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Pharmacokinetics of Isepamicin following a Single Administration by Intravenous Infusion or Intramuscular Injections

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The pharmacokinetics of isepamicin following administration of a 1-g dose were evaluated for 18 healthy male volunteers between the ages of 26 and 38. In a randomized crossover fashion, each volunteer received doses of isepamicin by a 30-min intravenous infusion and as an intramuscular injection. Blood samples were collected at specified times after dosing and assayed for isepamicin by a validated radioimmunoassay method. The individual plasma concentration-time curves were analyzed by noncompartmental methods. In general, the pharmacokinetics after intravenous infusion and intramuscular injection were similar. As expected, the maximum concentration of isepamicin in serum following intramuscular injection (37.2 μg/ml) was lower than the observed concentration at the end of infusion (66.7 μg/ml). The areas under the concentration-time curves from 0 h to infinity following intramuscular and intravenous administration were 164.8 and 154.5 μg · hr/ml, respectively, indicating complete absorption following intramuscular administration. The respective mean terminal-phase half-life ($t_{1/2}$) values were 2.6 and 3.6 h. Although $t_{1/2}$ was slightly longer following intravenous infusion, the small difference in the observed $t_{1/2}$ values was not considered to be clinically significant. Total body clearances following intramuscular injection and intravenous infusion were 1.3 and 1.4 ml/min/kg, respectively, which were similar to renal serum creatinine clearances in healthy volunteers (>1.14 ml/min/kg). The drug was safe and well tolerated. The results of the present study clearly show complete absorption of isepamicin following intramuscular administration. The similarity in the pharmacokinetics after intravenous infusion and intramuscular dosing would permit interchangeable administration of isepamicin by either route without compromising clinical efficacy.

Isepamicin is a novel aminoglycoside antibiotic with activity against bacteria containing aminoglycoside-inactivating enzymes (6, 8, 16). This is one of the first aminoglycosides being developed for once-daily dosing. Evidence to support this dosing regimen includes concentration-dependent bactericidal activity (13), relatively long postantibiotic effect (2), and first-exposure adaptive resistance (1). It has superior activity against clinical isolates of *Escherichia coli* and *Citrobacter*, *Klebsiella*, *Enterobacter*, and *Serratia* spp., none of which contain aminoglycoside-modifying enzymes (4, 11, 15). The activity spectrum of isepamicin is comparable to that of amikacin against *Proteus* spp. and *Pseudomonas aeruginosa*, which lack the inactivating enzymes (5, 7).

Isepamicin is not modified by the 2′-aminoglycoside adenyltransferase or aminoglycoside acetyltransferases that inactivate gentamicin, and it is less affected by the 6′-aminoglycoside acetyltransferase that inactivates amikacin. As a result, the frequency of strains that are resistant to isepamicin is lower than the frequency of strains resistant to gentamicin or amikacin.

In this two-way crossover study, the objective was to evaluate the pharmacokinetics of isepamicin following administration of a 1-g dose as either a 30-min intravenous infusion or as intramuscular injections (two injections of 2 ml each) to healthy male volunteers.

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MATERIALS AND METHODS

Subjects. Eighteen healthy male volunteers between the ages of 26 and 38 (mean ± standard deviation [SD], 31 ± 4 years) weighing between 143 and 200 lb (mean ± SD, 173 ± 19 lbs) and within 10% of their ideal weight range according to current actuarial tables were selected for these studies. Prior to enrollment, each subject was determined to be in good health through medical history, physical examination, electrocardiogram (ECG), and laboratory tests (hematology, blood chemistry, and urinalysis). Each subject signed a written informed consent form. No other drugs were taken during the course of the study.

In a randomized crossover fashion, each subject received a 1-g dose of isepamicin as a 30-minute intravenous infusion and as two 2-ml intramuscular injections. At least a 1-week washout period separated each phase of the crossover.

Prior to dilution of isepamicin into polyvinyl chloride (PVC) bags, volume adjustments were made. Each intravenous infusion set was prepared to deliver 63 ml of a 16-mg/ml solution at a rate of 125 ml/hr in order to infuse a 1-g dose in 30 min. Since each PVC bag contained 105 ml of normal saline, a total of 1.6 g of isepamicin prepared in 6.4 ml was injected into each PVC bag, from which a volume of 11.4 ml had been withdrawn in order to achieve the desired concentration of 16 mg/ml in a 100-ml volume.

For the intramuscular injection, a solution of isepamicin was used without dilution. Two 2-ml intramuscular injections were made into the opposite sides of the buttocks with a 1½-inch 21-gauge needle, with the volunteer lying in bed.

