Single-Dose Pharmacokinetics of Ceftriaxone in Healthy Chinese Adults

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The pharmacokinetics of ceftriaxone were investigated in six healthy mainland Chinese adults (four males and two females). A single 1.0-g dose was administered intravenously or intramuscularly in a two-way crossover design. Plasma and saliva samples were collected on 11 occasions between 0 and 36 h after dosing. Ceftriaxone was not detected in any saliva samples. The mean volume of distribution and mean elimination half-life of ceftriaxone in plasma were 8.5 liters and 8.1 h, respectively. The mean total body clearance after intravenous administration was 0.68 liter/h. The mean T_{max} and C_{max} after intramuscular injection were 1.4 h and 131 μg/ml, respectively. The area under the plasma concentration-time curves after intravenous and intramuscular administrations were 1,507 and 1,493 μg · h/ml, respectively. The bioavailability for a 1.0-g intramuscular dose of ceftriaxone was calculated to be 100%. These pharmacokinetic parameters for ceftriaxone in healthy Chinese adults were very similar to those previously reported in the literature. Thus, ceftriaxone may be administered to treat Chinese patients without any major modification in the standard dosing regimen.

Ceftriaxone is a new broad-spectrum parenteral cephalosporin with potent activity against gram-positive and gram-negative bacteria due, in part, to its resistance to various types of β-lactamase (1). Its most remarkable feature is a long elimination half-life of 6 to 9 h (8, 13), which makes possible a once-daily dosing schedule.

Studies conducted in Europe and North America have also shown that the bioavailability of intramuscular (i.m.) administration is the same as for the intravenous (i.v.) route (2–5), and this, in conjunction with the need for only a daily injection, has the advantages of convenience and cost effectiveness.

It is generally accepted that differences in drug metabolism occur among different races. The underlying cause could be genetic or environmental or both (2, 5, 8). The higher proportion of fast acetylators among Oriental populations are well known (6, 19). Comparison studies between Orientals and Caucasians has demonstrated differences between the two races in the disposition of drugs (7, 18). This might necessitate the use of a separate dosing scheme for patients of different ethnic origins.

The object of this study was to investigate the bioavailability and pharmacokinetics of ceftriaxone in healthy Chinese adults. This provides information on whether the dosing procedure established from experiences based predominantly on Caucasian subjects is applicable to Chinese subjects.

MATERIALS AND METHODS

Subjects. Six healthy Chinese adult volunteers (four males and two females) were enrolled in the study. Their ages ranged from 19 to 40 years (mean, 26.3 years). Body weight and height were 55 to 63 kg (mean, 58.5 kg) and 159 to 174 cm (mean 166.3 cm). All volunteers provided written informed consent. The study was approved by Hunan Medical College and the Public Health Department of Hunan Province. The subjects were all in good health as determined by history, physical examination, blood count, hemoglobin, hematocrit, blood urea nitrogen, creatinine, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, bilirubin, and urinalysis. A pregnancy test was performed on female subjects. No known or suspected hypersensitivity to the penicillins and cephalosporins was found in any of the subjects. The subjects had not taken any drug for at least 1 week before the study. Other medication was not allowed during the study.

Study design. According to a two-way crossover schedule, each subject received 1.0 g of ceftriaxone by i.m. injection at the start of the study. A 1-week washout period was allowed before the second 1.0-g dose was administered i.v. Ceftriaxone was supplied in ampoules containing 1.0-g equivalents of ceftriaxone. When given by the i.m. route, 1.0 g of ceftriaxone was diluted in 5.0 ml of 1% lidocaine solution. This was administered slowly over a 3-min period. When given by the i.v. route, 1.0 g of ceftriaxone was diluted in 10 ml of water and administered slowly over a 3-min period.

Specimen collection. Blood and saliva samples were collected before the administration of ceftriaxone and at 0.25, 0.5, 0.75, 1, 2, 4, 8, 12, 24, and 36 h after dosage. Blood samples were collected into tubes containing sodium EDTA. Plasma was separated by centrifugation and frozen (−20°C) until analyzed. Saliva samples were frozen (−20°C) until analyzed.

