Pharmacokinetics of Cephanone in Healthy Adult Volunteers

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Five volunteers received intramuscular injections of 7 mg (approximately 500 mg) of cephanone, a new cephalosporin for parenteral use per kg. Peak serum concentrations averaged 36 μg/ml, about four times as high as with the same doses of cephalothin, twice as high as with cephaloridine, and slightly lower than with cefazolin. With a constant intravenous infusion of 100 mg/h, a steady-state serum concentration of 31 μg/ml was attained in four volunteers. The serum half-life was similar for the intramuscular and intravenous studies, 2.4 and 2.6 h, respectively. Over 90% of the dose administered was recovered in the urine. The factor mainly responsible for the higher and more sustained serum concentrations of cephanone was its low renal clearance of 47 ml per min per 1.73 m². Cephanone has a small apparent volume of distribution, probably related to its high serum protein binding of 88%.

Cephanone, a new semisynthetic cephalosporin available for parenteral administration, is similar to cephalothin and cephaloridine in its antibacterial spectrum. Wick and Preston (12) found higher serum concentrations of cephanone than of cephalothin or cephaloridine after subcutaneous injections in mice, and Meyers et al. (8) reported serum levels in volunteers that were significantly higher than those obtained with equal doses of cephalothin or cephaloridine given intravenously or intramuscularly. These pharmacological characteristics of cephanone are similar to those of cefazolin (9), another heterocyclic cephalosporin with a closely related chemical structure.

In the present study, cephanone serum levels and urinary excretion were determined in healthy volunteers after intravenous infusions and intramuscular injections to elucidate the pharmacokinetic properties of this new antibiotic.

MATERIALS AND METHODS

Four male volunteers received an intravenous infusion of cephanone for 3 h through a pediatric scalp vein needle by using a constant-infusion pump (Harvard Apparatus Co.). A loading dose of 3.5 mg/kg (approximately 250 mg) was diluted in 50 ml of saline and injected over the 1st h, followed by a sustaining dose of 1.5 mg/kg (approximately 100 mg) in 50 ml of saline hourly for the next 2 h to obtain a steady state during the 3rd h. Blood samples for the measurement of antibiotic concentrations were drawn at 1 h, four times during the next 2 h (end of the infusion), and at least seven times from 3 to 10 h. The urinary excretion was determined by assays of timed urine collections over 24 h.

Single intramuscular injections of 7 mg (approximately 500 mg) of cephanone per kg were given to five volunteers. Twelve blood samples were drawn during the next 8 h, at short intervals during the 1st 2 h to define the peak concentration, and then at 0.5- and 1-h intervals during the declining phase. Antibiotic concentrations in the urine were determined by assays of specimens collected from 0 to 4, 4 to 8, and 8 to 24 h. A sample from a pool of all the urine collected throughout the 24-h period was also assayed, and the total excretion of cephanone determined in this manner agreed closely with the results obtained by adding the amounts recovered in the different fractions.

The 5-ml blood samples were allowed to clot and were centrifuged, and serum and urine were frozen at −20 C until time for bioassay. Cephanone concentrations were measured by an agar-well diffusion assay method (2) by using Bacillus subtilis ATCC 6633 as the indicator organism.

The serum half-life was calculated during the elimination phase (from 4 to 10 h for the intravenous infusion study and from 3 to 8 h after intramuscular injection), when the cephanone serum levels declined exponentially, with the formula

\[ T_{1/2} = \frac{(\ln 2)}{(K_e)} \]

where \( \ln 2 \) is the natural logarithm of 2 and \( K_e \) is the slope of the regression line determined by the method of least squares. The apparent volume of distribution was calculated during the 3rd h of the intravenous infusion study with the formula

\[ V_{app} = \frac{(ko)}{(C_0 - K_e)} \]