All subjects were confined to the study area for 12 h prior to the start of the study. Ten hours prior to dosing, a light snack was served, after which the volunteers fasted overnight. In the morning following the fast, isepamicin was administered by intravenous infusion or intramuscular injection. Each volunteer received both treatments in accordance with a computer-generated random code. During drug administration, the volunteers were confined to bed. Standard clinical precautions for intravenous infusions and intramuscular injections were followed. All volunteers, regardless of treatment, remained in bed until the 30-min infusion had been completed. Fasting continued for all volunteers until 4 h after drug administration. During the fasting period only water was permitted. A light lunch consisting of a cup of soup, sandwich, fruit, and water was served after the 4-h blood sample was collected. Regular meals resumed 8 h after dosing. All volunteers were confined to the study site until the 24-h blood sample

and vital signs were obtained. A physician was present for all drug administrations and remained at the study site for at least 4 h postdosing.

Blood samples were drawn into heparinized Vacutainer tubes immediately prior to drug administration (0 h); at 15, 30, and 45 min following initiation of the intravenous infusion; and then at 1, 1.5, 2, 3, 4, 6, 8, 12, 14, 16, 20, and 24 h following the initiation of the intravenous infusion or intramuscular injection. The samples were immediately centrifuged, and the plasma was immediately frozen to at least −20°C pending analysis for isepamicin.

Physical examinations, measurements of vital signs, ECGs, and routine laboratory tests were repeated at the completion of the study.

Analytical procedure. The radioimmunoassay (RIA) analysis of isepamicin was based on commercial RIA kits (Clinetics Corp., Tustin, Calif.). It involved the use of three different kits covering the range of concentration in the plasma. These kits were designated as RIA kit A (5 to 160 μg/ml), RIA kit B (0.1 to 10 μg/ml), and RIA kit C (0.001 to 0.1 μg/ml). Plasma samples (0.1 ml) diluted or undiluted were taken for analysis. To each aliquot, 0.5 ml of ^{125}I-TRACER SARGG premix was added, and the solution was mixed; this was followed by the addition of 0.1 ml of anti-isepamicin antibody. Samples were incubated for appropriate time periods depending on the RIA kit used and centrifuged for 5 min at 1,000 × *g*, and the pellets (containing bound ^{125}I) were counted in a gamma counter. The concentration of isepamicin, expressed as micrograms per milliliter of plasma, was determined directly from a standard curve (log-logit plot). The linearity of the RIA method was evaluated by subjecting the data to the linear regression equation $Y = bX + a$ where b is the slope, a is the y-intercept, X is the log concentration in plasma, and Y is the logit, which is equal to $\ln \{(B/B_0)/[1 - B_0)]\}$, where B is the mean OD value after subtraction of the nonspecific binding of bound enzyme conjugate at drug concentration C and B_0 is the mean OD value after subtraction of nonspecific binding of the bound enzyme conjugate at zero drug concentration. For all kits, A, B, and C, the bias was less than 11%, indicating good accuracy and precision of the RIA method.

Pharmacokinetic analysis. Plasma concentrations above the limit of quantitation of the analytical method (0.001 μg/ml) were used for pharmacokinetic analysis by noncompartmental methods (3). The maximum concentration (C_{max}) and time to reach maximum concentration (T_{max}) were the observed values. The terminal-phase rate constant (K) was calculated as the negative slope of the log-linear terminal portion of the plasma concentration-time curve by using linear regression. Goodness of fit was determined by an examination of the residuals and visual inspection of the data. The terminal-phase half-life, $t_{1/2}$, was 0.693/K.

The area under the plasma concentration-time curve to the time of the final quantifiable sample, AUC_{0-tf}, was calculated by using the linear trapezoidal rule and was extrapolated to infinity according to the following equation: $AUC_{0-\infty} = AUC_{0-tf} + C_{tf}/K$, where C_{tf} is the concentration at the time of the final quantifiable sample.

Total body clearance (CL) was calculated as the ratio of dose to $AUC_{0-\infty}$. The apparent volume of distribution (V) was calculated as the ratio of clearance to K. The absolute bioavailability of the intramuscular dose was determined from the ratio of the $AUC_{0-\infty}$ value following intramuscular injection to that following intravenous infusion.

Data were statistically analyzed with an analysis-of-variance model from which effects due to sequence, subject within sequence, phase, and treatment were extracted. The power to detect a 20% difference from each treatment mean was determined for AUC and C_{max} by assuming an alpha level of 0.05 (two tailed). Power calculations were made by using pooled SDs from the analysis of variance. Confidence intervals based on two one-sided t tests at alpha = 0.05 were calculated for AUC and C_{max} treatment mean differences by using the pooled standard deviations from the analysis of variance and were expressed as a percent of each treatment mean.

RESULTS

All prestudy and poststudy physical examinations, laboratory tests, and ECGs had no clinically meaningful abnormalities. No adverse reactions or abnormal infusion or injection site evaluation results were reported. In summary, isepamicin administered as a single 1-g dose, intravenously or intramuscularly, was safe and well tolerated.

