Pharmacokinetics and Pharmacodynamics of Cefpirome in Subcutaneous Adipose Tissue of Septic Patients

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The objective of the present study was to evaluate whether cefpirome, a member of the latest class of broad-spectrum cephalosporins, sufficiently penetrates subcutaneous adipose tissue in septic patients. After the administration of the drug at 2 g, tissue cefpirome concentrations in septic patients (n = 11) and healthy controls (n = 7) were determined over a period of 4 h by means of microdialysis. To assess the antibacterial effect of cefpirome at the target site, the measured pharmacokinetic profiles were simulated in vitro with select strains of Staphylococcus aureus and Pseudomonas aeruginosa. The tissue penetration of cefpirome was significantly impaired in septic patients compared with that in healthy subjects. For subcutaneous adipose tissue, the area under the concentration-versus-time curve values from 0 to 240 min were 13.11 ± 5.20 g · min/liter in healthy subjects and 6.90 ± 2.56 g · min/liter in septic patients (P < 0.05). Effective bacterial growth inhibition was observed in all in vitro simulations. This was attributed to the significantly prolonged half-life in tissue (P < 0.05), which kept the tissue cefpirome levels above the MICs for relevant pathogens for extended periods in the septic group. By consideration of a dosing interval of 8 h, the values for the time above MIC (T > MIC) in tissue were greater than 60% for pathogens for which the MIC was ≤4 mg/liter in all septic patients. The present data indicate that cefpirome is an appropriate agent for the treatment of soft tissue infections in septic patients. However, due to the high interindividual variability of the pharmacokinetics of cefpirome in tissue, dosing intervals of not more than 8 h should be preferred to ensure that susceptible bacterial strains are killed in each patient.

In septic patients, antibiotic therapy is commonly administered intravenously, and in most cases susceptible bacteria are eliminated from the blood. The eradication of bacteria from the infected tissue is more challenging, because sufficient penetration of an antibiotic to the site of infection is a prerequisite for the successful treatment of patients with soft tissue infections (STIs). However, the pharmacokinetics (PKs) of antimicrobial agents in tissue may differ substantially between critically ill patients, resulting in subinhibitory concentrations in tissue, even though effective levels are detected in the plasma of each individual (12, 27). Such ineffective or subinhibitory concentrations of antibiotics at the target site raise the risk of therapeutic failure, with life-threatening consequences.

Cefpirome, a member of the latest class of broad-spectrum cephalosporins, is characterized by a high degree of stability against hydrolytic bacterial enzymes (8) and is active against numerous gram-negative and gram-positive bacteria. This antibiotic, however, does not harm anaerobic bacteria; hence, it spares the intestinal flora, unlike other antibiotics (8, 31). Due to these favorable properties, cefpirome is frequently used for empirical therapy in severely ill patients in intensive care, oncology, and transplantation units (31).

Against this background we performed the present study to test the ability of cefpirome to penetrate the interstices of soft tissues. Subcutaneous adipose tissue was selected, because in many cases it is the target site of bacterial infection in septic patients. The interstitial space fluid of subcutaneous adipose tissue was collected by use of in vivo microdialysis, and the concentrations of free cefpirome were measured over time. In order to estimate bacterial growth inhibition at the target site, the time-concentration profiles for septic patients were simulated in vitro by use of an established PK-pharmacodynamic (PD) model (21, 22).

MATERIALS AND METHODS

Study protocol. The study protocol was approved by the Ethics Committee of the Medical University of Vienna and was in accordance with the Declaration of Helsinki in its last revised version (32), with the guidelines for Good Clinical Practice of the European Union (7), and with the Austrian drug law. Healthy volunteers were informed in detail about the purpose, procedures, and risks of the study. All healthy volunteers signed an informed consent prior to inclusion in the study. For comatose septic patients, written consent was sought as soon as it was medically possible. Concomitant therapy was not changed due to the study procedures.

