Pharmacokinetics of Cefoperazone in Ambulatory Elderly Volunteers Compared with Young Adults

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Two groups of 10 healthy ambulatory subjects, i.e., a group of 10 persons ≈30 years of age (mean age, 27.6 years) and a group of 10 persons ≈65 years of age (mean age, 70 years), were randomized in a single-trial crossover design to receive 1 and 2 g of cefoperazone with a 1-week washout between doses. The elderly subjects had both decreased estimated creatinine clearances and decreased albumin concentrations in serum. Cefoperazone concentrations in serum of elderly persons were significantly higher at each interval from 30 min to 6 h for the 2-g dose. Compared with that in younger persons, the total clearance in elderly subjects was significantly lower for both the 1- and 2-g doses, the renal clearance was significantly lower for the 2-g dose, and the area under the curve was significantly higher for the 2-g dose in the elderly persons. The half-life at β phase was higher in the elderly persons at both the 1- and 2-g doses but not significantly so. Changes in total clearance and area under the curve and higher levels in serum in the elderly persons suggest a longer duration of antimicrobial activity in this age group.

The elderly (persons of >65 years of age) represent a significant and growing portion of the U.S. population, making up 12% of the total population in 1980 and estimated to increase to 17% in the year 2030 (38). Disproportionate percentages of health care expenditures (25 to 30%) (22) and prescription drugs dispensed (25%) (9) are generated by this segment of the population. In addition, the incidence of adverse reactions to drugs has been clearly demonstrated to be greater in the elderly (18).

The newer extended-spectrum beta-lactam antimicrobial agents, with their potent antibacterial activity and relative lack of toxicity, are finding increased use as preferred agents for the treatment of elderly patients with infection. Their safety profile appears to be greater than that of the aminoglycosides that have been shown to be associated with increased rates of toxicity in the elderly (27).

In view of age-associated altered drug absorption and disposition, decreased protein binding, renal clearance, hepatic drug metabolism (30, 33), and albumin levels (5, 26), and increased drug-drug interactions, it is possible that the pharmacokinetics of the new beta-lactam agents are altered as well. The pharmacokinetic properties of ceftriaxone (25), ceftazidime (23), and cefotaxime (20) in the elderly have shown differences compared with those in younger subjects.

The pharmacokinetic properties of cefoperazone, a broad-spectrum antipseudomonal cephalosporin (19), have been studied in healthy young volunteers. Excretion is via dual pathways; 15 to 37% is excreted in urine, with the remainder excreted by nonrenal mechanisms, predominantly the hepatobiliary system (12, 17, 36). Additional studies have been done in patients with impaired renal and hepatic functions (2, 7, 8, 17) and in patients with renal dysfunction and active infection (32); altered pharmacokinetic parameters have been noted in these studies. We report here the pharmacokinetics of cefoperazone in healthy elderly subjects compared with those in younger controls.

**MATERIALS AND METHODS**

**Study subjects.** Twenty healthy adult subjects 24 to 78 years of age were divided into two groups. Group Y included five males and five females 24 to 30 years old, and group O included eight males and two females 65 to 78 years old. The study protocol was approved by The Mount Sinai School of Medicine Institutional Review Board, and written informed consent was obtained from each volunteer. Exclusion criteria included a history of penicillin or cephalosporin allergy, severe cardiovascular disease, or blood dyscrasia. Prestudy physical examinations, blood cell count, urinalysis, and blood chemistries, including liver function tests, were normal for all subjects.

**Clinical parameters.** Ideal body weight was estimated by the following formulas: 45.5 + 2.3 kg for every inch (2.54 cm) over 5 feet (1.524 m) for females and 50 + 2.3 kg for every inch over 5 feet for males (14). Body surface area was determined from a table derived from the method of Sendroy and Cecchini (1, 34). Creatinine clearance (CLCr) was estimated from the formula of Cockcroft and Gault (10) and normalized to 1.73 m² of body surface area.