Analytical method. Plasma and saliva samples were assayed for ceftriaxone by a reverse-phase ion-pairing high-pressure liquid chromatography (HPLC) procedure modified from Trautmann and Haeffelfinger (22). A 100-μl portion of a standard, unknown, or quality control sample was aliquoted into a 1.5-ml polypropylene microcentrifuge tube (Bio Plas Inc., San Francisco, Calif.). A 300-μl amount of internal standard solution (15 μg of diazepam per ml in ethanol) was added and vortexed for 30 s. The precipitated protein was separated by centrifugation in an MSE Micro Centaur (MSE...
Scientific Instruments, West Sussex, U.K.) for 1 min at 11,500 × g. A 40-µl portion of the supernatant was injected into an HPLC system. The HPLC system consisted of a Waters 6000A pump, U6K injector, M450 variable-wavelength detector, and M730 data module (Waters Associates, Milford, Mass.). The wavelength was set at 270 nm, with sensitivity at 0.01 absorbance unit full scale. The analytical column was a steel column (3.9-mm inside diameter by 30 cm) packed with UltraBondapak C18 (Waters Associates).

The mobile phase was prepared by mixing equal volumes of a 10% Titrisol-phosphate buffer, pH 7.0 (E. Merck AG, Darmstadt, Federal Republic of Germany), containing 0.8% hexadecyltrimethylammonium bromide (Eastern Kodak Co., Rochester, N.Y.) with an equal volume of HPLC-grade acetonitrile (Fisher Scientific Co., Fair Lawn, N.J.).

At a flow rate of 2.2 ml/min, the retention times for ceftriaxone and diazepam were 4.4 and 3.4 min, respectively. The concentrations of ceftriaxone in unknowns were calculated from peak height ratios, using the internal standard technique.

The lower limit of detection of the assay was 0.5 µg/ml (at a signal/noise ratio of 3). Linear response in the peak height ratio of ceftriaxone and the internal standard was observed at plasma ceftriaxone concentrations of 1 to 500 µg/ml. The between-day precision of the method at plasma ceftriaxone concentrations of 10.5, 96.5, and 452.6 µg/ml was 11.2, 4.6, and 4.1%, respectively (n = 10).

**Pharmacokinetic analysis.** The plasma concentration-time data after i.v. administration were analyzed according to a two-compartment model. The short i.v. infusion of ceftriaxone (approximately 3 min) was considered analogous to a bolus injection.

The following biexponential equation describes ceftriaxone plasma concentration, C, with respective to time, t = A · e^(-αt) + B · e^(-βt), where A and B are the coefficients of the biexponential equation, α is the disposition constant during the distribution phase, and β is the disposition constant during the elimination phase.

B and β were calculated from data obtained between 4 and 36 post-dose by the method of nonlinear least-squares fit. A and α were calculated with data obtained from the first four h by the method of residuals (3) and nonlinear least-squares fit.

The total area under the drug concentration-time curve (AUCo-w) was calculated by the following equation: AUCo-w = A/α + B/β. The total body clearance (CL) was calculated by the equation: CL = dose/AUCo-w. The volume of distribution at β phase (Vd) was calculated as follows: Vd = dose/(AUCo-w · β). The half-life at β phase (tβ/2) was calculated from 1/2β = 0.693/β.

With data obtained from the i.m. administration study, parameters for B, β, and tβ/2 were calculated by the same procedure as described above. AUCo-w was calculated by the method of trapezoidal rule. The tail area (AUC24-h) was obtained by using the equation C24/β, where C24 is the observed ceftriaxone plasma concentration at 36 h. Bioavailability (F) was calculated by the equation, F = AUCl/AUC after i.m./AUC after i.v.

**Statistical analysis.** Data was analyzed by Student’s t test for paired data.

### RESULTS

The subjects did not experience any major discomfort during the course of this study. No complications or adverse effects associated with the administration of ceftriaxone were observed.

Table 1 shows the mean ceftriaxone concentration in plasma for a 36-h period after a single i.m. or i.v. injection of 1.0 g of ceftriaxone. Data from one subject is presented graphically in Fig. 1.

After i.m. administration, the mean plasma concentration of ceftriaxone peaked after 1 h. The mean ceftriaxone concentration at 1 h was 125.7 µg/ml.

After i.v. administration, the plasma concentration of ceftriaxone decreased rapidly during the first 2 h. This was followed by a relatively slow elimination phase.

With either route of administration, a monoeponential elimination phase was observed at 4 to 36 h. During this period, the mean ceftriaxone concentrations after i.m. administration were 17 to 23% higher than those obtained after an i.v. dose. The elimination profiles were similar for the two routes of administration, and a parallel decline in concentration-time curves was observed.

