Pharmacokinetic Interpretation of Cephadrine Levels in Serum After Intravenous and Extravascular Administration in Humans

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Pharmacokinetic parameters were calculated from intravenous data based upon a two-compartment open model. These parameters were subsequently used to determine the absorption rates and bioavailability of cephradine administered intramuscularly and orally. The results indicate that cephradine obeys dose-independent kinetics and that biological availability is complete from all dosage forms.

Cephradine, a semisynthetic cephalosporin derivative chemically designated as 7-[D-2-amino(1,4-cyclohexadien-1-yl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, is structurally similar to cephalexin (Fig. 1). The compound is well absorbed from the gastrointestinal tract irrespective of the presence of food (3) and is effective in the treatment of both animal (1, 6) and human bacterial infections (4, 5). Cephradine is acid stable (1) and, after oral administration in mice, is rapidly absorbed and excreted virtually unchanged in the urine (10). Binding of cephradine to human plasma proteins is reversible and is less than 20% *in vitro* (7). The purpose of this paper is to elucidate the pharmacokinetics in humans and to determine the bioavailability of the drug administered intramuscularly and orally at various dosage levels in capsule and suspension forms.

MATERIALS AND METHODS

Intravenous administration. Each of eight fasting, normal, adult male subjects, ranging in age from 22 to 39 years and weighing between 145 and 188 pounds (ca. 65.8 and 85.3 kg), was given a single 1,000-mg dose of cephradine intravenously. Blood samples were taken prior to drug administration and at 5, 15, 30, 60, 120, 240, and 360 min after administration.

Urine samples were collected prior to drug administration and for the time periods 0 to 2, 2 to 4, and 4 to 6 h after injection of the drug.

Blood and urine samples were collected, frozen, and then analyzed for drug concentration by a *Bacillus subtilis* agar disk plate method (2).

Intramuscular administration. Each of 20 fasting, normal, adult male subjects, ranging in age from 20 to 60 years and weighing between 145 and

195 pounds (ca. 65.8 and 86.5 kg), received a single 1,000-mg dose of cephradine intramuscularly. Blood samples were obtained prior to drug administration and at 15, 30, 45, 60, 90, 120, 150, 180, 240, and 360 min after injection.

Urine samples were collected prior to drug administration and for the time periods 0 to 2, 2 to 4, and 4 to 6 h after injection of the drug.

Blood and urine samples were collected, frozen, and then analyzed as described in the intravenous study.

Oral administration. A crossover study was carried out in 20 normal, adult male subjects ranging in age from 21 to 54 years and weighing between 140 and 208 pounds (ca. 63.5 and 94.3 kg). On test day 1, each subject was given either a single 250-mg or a 500-mg capsule according to a randomized dosing schedule. The subjects fasted 8 h before and 3 h after administration of the drug. Blood samples were taken prior to drug ingestion and at 30, 60, 90, 120, 180, and 360 min after administration. Urine samples were collected prior to drug administration and for the time periods 0 to 3, 3 to 6, 6 to 12, and 12 to 24 h after ingestion of the drug. After 1 week, the subjects were crossed over so that those who received a 250-mg capsule were given a 500-mg capsule and vice-versa.

In an additional study, 22 normal, adult male subjects, ranging in age from 21 to 50 years and weighing between 145 and 190 pounds (ca. 65.8 and 86.2 kg), received a single 1,000-mg (two 500-mg capsules) dose. Each subject fasted 8 h before and 3 h after drug administration. Blood samples were taken prior to drug ingestion and at 30, 60, 120, 180, 360, 480, and 600 min after administration.

Urine samples were collected prior to drug administration and for the time periods 0 to 3, 3 to 6, 6 to 12, and 12 to 24 h after ingestion of the drug.

Blood and urine samples were collected, frozen, and then analyzed as described in the intravenous study.

Each of 24 normal female subjects, ranging in age

FIG. 1. Structure of cephadrine.

from 20 to 52 years and weighing between 108 and 170 pounds (ca. 49.0 and 77.1 kg), was given 10 ml of cephadrine oral suspension equivalent to 500 mg of cephadrine. Each subject fasted 8 h before and 3 h after drug administration.