**Study design.** Single cefoperazone doses of 1 and 2 g were given using a single-blind, randomized, crossover design with a minimum 1-week interval between doses. Cefoperazone was reconstituted in sterile saline and infused intravenously in 50 ml of 5% glucose in water via Soluset for 30 min. Subjects fasted overnight before administration and 2 h thereafter and were advised to refrain from alcohol or caffeine intake for the duration of the study and for at least 72 h after the last dose.

**Specimen collection.** Blood samples were obtained from a contralateral vein before infusion and at 0.5, 0.58, 0.75, 1, 2, 3, 4, 5, 6, 8, 12, and 24 h after the start of infusion. Serum was separated by centrifugation and frozen (−70°C) until analyzed. Urine was collected before dosage and at 0 to 6, 6 to 12, and 12 to 24 h thereafter. The volumes voided were

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recorded, and samples were retained and frozen (−70°C) until analysis. The specimens were shipped in dry ice to the University of Texas Health Science Center, where they were received in the frozen state.

Cefoperazone assay. Concentrations of cefoperazone in serum and urine were determined by a standardized high-pressure liquid chromatography method using a Waters Associates, Inc. (Milford, Mass.), high-pressure liquid chromatography system (4). The mobile phase consisted of 76% 0.1 M PO4 buffer (pH 6.0) and 24% acetonitrile. The flow rate was 2.7 ml/min, and the retention time of cefoperazone was 2.5 min. The recovery of cefoperazone was 99%, and the correlation coefficient of the standard curve was 0.999 (4).

Pharmacokinetic analysis. Curves of cefoperazone concentration in plasma versus time for each of the subjects were described by a two-compartment model with constant-rate input. The best coefficient of determination, r², from initial JANA stripping of data was used to determine the compartmental analysis (15). Two-compartmental analysis was done by using PCNONLIN (37). The two exponential terms with no constraints on coefficient algorithm corrected for infusion were used for pharmacokinetic parameter determination. The data were weighted 1/y².

The following parameters were calculated: peak concentration in serum, Cmax (milligrams per liter); elimination and steady-state volumes of distribution, Varea (liters per 1.73 m²) and Vd (liters per kilogram per 1.73 m²), respectively; volume of distribution in the central compartment, V1 (liters per kilogram per 1.73 m²); terminal half-life, t1/2b (hours); area under the serum concentration-versus-time curve, AUC (mg · h/liter per 1.73 m²); and total (CL), renal (CLr), and nonrenal (CLNR) clearances (milliliters per minute per 1.73 m²).

To determine the effect that CLCR had on the pharmacokinetics of cefoperazone, Varea, V1, Vss, t1/2b, CL, CLR, CLNR, and AUC versus CLCR curves for the 1- and 2-g dosage regimens were plotted. A linear regression value of r > 0.7 was used to determine whether renal function had a significant impact on the above pharmacokinetic parameters.

Statistical analysis. A two-tailed independent t test was used to analyze significant differences in independent variables when comparing the elderly with the young.

RESULTS

Clinical data for the 20 subjects are listed in Table 1. Serum albumin and CLCR were reduced in group O. Elderly subjects weighed more (P < 0.01) than the young and had higher creatinine levels in serum (P < 0.05). Table 2 gives the mean concentrations of cefoperazone in serum following intravenous administration of 1- and 2-g doses. The mean concentration-versus-time profiles following 1- and 2-g doses of cefoperazone administered intravenously are shown in Fig. 1 and 2. At the 2-g dose, the concentrations in serum from 30 min to 6 h were significantly higher at each interval for the elderly than for the young (P < 0.05).