The pharmacokinetic parameters were calculated from plasma concentration data obtained from each volunteer. These are presented in Tables 2 and 3. For i.m. administration (Table 2), mean values for time to maximum concentration, maximum concentration, and tβ/2 were 1.4, 130.6 µg/ml, and 8.2 h, respectively. For i.v. administrations (Table 3) mean values for tβ/2, Vd, and CL were 8.1 h, 8.5 liters, and 0.68 liter/h, respectively.

Data were also obtained from one male Caucasian who participated in the i.v. phase of the study. The subject was 45 years old, weighed 71.7 kg, and measured 175 cm in height. For the 8 years before the study, he had been living...
in Southeast Asia. The subject’s diet has been approximately three-quarters Chinese and one-quarter Western. Values of 8.9 h, 8.4 liters, and 0.65 liter/h were obtained for $t_{1/2}$, $V_d$, and $CL$, respectively.

There were no significant differences ($P > 0.05$) in the mean values obtained for $t_{1/2}$ and $AUC$ by the two different modes of drug administration.

**DISCUSSION**

After i.m. administration, the plasma concentration-time data for ceftriaxone could be described by a one-compartment open model with a monoeXponential decline, whereas the data obtained from i.v. administration exhibited a biexponential decline.

With i.m. administration, a mean $T_{max}$ of 1.4 h was obtained in this study. This agrees well with values of 1.7 and 2.0 h reported earlier (2, 9).

**TABLE 2.** Pharmacokinetic parameters of ceftriaxone after single-dose i.m. administration (dose = 1.0 g)*

<table>
<thead>
<tr>
<th>Subject</th>
<th>$T_{max}$ (h)</th>
<th>$C_{max}$ (μg/ml)</th>
<th>$t_{1/2}$ (h)</th>
<th>AUCO-∞ (μg · h/ml)</th>
<th>Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>151.0</td>
<td>8.1</td>
<td>1,261</td>
<td>1.09</td>
</tr>
<tr>
<td>2</td>
<td>1.3</td>
<td>101.2</td>
<td>8.7</td>
<td>1,474</td>
<td>1.01</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>131.9</td>
<td>7.5</td>
<td>1,577</td>
<td>0.96</td>
</tr>
<tr>
<td>4</td>
<td>0.9</td>
<td>144.3</td>
<td>8.6</td>
<td>1,632</td>
<td>0.97</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>122.0</td>
<td>8.5</td>
<td>1,370</td>
<td>0.98</td>
</tr>
<tr>
<td>6</td>
<td>2.3</td>
<td>133.1</td>
<td>7.6</td>
<td>1,646</td>
<td>0.97</td>
</tr>
<tr>
<td>Mean</td>
<td>1.4</td>
<td>130.6</td>
<td>8.2</td>
<td>1,493</td>
<td>1.00</td>
</tr>
<tr>
<td>SD</td>
<td>0.5</td>
<td>17.6</td>
<td>0.5</td>
<td>154</td>
<td>0.05</td>
</tr>
</tbody>
</table>

* Parameters are defined in the text.

**TABLE 3.** Pharmacokinetic parameters of ceftriaxone after single-dose i.v. administration (dose = 1.0 g)*

<table>
<thead>
<tr>
<th>Subject</th>
<th>$t_{1/2}$ (h)</th>
<th>$V_d$ (liters)</th>
<th>AUCO-∞ (μg · h/ml)</th>
<th>$CL$ (liters/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.2</td>
<td>10.9</td>
<td>1,160</td>
<td>0.86</td>
</tr>
<tr>
<td>2</td>
<td>8.1</td>
<td>8.5</td>
<td>1,454</td>
<td>0.69</td>
</tr>
<tr>
<td>3</td>
<td>7.6</td>
<td>7.6</td>
<td>1,647</td>
<td>0.61</td>
</tr>
<tr>
<td>4</td>
<td>8.6</td>
<td>7.8</td>
<td>1,685</td>
<td>0.59</td>
</tr>
<tr>
<td>5</td>
<td>8.1</td>
<td>8.9</td>
<td>1,399</td>
<td>0.72</td>
</tr>
<tr>
<td>6</td>
<td>8.0</td>
<td>7.2</td>
<td>1,695</td>
<td>0.59</td>
</tr>
<tr>
<td>Mean</td>
<td>8.1</td>
<td>8.5</td>
<td>1,507</td>
<td>0.68</td>
</tr>
<tr>
<td>SD</td>
<td>0.3</td>
<td>1.3</td>
<td>210</td>
<td>0.11</td>
</tr>
</tbody>
</table>