In another study 18 normal female subjects, ranging in age from 21 to 52 years and weighing between 139 to 199 pounds (ca. 63.1 and 90.3 kg), were given a single 5-ml dose of cephadrine oral suspension equivalent to 250 mg of cephadrine. Each subject fasted 8 h before and 3 h after drug administration. Blood samples were taken prior to drug ingestion and at 30, 60, 90, 120, 180, and 360 min after drug administration in both studies.

Urine samples were also collected prior to drug administration and for the 6-h period after ingestion of the drug.

Blood and urine samples were collected, frozen, and then analyzed as described in the intravenous study.

RESULTS

Intravenous administration. The average serum levels of cephadrine obtained from the data of eight subjects dosed intravenously with 1,000 mg are shown in Fig. 2. It can be seen that the serum level declines in a biexponential manner. Therefore, the data can be fitted mathematically with a two-compartment model according to equation 1.

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

The serum concentrations were used as input data for a digital computer (model PD12) program to provide a biexponential least-square regression fit to the data from which the coefficients A and B and the hybrid rate constants α and β were determined. The area under the serum level curve was calculated by using the expression $(A/\alpha) + (B/\beta)$ and determined by the trapezoidal rule. The parameters of equation 1 are as follows: A , 89; B , 27.8; α , 4.948; β , 0.809; C_p^0 , 116.8; calculation of area, 52.32; area determined by trapezoidal rule, 52.65. The values are in close agreement. Utilizing these values, the rate constants k_{12} , k_{21} , and k_{e1} and the serum $t_{1/2}$ were calculated: k_{12} , 1.731/h; k_{21} , 1.796/h; k_{e1} , 2.23/h; $t_{1/2}$, 0.85 h.

The serum-tissue distribution of cephadrine was estimated by calculating the fraction of the administered intravenous dose in the peripheral and central compartments at various

times from known equations (8). Figure 3, a plot of the fractional serum-tissue distribution for the intravenous dose of cephadrine, illustrates that the compound is well distributed throughout the tissue compartment.

Intramuscular administration. All data obtained from the intramuscular and oral routes of administration were fitted based upon a two-compartment open model. Assuming a first-order absorption process, the model is described by equation 2 (9).

$$C_p = \frac{k_a D}{V_p} \left[\left\{ \frac{k_{21} - \alpha}{(k - \alpha)(\beta - \alpha)} \right\} e^{-\alpha t} + \left\{ \frac{k_{21} - \beta}{(k - \beta)(\alpha - \beta)} \right\} e^{-\beta t} + \left\{ \frac{k_{21} - k}{(\alpha - k)(\beta - k)} \right\} e^{-kt} \right] \quad (2)$$

In each case the absorption rate constants were determined utilizing the pharmacokinetic parameters obtained from the intravenous data.

FIG. 2. Serum levels after a 1-g intravenous dose of cephadrine; average of eight subjects. Solid line is the computer-generated curve. Vertical bars represent the standard deviation of the mean.

FIG. 3. Percentage of cephadrine dose estimated in the peripheral compartment ($\square$) and in the central compartment ($\circ$) after a 1-g intravenous dose (average of eight subjects).

Semilog plots of the average serum levels of cephadrine (20 subjects) after a 1,000-mg intramuscular dose versus time are shown in Fig. 4. The averages are a good representation of the data of all the individual subjects. Cephadrine was rapidly absorbed by this route, as noted by the attainment of peak serum levels of $19.66 \pm 5.70 \mu\text{g/ml}$ after 30 min. Good agreement was also obtained between the computer-generated curve and the experimental data after administration by the intramuscular route. Table 1 contains the values for the absorption rate constant and the area under the serum level curve. Ninety-seven percent of the administered dose was accounted for by this route of administration.

Oral administration. Semilog plots of average serum levels versus time after oral administration of 250, 500, and 1,000 mg of cephadrine as capsules are shown in Fig. 5. Again, good agreement was obtained between the computer-generated curve and the experimental data. Rapid absorption is obvious, with peak serum concentrations being obtained in approximately 30 min. The absorption rate constants and the area under the serum level

curves are also shown in Table 1. The absorption rate constants were in good agreement, and 92, 92, and 104% of the administered dose for the 250-, 500-, and 1,000-mg capsules, respectively, were accounted for by this route of administration.