Clearance of cefoperazone was lower in elderly than in young subjects (Table 3). For the 1- and 2-g doses, respectively, the CL values in groups Y and O were 96.73 and 64.87 ml/min per 1.73 m² (P < 0.04) and 85.2 and 59.8 ml/min per 1.73 m² (P < 0.04); and the CLr values were 37.48 and 19.69 ml/min per 1.73 m² (not significant) and 26.6 and 14.6 ml/min per 1.73 m² (P < 0.05). The Cmax was significantly higher (P < 0.05) following 2-g doses in elderly than in young subjects. Following 1- and 2-g doses, the t1/2b was prolonged in the elderly (not significant). The AUC was significantly greater (P < 0.05) for the 2-g dose and greater (not significant) for the 1-g dose in elderly subjects. V1 and Varea were larger (P

### Table 1. Clinical data

<table>
<thead>
<tr>
<th>Subject group</th>
<th>Age (yr)</th>
<th>Serum creatinine (mg/dl)</th>
<th>Serum albumin (g/dl)</th>
<th>Ht (cm)</th>
<th>Wt (kg)</th>
<th>Ideal body wt (kg)</th>
<th>Body surface area (m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly</td>
<td>70.4 ± 4.9</td>
<td>1.1 ± 0.2</td>
<td>57.3 ± 10.4</td>
<td>4.1 ± 0.2</td>
<td>171.3 ± 7.9</td>
<td>74.9 ± 17.2</td>
<td>66.2 ± 8.5</td>
</tr>
<tr>
<td>Young</td>
<td>27.8 ± 1.9</td>
<td>0.9 ± 0.1</td>
<td>104.0 ± 21.5</td>
<td>4.5 ± 0.1</td>
<td>172.4 ± 10.0</td>
<td>65.6 ± 11.7</td>
<td>65.6 ± 11.1</td>
</tr>
</tbody>
</table>

* Values are means ± standard deviation.
* a P < 0.02.
* b P < 0.01.
* c Not significant.

### Table 2. Concentrations of cefoperazone in serum

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Young (1-g dose)</th>
<th>Elderly (1-g dose)</th>
<th>Young (2-g dose)</th>
<th>Elderly (2-g dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.50</td>
<td>154.9 ± 69.65</td>
<td>157.0 ± 36.24</td>
<td>221.83 ± 50.92</td>
<td>338.40 ± 143.64</td>
</tr>
<tr>
<td>0.58</td>
<td>117.18 ± 40.32</td>
<td>114.87 ± 36.43</td>
<td>168.89 ± 37.52</td>
<td>258.82 ± 95.91</td>
</tr>
<tr>
<td>0.75</td>
<td>85.02 ± 31.20</td>
<td>86.35 ± 27.69</td>
<td>136.74 ± 23.87</td>
<td>196.13 ± 75.60</td>
</tr>
<tr>
<td>1.00</td>
<td>60.69 ± 19.83</td>
<td>76.63 ± 25.80</td>
<td>113.79 ± 24.02</td>
<td>160.46 ± 69.77</td>
</tr>
<tr>
<td>1.50</td>
<td>57.03 ± 23.79</td>
<td>60.95 ± 12.34</td>
<td>88.22 ± 25.91</td>
<td>142.87 ± 72.00</td>
</tr>
<tr>
<td>2.00</td>
<td>30.37 ± 20.70</td>
<td>43.73 ± 12.78</td>
<td>61.26 ± 15.15</td>
<td>111.11 ± 58.50</td>
</tr>
<tr>
<td>2.50</td>
<td>26.11 ± 19.88</td>
<td>34.78 ± 5.59</td>
<td>55.03 ± 15.68</td>
<td>97.52 ± 54.83</td>
</tr>
<tr>
<td>3.00</td>
<td>20.13 ± 14.00</td>
<td>29.30 ± 4.55</td>
<td>46.48 ± 9.64</td>
<td>77.79 ± 40.66</td>
</tr>
<tr>
<td>4.00</td>
<td>12.49 ± 6.56</td>
<td>20.80 ± 7.14</td>
<td>30.21 ± 7.18</td>
<td>58.73 ± 36.23</td>
</tr>
<tr>
<td>5.00</td>
<td>8.63 ± 5.49</td>
<td>17.14 ± 5.70</td>
<td>19.36 ± 9.20</td>
<td>44.63 ± 31.83</td>
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<tr>
<td>6.00</td>
<td>5.15 ± 2.72</td>
<td>10.90 ± 4.12</td>
<td>13.27 ± 8.26</td>
<td>22.15 ± 8.25</td>
</tr>
<tr>
<td>8.00</td>
<td>2.79 ± 1.72</td>
<td>5.74 ± 2.48</td>
<td>8.40 ± 4.20</td>
<td>15.32 ± 12.24</td>
</tr>
<tr>
<td>12.00</td>
<td>1.34 ± 1.12</td>
<td>1.96 ± 1.13</td>
<td>3.04 ± 1.97</td>
<td>8.44 ± 10.36</td>
</tr>
<tr>
<td>24.00</td>
<td>0.80 ± 0.39</td>
<td>1.24 ± 2.03</td>
<td>1.72 ± 5.05</td>
<td>1.10 ± 1.12</td>
</tr>
</tbody>
</table>
PHARMACOKINETICS OF CEFOPERAZONE