The mean plasma isepamicin concentration-time data following a 30-min intravenous infusion or intramuscular injections are illustrated in Fig. 1. The mean pharmacokinetic parameters are provided in Table 1. Following intravenous infusion, the C_{max} (66.7 μg/ml) was reached at the end of the infusion, i.e., at 0.5 h; following intramuscular administration, C_{max} (37.2 μg/ml) was reached at 1.3 h postadministration. The mean values for the pharmacokinetic parameters of isepamicin (AUC_{0-tf}, $AUC_{0-\infty}$, $t_{1/2}$, V, and CL) following intravenous infusion and intramuscular injections were similar.

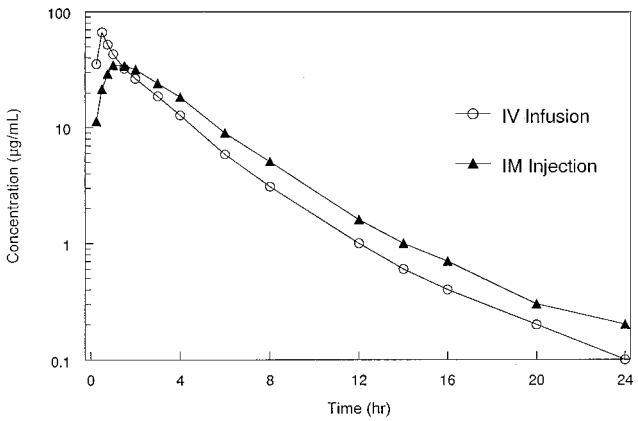

FIG. 1. Mean plasma concentration-time profiles for isepamicin following a 30-min intravenous (IV) infusion and intramuscular (IM) injections of 1-g doses to 18 healthy male volunteers.

DISCUSSION

As expected, plasma concentrations of isepamicin were significantly greater following intravenous infusion than after intramuscular administration within the first hour following drug administration. Thereafter, plasma concentrations after intravenous infusion or intramuscular injection declined in a parallel manner and could be best described as having a monoexponential disposition. Isepamicin was rapidly cleared from the body. CL ranged from 103 to 112 ml/min and was independent of the route of administration. $t_{1/2}$ was 2.6 and 3.6 h following intramuscular injection and intravenous infusion, respectively. Half-life calculations are sensitive to the number of data points in the terminal phase as well as the final time point in the terminal phase. Following intravenous administration, isepamicin could be measured up to the final sampling time of 24 h (mean, 22.4 h) for most subjects, whereas, following intramuscular administration, for most of the subjects isepamicin could be measured up to 20 h (mean, 21.3 h). This could account for the slightly longer $t_{1/2}$ following intravenous administration. The respective V values were 23 and 35 liters, indicating that isepamicin was extensively distributed throughout the body.

The absolute bioavailability following intramuscular administration was 109%, indicating that isepamicin was completely absorbed. The confidence interval for the $AUC_{0-\infty}$ point estimate of intramuscular administration to intravenous infusion was 99 to 113% ($P = 0.084$), indicating that the two treatments were equivalent with regards to systemic availability.

Administering antibiotics by the intramuscular route is an economically and clinically efficient approach (10, 12) since it enables dose administration in an outpatient setting. McCue (9) recommends the intramuscular route whenever possible, pointing out that the cost is one-fourth that of the intravenous route. Isepamicin joins a host of other antibiotics (i.e., cefazolin, gentamicin, penicillin G, and imipenem [10]) that have been administered interchangeably without compromising clinical efficacy. On the other hand, caution should be exercised in treating patient populations that may have impaired absorption. It has been noted that the rate of absorption of gentamicin is decreased in patients with spinal cord injuries who received an intramuscular injection of gentamicin below the level of the spinal cord injury (14).

Isepamicin was shown to be safe and well tolerated. Isepamicin has major advantages over other marketed aminoglycosides. It is the only aminoglycoside developed for once-a-day

TABLE 1. Pharmacokinetic parameters for isepamicin[a]

Method of administration[b]	C_{max} (μg/ml)	T_{max}[c] (h)	$AUC_{0-\infty}$ (μg · h/ml)	F[d]	$t_{1/2}$ (h)	CL (ml/min)	CL (ml/min/kg)	V (liters)	V (liters/kg)
i.v. infusion	66.7 (15)	0.5 (0)	154.5 (19)		3.6 (18)	112.1 (21)	1.4 (22)	35.4 (35)	0.5 (38)
i.m. injection	37.2 (21)	1.3 (29)	164.8 (14)	1.09 (17)	2.6 (14)	102.9 (13)	1.3 (15)	22.7 (12)	0.3 (10)

[a] Values are means (n = 18), with percent coefficients of variation in parentheses.
[b] i.v., intravenous; i.m., intramuscular.
[c] T_{max}, time to reach C_{max}.
[d] F, bioavailability.

dosing; it is completely absorbed following intramuscular administration, and its pharmacokinetics are similar after intramuscular and intravenous administration, lending itself easily to an outpatient setting. Its pharmacodynamics, i.e., the long postantibiotic effect and first-exposure adaptive resistance, support the efficacy observed in phase II trials involving patients with lower respiratory tract, urinary tract, and skin infections.

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