where \( V_{app} \) is defined as the volume of distribution in liters under steady-state conditions; \( ko \) is the steady-state infusion rate in milligrams per h, and \( C_0 \) is the
steady-state serum concentration in $\mu g/ml$. The total or serum clearance was calculated from the steady-state data with the formula $P_{cl} = (ko/Co) \times (1.73 m^2/BSA)$ where BSA is the body surface area. The renal clearance was calculated in two volunteers during the intravenous infusion study by using urine collected at from 3 to 7 h, and the serum level at 5 h was obtained by interpolating the serum concentration from the regression line, and in five volunteers renal clearance was calculated during the intramuscular injection study by using the urine collected at from 4 to 8 h as was the corresponding serum level at 6 h, with the usual formula $U_{cl} = (U \times V/C) \times (1.73 m^2/BSA)$ where $U$ is the concentration of cephanone in the urine, $V$ the timed urine volume, and $C$ the antibiotic concentration in the serum.

RESULTS

With an intravenous infusion of approximately 250 mg (3.5 mg/kg) of cephanone, an average serum concentration of 31.9 $\mu g/ml$ was present at the end of the 1st h. During the 3rd h, with a sustaining dose of approximately 100 mg/h (1.5 mg per kg per h), a steady state with an average serum level of 31.2 $\mu g/ml$ was attained for the four volunteers (Fig. 1). After an intramuscular injection of approximately 500 mg (7 mg/kg), peak serum concentrations occurred between 0.75 and 1.5 h and averaged 36.0 $\mu g/ml$. At 6 and 8 h later, the average serum concentrations were 11.2 and 6.6 $\mu g/ml$, respectively (Fig. 2). Thus, similar serum concentrations were obtained with a single 250-mg dose of cephanone administered intravenously over 1 h and with 500 mg injected intramuscularly.

Urinary recovery of cephanone was similar after intravenous and intramuscular injections. About 55% of the dose administered was excreted in the 1st 4 h, 80% in 8 h, and 92% in 24 h. Antibiotic concentrations of over 900 $\mu g/ml$ were present in the urine collection from 0 to 4 h, 200 $\mu g/ml$ from 4 to 8 h, and at least 20 $\mu g/ml$ from 8 to 24 h.

The serum half-life of cephanone, measured after the intravenous infusion had been stopped, was 2.40 h. A similar half-life of 2.63 h was calculated for the interval between 3 and 8 h after intramuscular injection. The exponential decline of the serum levels was confirmed by obtaining coefficients of correlation of a straight line of $\geq 0.98$ for each of the regression lines when they were plotted on a semilogarithmic scale.

The apparent volume of distribution calculated at the steady state, during the 3rd h of the intravenous infusion, was 13.6 liters, or 16.6% of the total body weight. The total or serum clearance, measured at the same time, was 56.3 ml per min per 1.73 m². The renal clearance of cephanone was 46.6 ml per min per 1.73 m². Creatinine clearances were determined on the same day over 24 h and averaged 121.7 ± 6.9 ml per min per 1.73 m² (standard error of the mean). The ratio of the renal clearance of cephanone to the creatinine clearance was 0.40 (±0.02), not significantly different from the ratio of the total or serum clearance of cephanone to the creatinine clearance, namely 0.47 (±0.05).

DISCUSSION

Remarkably high serum concentrations of cephanone as compared with cephalothin and cephaloridine were obtained in the present study (Table 1). Previously, in our laboratory (7, 10), steady-state serum concentrations of 17.4 and 24.7 $\mu g/ml$ were obtained with 500 and 250 mg of cephalothin and cephaloridine per h, respectively, as compared with a level of 31.1 $\mu g/ml$ with only 100 mg/h in the present study. Intramuscularly, single 0.5-g injections of cephalothin gave peak blood levels about 0.25 (1, 6), and cephaloridine about 0.50 (1, 5), of those obtained with cephanone. In addition to its higher peak blood levels, the serum concentration of cephanone declined more slowly, giving a half-life of about 2.5 h as compared with 1.1 for cephaloridine and 0.5 for cephalothin (7). The
serum half-life of cephanone was similar for the intramuscular and intravenous studies, 158 and 144 min (P > 0.40), due to using only the pure elimination phase, i.e., from 4 to 10 h after the intravenous infusion had been stopped and from 3 to 8 h after intramuscular injection. In contrast, Meyers et al. (8) observed half-lives of 174 and 126 min after intramuscular and intravenous administration, respectively, and the discrepancy may have been due to using different intervals after administration of the antibiotic.