Septic patients. Since previous PK studies revealed higher degrees of variability in the values of PK parameters in severely ill patients than in healthy volunteers, we decided to include 12 patients and only 8 healthy controls in the present study. All patients required sedation and mechanical ventilation. Sepsis was defined according to the criteria of the American College of Chest Physicians-Society of Critical Care Medicine Consensus Conference Committee (3). Eight male patients and three female patients (n = 11), all Caucasian, were eligible for data analysis. The demographic and clinical characteristics of the study population are shown in Table 1. The diagnoses at the time of admission to the intensive care unit were coronary heart disease with or without myocardial infarction in seven patients. Decompensated stenosis of the aortic valve, hematothermal linked to surgical complications, carcinoma, and pneumonia were diagnosed in one patient each. Four of 11 patients died during their stays in the...
TABLE 1. Demographic characteristics of the study groupsa

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n = 11)</th>
<th>Volunteers (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>66</td>
<td>28</td>
</tr>
<tr>
<td>Ht (cm)</td>
<td>172</td>
<td>160</td>
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<tr>
<td>Wt (kg)</td>
<td>76</td>
<td>63</td>
</tr>
<tr>
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<td>26</td>
<td>22</td>
</tr>
<tr>
<td>Heart rate (no. of beats/min)</td>
<td>89</td>
<td>64</td>
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<td>Arterial pressure, systolic (mm Hg)</td>
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<td>120</td>
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<td>Arterial pressure, diastolic (mm Hg)</td>
<td>56</td>
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<td>Arterial pressure, mean (mm Hg)</td>
<td>73</td>
<td>78</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>31</td>
<td>42</td>
</tr>
<tr>
<td>Hemoglobin concn (g/dl)</td>
<td>9.6</td>
<td>11.1</td>
</tr>
<tr>
<td>Leukocyte count (10³/liter)</td>
<td>12</td>
<td>6.5</td>
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<tr>
<td>Platelet count (10³/g/liter)</td>
<td>55</td>
<td>68</td>
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<td>Serum creatinine level (mg/dl)</td>
<td>1.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Blood urea nitrogen level (mg/dl)</td>
<td>38</td>
<td>25</td>
</tr>
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<td>CLCR (ml/min)</td>
<td>67</td>
<td>33</td>
</tr>
<tr>
<td>Lactate concn (mmol/liter)</td>
<td>1.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Fibrinogen concn (mg/dl)</td>
<td>586</td>
<td>160</td>
</tr>
<tr>
<td>Body temp (°C)</td>
<td>37.5</td>
<td>37.0</td>
</tr>
<tr>
<td>Arterial O₂ saturation (%)</td>
<td>96</td>
<td>92</td>
</tr>
<tr>
<td>SOFA score</td>
<td>5.5</td>
<td>2.0</td>
</tr>
</tbody>
</table>

a Values are presented as means ± SDs. Abbreviations: pCO₂, partial pressure of carbon dioxide; pO₂, partial pressure of oxygen; SOFA, sepsis-related organ failure assessment.

carefully moved backwards about 1.5 cm in a way that the membrane at the tip of the probe remained positioned in the subcutaneous adipose tissue. The probes were fixed and constantly perfused with Ringer solution (Mayr-Boher, Linz, Austria) at a flow rate of 1.5 μl/min by means of a precision pump (Precidor; Infors-AG, Basel, Switzerland). After an equilibration period of approximately 1 h, retrodialysis was performed for 30 min. The probes were perfused with Ringer solution containing cefpirome at a concentration of 30 mg/liter to determine the in vivo recovery rate.

Then, 2.0 g of cefpirome (Cefroz; Trockensteichampulle; Usiphar, Compiegne, France) was dissolved in 50 ml of aqua bidest (Fresenius Pharma, Graz, Austria), and the solution was administered intravenously as a single dose to patients and healthy subjects over a period of approximately 15 min. Blood samples were drawn via an intravenous catheter for the determination of the PKs of cefpirome in plasma. Blood and microdialysate samples were collected at 20-min intervals over a period of 240 min and were stored at −80°C until analysis.