FIG. 1. Levels in serum following administration of a 1-g intravenous dose of cefoperazone in young (Y) and elderly (O) volunteers.

< 0.03 for \( V_1; \) \( P < 0.04 \) for \( V_{\text{area}} \) in young than in elderly subjects for the 1-g dose.

\( C_{\text{L}_{\text{CR}}} \) was not a factor for the following pharmacokinetic differences seen between the elderly and the young: \( V_{\text{area}} \) (r = 0.16, 1 g; 0.20, 2 g), \( V_1 \) (r = 0.51, 1 g; 0.12, 2 g), \( V_{\text{Cu}} \) (r = 0.02, 1 g; 0.16, 2 g), \( t_{1/2p} \) (r = 0.36, 1 g; 0.25, 2 g), \( CL \) (r = 0.37, 1 g; 0.45, 2 g), \( CL_{R} \) (r = 0.43, 1 g; 0.31, 2 g), \( CL_{\text{NR}} \) (r = 0.04, 1 g; 0.32, 2 g), and \( AUC \) (r = 0.25, 1 g; 0.33, 2 g). Each of the parameters listed above except \( CL_{R} \) showed flat response curves; \( CL_{CR} \) had no effect on the parameter. The \( CL_{R} \) at 1 and 2 g plotted versus \( CL_{CR} \) was the only parameter that did show linearity, although the \( r \) value did not show a significant correlation between \( CL_{R} \) and \( CL_{CR} \).

There were three episodes of diarrhea and three disulfiramlike reactions, characterized by tachycardia, sweating, and dizziness, in group Y. All symptoms were reversible and of short duration. There were no changes in laboratory values after drug administration in either group.

**DISCUSSION**

Analysis of the demographic data revealed significant decreases in \( CL_{CR} \) and serum albumin in the elderly compared with the younger population. The decreases in renal function were not unexpected since it is known that renal function decreases with age (31). The differences in serum albumin level were slight but significant for these healthy ambulatory elderly volunteers.

The pharmacokinetic data derived in our young subjects are comparable with those of previous studies in this age group (12, 17, 36). There were significant decreases in the serum and renal clearances in the elderly compared with the young. With the 2-g dose, significant increases in \( C_{\text{max}} \) and \( AUC \) were noted in the aged population; the CL and \( CL_{R} \) of cefoperazone were decreased.

Recently, the influence of changes in serum protein and drug binding and their effects on total and free drug fractions have been considered (16). Higher free-drug levels have been demonstrated when highly protein-bound antibiotics were studied in elderly compared with younger patients (25). Cefoperazone is highly protein bound to the extent of 87 to 93% of the concentration in serum (17). Other compounds that are highly protein bound, such as ceftriaxone, have been studied in the elderly (25). There is an increased concentration of free drug in the first 4 h of administration in elderly compared with younger subjects. This may be related to a decrease in protein binding that is more pronounced than can be accounted for by decreases in albumin alone (25). An other contributing factor may be the decreased excretion of free drug due to age-related decline in renal function. These same factors thus would be expected to prolong the level in serum and the time of free circulating drug in patients given cefoperazone.