Semilog plots of the average serum levels

FIG. 4. Serum levels after a 1-g intramuscular dose of cephadrine (average of 20 subjects). Solid line is the computer-generated curve. The standard deviation of the mean is represented by the vertical bars.

TABLE 1. Absorption rate constants and area under serum level curve

Route of administration	Dose (mg)	Absorption rate constant k_a (per h)	Area under serum level curve ($\mu\text{g/h/ml}$)
Intravenous	1,000		52.65
Intramuscular	1,000	1.1	50.97
Oral (capsule)	250	1.5	12.10
Oral (capsule)	500	1.1	24.29
Oral (capsule)	1,000	1.0	54.78
Oral (suspension)	250	3.0	13.70
Oral (suspension)	500	2.8	30.05

FIG. 5. Average serum levels after oral administration of 250-, 500-, and 1,000-mg cephradine capsules, respectively. Symbols: $\circ$, 1,000 mg; $\square$, 500 mg; $\triangle$, 250 mg. Solid lines are the computer-generated curves. Vertical bars represent the standard deviation of the mean.

versus time after administration of 250 and 500 mg of cephradine as a suspension are shown in Fig. 6. A good fit is seen between the computer-generated curve and the experimental data. The oral suspension is rapidly absorbed, with peak serum concentrations being attained in less than 30 min. Since the oral suspension is essentially a saturated solution of cephradine, it is not surprising that peak levels are achieved earlier with this dosage form. The absorption rate constants and the area under the serum level curves are shown in Table 1. The data indicate that cephradine is completely available from this dosage form.

The relationships among the areas under serum level-time curves, the urine output of drug activity, and the bioavailability of var-

ious dosage forms of cephradine are only meaningful if the drug obeys dose-independent kinetics. Cephradine was found to obey dose-independent kinetics. This is illustrated in Fig. 7, which is a plot of the area under the serum level curves versus the total amount of drug eliminated for cephradine administered intravenously, 800 mg; intramuscularly, 770 mg; orally in capsules, 905, 495, and 245 mg for the 1,000-, 500-, and 250-mg strengths; orally in suspension, 363 and 225 mg for the 500- and 250-mg doses. Consequently, the bioavailability of extravascular dosage forms of cephra-

FIG. 6. Average serum levels after oral administration of 250 and 500 mg of cephradine suspension. Symbols: $\square$, 500 mg; $\circ$, 250 mg. Solid lines are the computer-generated curves. The standard deviation of the mean is represented by the vertical bars.

FIG. 7. Plot illustrating dose-independent kinetics for cephadrine over the dose range studied. The slope of the line is the reciprocal of the total clearance rate of cephadrine. Symbols: ○, intravenous; ◇, intramuscular; □, capsules; △, suspension.

dine may be evaluated by comparing the area under the serum level-time per milligram of extravascular dose with the area per milligram of intravenous dose if the doses are within the range of 250 to 1,000 mg. Since dose-independent kinetics is obeyed, the slope of the plot in Fig. 7 is equal to the reciprocal of the total clearance rate of the drug from the body. A total clearance rate of 14.8 liters/h calculated from the slope of Fig. 7 compares favorably with the total clearance rate of 14.9 liters/h calculated from the pharmacokinetic parameters for cephadrine determined in the intravenous study. The mean apparent volume of distribution, v_0 , also calculated from these parameters was found to be 22.53 liters/1.73 m².

DISCUSSION

The pharmacokinetic parameters for cephadrine were determined after intravenous administration. This was achieved by using a two-compartment open model. These parameters were subsequently used to determine the rate of absorption and the extent of cephadrine bioavailability after extravascular administration. Cephadrine is rapidly absorbed from all dosage forms. The oral suspension shows

earlier peak levels, which is consistent, in part, with the characteristics of this dosage form. Cephadrine is essentially completely absorbed from all the dosage forms and has a serum half-life of approximately 50 min.

The pharmacokinetic parameters determined from these studies can serve as guidelines in establishing proper dosage regimens during the clinical use of cephadrine.

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