Cefpirome concentrations. The free cefpirome concentrations in the plasma and microdialysate samples were measured by micellar electrokinetic chromatography, as described previously (20). In brief, the unbound fraction of cefpirome was separated from the protein-bound fraction by ultrafiltration. Ultrafiltrated plasma samples and microdialysis samples were injected into a capillary electrophoresis instrument (18°C model 1600A) equipped with a UV detector operating at 270 nm (Agilent Technologies, Waldbronn, Germany). Calibration curves for the plasma and microdialysis samples were generated by spiking drug-free plasma samples and cefpirome in Ringer solution. The accuracy was determined on three different days by analyzing spiked plasma samples and cefpirome in Ringer’s solution and ranged from 90 to 103% with a precision lower than 7%. The limits of quantification in plasma and microdialysis samples were 2 and 0.3 mg/liter, respectively.

The concentrations of cefpirome measured in microdialysate samples were adjusted by the following equation to determine absolute, free concentrations in tissue: C_{tissue} = (C_{dialysate}×100)/recovery rate.

In the septic patients, creatinine clearance (CLCR) was assessed by the equation (C_{creatinine in urine}×volume_{urine})/(C_{creatinine in plasma}×urine collection time). In one patient CLCR was estimated by the formula of Cockcroft and Gault (29), [(140−age)×weight]/(72×C_{creatinine in plasma}), because no measured CLCR value was available.

PK analysis. The values of the PK parameters for plasma and tissue were calculated by standard noncompartmental analysis by including all datum points without regression analysis or weighting. This was performed by using Kinetics (version 3.0) software (Innaphase Corporation, Philadelphia, Pa.).

For the in vitro experiments, Staphylococcus aureus ATCC 29213, for which the cefpirome MIC is 1 mg/liter, and a clinical isolate of Pseudomonas aeruginosa for which the cefpirome MIC is 8 mg/liter were chosen, since these values have frequently been reported as the MICs at which 50% of isolates are inhibited (MIC₅₀) or the MIC₉₀ for these pathogens (1, 2, 4, 16, 19, 26, 30). The susceptibilities of the bacteria to cefpirome were determined by the broth microdilution method, according to the criteria of the NCCLS (24).

In vitro PDs. An established in vivo PK-in vitro PD model was used (6, 33) to evaluate the antibacterial effects of the measured cefpirome concentrations. The PK profiles for those patients with the lowest levels of tissue penetration (AUC₀–240, 3.271 g·min/liter) and the highest levels of tissue penetration...
As means (106 CFU/ml. The strains were then incubated at 37°C for 8 h and were exposed to cefpirome concentrations in plasma and in the interstitium of subcutaneous adipose tissue for septic patients (n = 11) and healthy subjects (n = 7) after administration of 2 g of cefpirome. Values are presented as means ± SDs.

Briefly, 3 ml of Mueller-Hinton broth (Merck, Darmstadt, Germany) was inoculated with test strains in order to achieve a concentration of 5 × 10^7 to 1 × 10^8 CFU/ml. The strains were then incubated at 37°C for 8 h and were exposed to cefpirome concentrations that changed dynamically in broth, according to the PK profile measured over time in tissue in vivo.

The drug concentrations in the culture tubes containing the test strains were adjusted at 20-min intervals during the first 4 h and were then adjusted at 60-min intervals. Increasing antibiotic concentrations were simulated by the addition of Mueller-Hinton agar plates (Biomerieux, Marcy l’Etoile, France). The agar plates were cultured overnight, and the bacterial counts were determined and backextrapolated to the original volume to account for the respective dilution. Each simulation was performed in triplicate. Bacterial growth control experiments were performed in culture tubes without antibiotic. Fifty CFU was considered the minimum accurately countable number of bacteria in 1 ml of broth. The concentrations in the dialysates into absolute concentrations in the experiments in these subjects for several hours, but unfortunately, the concentrations did not reach levels below the limit of detection, as the sensitivity of the assay was very high. Thus, the baseline levels in the plasma and interstitium of these subjects were very low but resulted in a mean baseline cephirome level of greater than the detection limit of 2 mg/liter in the patients and the healthy controls. These low baseline concentrations were not considered relevant to the overall calculations, results, and conclusions drawn in the present study.

