 1 h after injection. Serum concentrations decreased during the ensuing 8 h, and no drug was detectable at 24 h. Of the total injected dose of sisomicin, 33.5% was excreted in the urine during the first 8 h, followed by only 6.3% during the next 16 h. The average urine concentration of sisomicin during the first 8 h was 87 $\mu\text{g/ml}$, and that during the 8- to 24-h period was 10 $\mu\text{g/ml}$.

After i.v. administration of 1-mg/kg doses of sisomicin, an average peak serum level of 7.12 $\mu\text{g/ml}$ was obtained 30 min after infusion (Ta-

ble 1). Serum levels decreased over the next 5.5 h, and no drug was detected in the serum at 24 h (Table 1). The average urine concentration of sisomicin during the first 8 h after infusion was 64 $\mu\text{g/ml}$, and that during the next 16-h period was 5.1 $\mu\text{g/ml}$. Of the total dose administered, 29.5% was excreted during the first 8 h and only 3.7% was excreted during the following 16 h.

The volunteers tolerated the administration of sisomicin without mishap. There were no complaints of prolonged or excessive pain after i.m. injection. The laboratory tests examined remained normal after administration of sisomicin.

The pharmacokinetic parameters derived from sisomicin from the i.m. and i.v. studies with these 10 volunteers were quite similar (Table 2). The elimination constants (K_e) after i.m. and i.v. administration of sisomicin were 0.449 and 0.51/h, respectively. The transfer constants, K_{21} and K_{12} , also were quite similar for the two studies. The $t_{1/2\beta}$ was 158 min after i.m. injection and 153 min after i.v. injection. The total apparent volume of distribution (V_d) derived from the study with i.m. doses of sisomicin was 25 liters/100 kg, and a very similar value of 24 liters/100 kg was obtained from the i.v. study (Table 2). A plasma clearance value of 72 ml/min was derived from both studies.

DISCUSSION

The serum concentrations after parenteral administration of sisomicin were comparable to those reported previously from this laboratory (6) for two other aminoglycoside antibiotics, gentamicin and tobramycin, except that the serum concentrations of gentamicin and tobramycin were slightly higher from the 1st to 4th h after i.v. infusion (6). However, greater percentages of the administered doses of both gentamicin (59%) and tobramycin (79%) were excreted during the first 24 h than were found

TABLE 2. Pharmacokinetic parameters of sisomicin after parenteral administration of 1-mg/kg doses

Route	Parameter						
	K_e (per h)	K_{21} (per h)	K_{12} (per h)	A ($\mu\text{g/ml}$ per h)	$t_{1/2\beta}$ (h)	V_d (liters/ 100 kg)	Clearance (ml/ min)
i.m.	0.449	0.463	0.141	15.11	2.63	25	72
i.v.	0.51	0.499	0.2	15.21	2.55	24	72

with sisomicin. The average concentration of these antibiotics in the urine (6) also was greater than that found with sisomicin.

In our previous studies with tobramycin and gentamicin (6), we found that the regression lines constructed for the drug elimination data could be fitted to a one-compartment model; other investigators reported similar findings (8, 10). However, the elimination data we obtained after parenteral administration of sisomicin were clearly best resolved into two regression lines. Indeed, the alpha distribution phase (2) was much more prolonged with sisomicin than what we previously found for both tobramycin and gentamicin. The pharmacokinetic parameters we derived in this study for sisomicin are different from those reported by both Rodriguez et al. (9) and Lode et al. (3). Rodriguez et al. (9) appear to have analyzed their data by a one-compartment model. Curiously, these authors stated that the serum half-life of sisomicin after i.m. doses of 20 mg of sisomicin per m^2 was 120 min, whereas the serum half-life determined after a 30-min i.v. infusion of sisomicin at a dose of 30 mg/ m^2 was 160 min. It is difficult to resolve these differences in the half-life. These data were obtained in hospitalized patients with neoplasms. Indeed, close perusal of the data presented by Rodriguez et al. (9) shows a prolonged alpha elimination phase. We cannot directly compare our study with that presented by Lode and co-workers (3). These authors determined pharmacokinetic parameters for gentamicin, tobramycin, and sisomicin after 1-h infusions of 1-mg/kg doses of the three aminoglycoside antibiotics; the antibiotics were dissolved in 50 ml of saline and, to achieve a steady-state serum concentration, 70% of the dose was infused during the first 10 min and the remainder was infused over 50 min. The half-life derived for sisomicin was 122 ± 27 min. However, if we calculate the pharmacokinetic parameters of our i.v. data according to a one-compartment model, then a half-life of 130 min is obtained approximating that given by Lode et al. (3); the apparent volume of distribution derived from our i.m. data according to a one-

TABLE 1. Serum concentrations after 1-mg/kg parenteral doses of sisomicin

Time after dose (h)	Serum concn ($\mu\text{g/ml}$)	
	i.m.	i.v.
0.25		2.7 ± 0.68
0.5	2.58 ± 0.3^a	7.12 ± 1.56
1	3.08 ± 0.39	3.1 ± 0.91
1.5		2.5 ± 0.54
2	1.4 ± 0.3	1.6 ± 0.48
4	0.95 ± 0.3	1.02 ± 0.39
6	0.61 ± 0.16	0.54 ± 0.17
8	0.28 ± 0.14	
24	0	0

^a Mean \pm standard deviation.

compartment analysis was 22 liters, a value similar to those given by Regamey et al. (8) for gentamicin (21 liters) and tobramycin (23 liters), also calculated from i.m. studies according to a one-compartment system. Clearly, tobramycin and gentamicin yield almost identical pharmacokinetic parameters, yet the elimination data we found with sisomicin definitely showed two phases. Furthermore, one of the basic assumptions of the two-compartment model (2) is that the pharmacokinetic data derived from i.v. and i.m. studies should be the same. Our results after i.m. and i.v. administration of sisomicin in the volunteers yielded similar pharmacokinetic parameters.

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