* Parameters are defined in the text.
At 2 h after dosage, the ceftiraxone concentrations in plasma were very similar for i.m. and i.v. administration. Apart from a slightly higher plasma concentration after i.m. administration, the two mean plasma concentration-time curves after the second hour could almost be superimposed. Similar observations have been made by previous investigators (2, 4). Thus, our data provide additional evidence that i.m. administration is an appropriate alternative for i.v. administration of ceftiraxone.

The apparent volume of distribution for ceftiraxone is fairly low compared with that for other cephalosporins. It was found to be 8.5 liters. Ceftriaxone is primarily distributed into vascular fluids, highly vascular organs, and some extravascular fluid (11). Similar values have been reported by others (6, 8, 9).

In spite of the low apparent volume of distribution, the half-life of ceftiraxone is long relative to that of other cephalosporins. Mean terminal half-lives of 8.2 (i.m.) and 8.1 (i.v.) h obtained from this study are similar to reported values. A mean t½ of 6 to 9 h has been reported previously (2, 8, 9, 13).

One Caucasian subject was included in the i.v. study. The pharmacokinetic parameters obtained were not different from those calculated with Chinese subjects.

The mean AUC values after i.m. and i.v. administration of ceftiraxone were 1,493 and 1,507 µg·h/ml, respectively. Consequently, the calculated clearance was essentially identical, and the value of 1.0 was obtained for bioavailability. This suggests that a 1.0-g i.m. dose of ceftiraxone is completely absorbed. However, ceftiraxone has been shown to display nonlinear kinetics due to concentration-dependent plasma protein binding (4, 13, 14). At plasma concentrations above 150 µg/ml, an increase in the unbound fraction of ceftiraxone together with an increase in total plasma clearance has been demonstrated (14).

In the present study, the plasma ceftiraxone concentration did not exceed 150 µg/ml after i.m. administration. However, with i.v. administration plasma ceftiraxone concentrations of >150 µg/ml were observed in all subjects during the first hour of monitoring. Binding of ceftiraxone to plasma protein was not studied in this investigation. It is likely that concentration-dependent plasma protein binding of ceftiraxone also occurred in our subjects. This would result in a larger proportion of unbound ceftiraxone during the initial 1 h. Ceftriaxone is eliminated mainly by renal and biliary excretion (6). The rate of elimination of both mechanisms is proportional to the concentration of the unbound drug. Thus, a larger fraction of ceftiraxone in the circulation would be eliminated during the first hour after i.v. administration than during any other period. This in turn would result in a smaller calculated value for the AUC after i.v. administration. Consequently, although a bioavailability of 1.0 was calculated, the actual amount of ceftiraxone absorbed might be <100% of the 1-g dose administered i.m.

Although the HPLC procedure used in this study has a lower detection limit of 0.5 µg/ml, ceftiraxone was not detected in any of the saliva samples collected. Most drugs are transported across the epithelial cell layer separating plasma and saliva mainly by passive diffusion and for some drugs by active transport (12). Passive diffusion is governed by the concentration gradient of the non-protein-bound, lipid-soluble moiety of the drug, lipid solubility, degree of ionization, and extent of protein binding. Ceftriaxone is 95% bound to plasma protein at concentrations below 70 µg/ml. At 300 and 600 µg/ml, ceftiraxone is 84 and 58% bound to plasma protein, respectively (10, 14). The Pₖₐ for ceftiraxone is between 2.0 and 4.5 (13, 14). At a physiological plasma pH of 7.4, ceftiraxone exists predominantly in the ionized state. Thus, passive diffusion is unlikely to be important for transport of ceftiraxone into saliva. That ceftiraxone was not detected in any saliva samples from this study suggests that active transport for ceftiraxone is also unlikely.

In summary, this study demonstrates that the pharmacokinetic parameters obtained from healthy Chinese subjects are very similar to those previously described for healthy European or North American subjects. Thus, it may be concluded that no major modification in the established dosing regimen is required when ceftiraxone is used to treat Chinese patients.

**ACKNOWLEDGMENTS**

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**LITERATURE CITED**