PKs in plasma. The mean concentration-versus-time profiles of cefpirome in plasma and subcutaneous adipose tissue are shown in Fig. 1. The main PK parameters are presented in Table 2. The maximum concentration of drug in plasma (Cmax) and the time to reach Cmax (Tmax) for cefpirome were not significantly different between septic patients and healthy volunteers (P = 0.82 and 0.83, respectively). However, the t1/2b of cefpirome in plasma was significantly longer for patients than for healthy controls (P < 0.05).

PKs in tissue. In the microdialysis experiments the mean recovery rate from subcutaneous adipose tissue was 25.9% ± 10.7%. Individual recovery rates were used to convert the concentrations in the dialysates into absolute concentrations in tissue. For tissue, the Cmax was significantly lower in patients than in the healthy subjects (P < 0.05). In the subcutaneous adipose tissue of patients, Cmax was reached significantly later than it was in healthy controls (P < 0.05 for Tmax). Thus, the penetration of cefpirome from plasma into subcutaneous adipose tissue occurs rapidly in healthy subjects, whereas it is strongly delayed in septic patients. This is also illustrated in Fig. 2, which presents the ratios of the concentrations in tissue to the concentrations in plasma over time. In three patients, the equilibration from plasma to tissue was not completed within the observation period of 4 h, and thus, t1/2b was not determined.

**RESULTS**

After intravenous administration of 2 g of cefpirome, the concentrations in plasma and in the interstitium of subcutaneous adipose tissue were measured over a period of 4 h.

**Tolerability and dropouts.** Cefpirome administration was well tolerated by the healthy volunteers and the septic patients. No drug-related adverse effects were detected in the study population. The microdialysis probes provided inaccurate volumes of dialysate in one patient and in one healthy volunteer. After removal of the probes, visible damage of the semipermeable membrane was detected in both probes, and the PK data derived from these subjects were abandoned.

For two healthy volunteers and two septic patients, an initial dose of less than 200 mg of cefpirome (less than 10% of the total dose) was erroneously administered before the microdialysis experiments were started. We subsequently postponed the experiments in these subjects for several hours, but unfortunately, the concentrations did not reach levels below the limit of detection, as the sensitivity of the assay was very high. Thus, the baseline levels in the plasma and interstitium of these subjects were very low but resulted in a mean baseline cephirome level of greater than the detection limit of 2 mg/liter in the patients and the healthy controls. These low baseline concentrations were not considered relevant to the overall calculations, results, and conclusions drawn in the present study.

**TABLE 2. Values of PK parameters for cefpirome in plasma and interstitium of subcutaneous adipose tissue**

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Population</th>
<th>Cmax (mg/liter)</th>
<th>Tmax (min)</th>
<th>AUCl-240 (g · min/liter)</th>
<th>t1/2b (min)</th>
<th>CL (ml/min)</th>
<th>V (liters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>Septic (n = 11)</td>
<td>166 ± 50</td>
<td>24 ± 8</td>
<td>16.19 ± 4.08</td>
<td>183 ± 54</td>
<td>80 ± 26</td>
<td>21.9 ± 4.5</td>
</tr>
<tr>
<td></td>
<td>Healthy (n = 7)</td>
<td>188 ± 82</td>
<td>23 ± 8</td>
<td>16.50 ± 5.20</td>
<td>95 ± 30</td>
<td>105 ± 31</td>
<td>15.8 ± 5.6</td>
</tr>
<tr>
<td>Subcutis</td>
<td>Septic (n = 11)</td>
<td>41 ± 17b</td>
<td>129 ± 63b</td>
<td>6.90 ± 2.56b</td>
<td>310 ± 145b</td>
<td>NDc</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>Healthy (n = 7)</td>
<td>116 ± 48</td>
<td>51 ± 16</td>
<td>13.11 ± 5.20</td>
<td>93 ± 22</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