Another factor to be considered in the pharmacokinetics of cefoperazone in the elderly is its dual pathway of excretion (hepatobiliary and renal). Under ordinary circumstances in patients with normal hepatobiliary function but compromised renal function, significant differences in levels in serum, volume of distribution, beta half-life, and total body clearance have not been noted (7). This can be attributed to the increase in nonrenal clearance afforded by a normal hepatobiliary pathway. In contrast, when patients with significant hepatobiliary dysfunction were compared with normal controls, the half-life of cefoperazone was increased up to fourfold (8, 17). However, because of a marked increase in \( CL_{R} \) and lack of significant accumulation in serum, dosage modifications (<1 g every 12 h) of cefoperazone are generally not necessary in patients with hepatic dysfunction and relatively normal renal function. When patients with concomitant hepatic and renal dysfunctions have been studied, a marked prolongation of half-life (10 to 14 h) has been reported (3, 8). The impairment of renal function in the elderly demonstrated in our patients, as well as impairment of hepatic drug elimination described in the elderly (30, 35), may contribute to the prolonged half-life and decreased clearance from serum that we observed in the elderly subjects. This suggests that the hepatobiliary pathway cannot fully compensate with an increase in excretion when decreased \( CL_{R} \) occurs in elderly subjects.

In addition, decreases in renal function, drug metabolism, and serum albumin may be more pronounced in advanced illness associated with serious infection in the elderly. A greater alteration in these pharmacokinetic parameters of cefoperazone may be expected in elderly patients who are septic or seriously infected. Studies in patients with renal dysfunction and infection treated with cefoperazone have demonstrated prolongation of half-life, as well as higher trough and peak levels in serum, compared with noninfected patients (32). A potential decrease in hepatic blood flow associated with septicemia and serious infection may account for the lack of full compensatory excretion of cefoperazone via the hepatic pathway in infected patients with impaired renal function. Such exaggeration of altered kinetics in elderly patients has been demonstrated in studies with other beta-lactam antibiotics. Studies with cefazidime in acutely ill infected elderly patients (24, 28) demonstrated

FIG. 2. Levels in serum following administration of a 2-g intravenous dose of cefoperazone in young (Y) and elderly (O) volunteers.
more pronounced differences in pharmacokinetic parameters than those observed in healthy noninfected elderly patients as compared with younger subjects (23). Parameters with significant differences included longer half-life and larger AUC in infected elderly patients in addition to decreased CL and CL/F as observed in healthy elderly volunteers.

Decreases in serum albumin, protein binding, renal function, and hepatic function would tend to prolong the circulation of free drug. This form of the antibiotic is the active antibacterial agent in tissue spaces (13, 21). The increased AUC at both dosages and changes in t1/2 in the elderly compared with the young suggest that the duration of antimicrobial activity may be increased in the elderly. It is believed that the AUC is a good indicator of antimicrobial activity in vivo (11).

A disulfiram-like reaction with alcohol has been described in patients taking a variety of antimicrobial agents; compounds containing the N-methyl thiotetrazole ring are believed to be associated with these reactions (6, 29). Although all volunteers in this study were warned of the effects of alcohol (i.e., not to have any intake until >72 h after study drug administration), several members of the younger age group admitted to being noncompliant with this recommendation. Alcohol consumption in a hospital setting is not common. At home, however, when drugs with N-methyl thiotetrazole rings are prescribed, patients must be cautioned about abstinence from alcohol.

In summary, our data suggest prolongation of cefoperazone antimicrobial activity due to increased AUC and t1/2 in the elderly. These differences would be expected to be even greater when treating infected elderly patients as reported in studies with other beta-lactam antibiotics (20, 24, 28). Treatment schedules with lower doses and at increased intervals as recently reported with cefotaxime may well apply to cefoperazone and warrant further investigation. If such treatment regimens are effective, then reduced costs and toxicity should follow.

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