The factor mainly responsible for the higher and better-sustained blood levels of cephanone is its slower rate of renal clearance, 47 versus 125 and 274 ml per min per 1.73 m² for cefaloridine and cephalothin (7). It is apparent that cephanone leaves the body chiefly through the kidneys, because its serum clearance was only slightly greater than its renal clearance, and about 95% of the dose administered appeared in the urine. The two components making up renal clearance, glomerular filtration and tubular secretion, both contribute to the low renal clearance value for cephanone. Only a small amount (about one-seventh) is filtered through the glomeruli because of its high serum protein binding, 88%, and a larger, more significant element of tubular secretion (about six-sevenths) makes up the rest. For the cephalosporins and penicillins, renal clearance has a more important influence than serum protein binding on serum concentrations and half-lives because of the important influence of tubular secretion, which operates independently of protein binding (4). For example cephaloridine, with serum protein binding of only 20%, has blood levels and a serum half-life twice as great as cephalothin, which is 65% bound, because of its much slower renal clearance, noted above (10). Cephalexin, with serum protein binding of 15%, has the same renal clearance as cephalothin, 65% bound (W. M. M. Kirby and C. Regamey, 1973, J. Infect. Dis., in press). Ampicillin has a steady-state blood level 80% higher than penicillin G, despite its much lower serum protein binding (15 versus 70%), because of its much slower renal clearance (210 versus 386 ml per min per 1.73 m²) (11). The small apparent volume of distribution of cephanone (13.6 liters) is directly related to its high serum protein binding (88%), and this factor also is partly responsible for the high blood levels and long half-life.

These pharmacological properties of cephanone are similar to those of cefazolin, which has a closely related chemical structure, with a tetrazol-1-y1 rather than a sydnone group in the side chain. Peak blood levels were found to be slightly higher with cefazolin, 42 versus 36

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**Table 1. Pharmacological characteristics of cephanone**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value obtained</th>
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<tbody>
<tr>
<td>Serum concn after intravenous infusion of 3.5 mg/kg over 1 h (approx. 250 mg)</td>
<td>31.9 ± 1.3 μg/ml*</td>
</tr>
<tr>
<td>Serum concn at steady state with infusion rate of 1.5 mg per kg per h (approx. 100 mg)</td>
<td>31.2 ± 1.1 μg/ml</td>
</tr>
<tr>
<td>Peak serum concn after intramuscular injection of 7 mg/kg (approx. 500 mg)</td>
<td>36.0 ± 2.8 μg/ml</td>
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<tr>
<td>Half-life intravenous study</td>
<td>2.40 ± 0.04 hours</td>
</tr>
<tr>
<td>Half-life intramuscular study</td>
<td>2.63 ± 0.13 hours</td>
</tr>
<tr>
<td>Apparent volume of distribution in liters</td>
<td>16.6 ± 0.7</td>
</tr>
<tr>
<td>Apparent volume of distribution in % of total body weight</td>
<td>56.3 ± 1.8 ml/min/1.73 m²</td>
</tr>
<tr>
<td>Total or serum clearance</td>
<td>46.6 ± 3.7 ml/min/1.73 m²</td>
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* Standard error of the mean.
\( \mu \text{g/ml} \) with 0.5 g intramuscularly, whereas the serum half-life was longer with cephanone (2.5 versus 1.8 h). These differences appear to be due to a lower renal clearance (47 versus 64 ml per min per 1.73 m\(^2\)) and a slightly larger volume of distribution (13.6 versus 11.0 liters) for cephanone (C. Regamey, R. C. Gordon, and W. M. M. Kirby, 1973, Arch. Intern. Med., in press).

**LITERATURE CITED**