* Values are presented as means ± SDs.

b Significantly different compared with the results for healthy subjects (P < 0.05).

c n = 8, because in three patients the plasma-to-tissue distribution process was not completed within the observation period of 4 h.

d ND, not determined.
To assess the antimicrobial and clinical efficacies of cefpirome, $T > \text{MIC}$, which is an adequate surrogate parameter for beta-lactam antibiotics, was calculated for subcutaneous adipose tissue and plasma. By using the individual $k_{el}$ values, the measured concentrations in tissue were extrapolated from 4 to 8 h, because 8 h is the dosing interval frequently applied for cefpirome. The PK extrapolation to 8 h was not performed for the three patients in whom the process of distribution from plasma to tissue was not completed within the observation period. The values of $T > \text{MIC}$ were calculated for three relatively high MICs, namely, 4 and 8 mg/liter (susceptible) and 16 mg/liter (intermediately resistant) (24). Table 3 presents the range of values of the $T > \text{MIC}$ and the numbers of patients assigned to three categories of $T > \text{MIC}$: less than 60, 60 to 90, or more than 90%. Apparently, for plasma and the subcutis, the values of $T > \text{MIC}$ tended to be higher in patients than in healthy subjects, although statistical significance was not reached due to the relatively small sample size (Table 3).

**CL<sub>CR</sub> and CL.** CL<sub>CR</sub> ranged from 24.1 to 103.8 ml/min and the CL of cefpirome ranged from 38.1 to 122.5 ml/min in septic patients. The Spearman $\rho$ for these parameters was 0.945 ($P < 0.05$) (Fig. 3).

### DISCUSSION

The rapid penetration of cefpirome into the subcutaneous adipose tissue of healthy subjects (10, 14, 23) and into the lung tissue of patients with tumors (9) was reported previously. The present study shows that the equilibration of cefpirome from plasma to tissue is considerably delayed in septic patients compared with that in healthy controls (Fig. 2), a finding that closely resembles the findings of previous investigations with piperacillin (12), levofloxacin (33), and cefpirome (13) in muscle tissue.

#### In vitro PDs.

Strains of *P. aeruginosa* (MIC, 8 mg/liter) and *S. aureus* (MIC, 1 mg/liter) were exposed in vitro to the cefpirome concentrations measured in tissue in vivo. To evaluate the relevance of the variability in PKs in tissue on bacterial growth inhibition, the PK profiles were simulated for those patients with the lowest level of tissue penetration ($\text{AUC}_{0-240}$, 3.271 g·min/liter) and the highest level of tissue penetration ($\text{AUC}_{0-240}$, 11.257 g·min/liter) and the mean curve for the septic population ($\text{AUC}_{0-240}$, 6.899 g·min/liter). The PK-PD growth inhibition curves are shown in Fig. 4, which indicates that all experiments resulted in effective antimicrobial activity against both strains.

#### TABLE 3. $T > \text{MIC}$<sup>a</sup> in plasma and interstitium of subcutaneous adipose tissue of septic patients and healthy subjects after administration of 2 g of cefpirome

<table>
<thead>
<tr>
<th>MIC (mg/liter)</th>
<th>Population&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Plasma</th>
<th>Subcutis&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of subjects with $T &gt; \text{MIC}$ of:</td>
<td>$T &gt; \text{MIC}$ range (%)</td>
<td>No. of subjects with $T &gt; \text{MIC}$ of:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;60%</td>
</tr>
<tr>
<td>4</td>
<td>Septic</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Healthy</td>
<td>75–100</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Septic</td>
<td>81–100</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Healthy</td>
<td>60–100</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>Septic</td>
<td>57–100</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Healthy</td>
<td>45–91</td>
<td>3</td>
</tr>
</tbody>
</table>

<sup>a</sup> $T > \text{MIC}$ categories in percent refer to a dosing interval of 8 h.

<sup>b</sup> Eleven septic patients and seven healthy subjects were tested.

<sup>c</sup> Data for 3 of 11 patients were excluded from the $T > \text{MIC}$ calculation, because the distribution from plasma to tissue was not completed within the observation period.
The low concentrations of cefpirome in the interstitium of subcutaneous adipose tissue of severely ill patients might be explained by systemic inflammation with subsequent changes in the permeability of the vascular wall (15). The loss of capillary integrity is associated with a shift of fluid and albumin to the extravascular space, resulting in edema. This increase in the extracellular fluid volume is augmented by attempts to keep the mean arterial blood pressure sufficiently high for organ perfusion by the therapeutic restoration of the intravascular volume. Since cefpirome is a highly hydrophilic compound and the $V$ of cefpirome approximates the volume of extracellular water (18, 31), the PKs of cefpirome in tissue are substantially affected by interstitial edema (Table 2). The increase in the amount of albumin in the interstitium is expected to be of minor relevance, because the level of binding of cefpirome to plasma proteins was reported to range only from 5 to 10% (31).

In addition, septic shock patients commonly receive vasoconstrictive catecholamines, which reduces the number of capillaries available for the distribution of drugs from plasma to tissue. Thus, pathophysiological changes and subsequent therapeutic interventions are expected to account, at least in part, for the delayed or incomplete process of equilibration of antimicrobial agents from plasma to tissue observed in septic patients.

For the physician, it is relevant to know whether the impaired penetration of cefpirome into tissues, in combination with given susceptibility data, affects the efficacy of the antibiotic at the target site in septic patients. Therefore, the cefpirome concentrations in the subcutis were simulated in vitro by use of an established PK-PD model. Importantly, effective bacterial growth inhibition was observed in all simulations (Fig. 4), despite the high level of interindividual variability in $C_{\text{av,ss}}$ and $\text{AUC}_{0-240}$ in septic patients.

This finding is probably due to the fact that beta-lactams are most effective when $T > \text{MIC}$ is maximized (5, 11, 25, 28). In the present study the individual $T > \text{MIC}$s tended to be higher in the septic patients than in the healthy controls (Table 3), although this trend was statistically not significant due to the relatively small sample size. Apparently, the values of $T > \text{MIC}$ for the tissue of septic patients were sufficient to achieve effective bacterial growth inhibition. Thus, these PK-PD data suggest that effective bacterial growth inhibition is achieved with cefpirome for the treatment of STIs in septic patients, despite the impaired tissue penetration, and can be interpreted as the net effect of delayed total drug elimination in patients.

All these thoughts are based on the assumption that a dosing regimen of cefpirome, along with $T > \text{MICs}$ of more than 60% of the dosing interval, is effective for the treatment of STIs in septic patients. In order to avoid underdosing and the low trough levels in plasma and tissue that might occur upon twice-daily dosing, the shortening of the intervals of cefpirome dosing appears to be advisable (10, 17, 18). By using our data to calculate the average concentration at steady state $[C_{\text{av,ss}}]$ for cefpirome by the equation $\text{AUC}_{\text{total}}/\text{dosing interval}$ and given a dosing regimen of 2 g every 8 h, the values of free $C_{\text{av,ss}}$ of cefpirome in plasma would be about 57 ± 21 mg/liter (range, 34 to 109 mg/liter) and 41 ± 12 mg/liter (range, 26 to 63 mg/liter) for patients and healthy controls, respectively. Accordingly, the values of $C_{\text{av,ss}}$ for cefpirome in subcutaneous adipose tissue would be 36 ± 30 mg/liter (range, 12 to 109 mg/liter) for patients and 34 ± 14 mg/liter (range, 15 to 55 mg/liter) for controls. Thus, given a dosing regimen of 2 g of cefpirome three times a day, the calculated values of $C_{\text{av,ss}}$ indicate that cefpirome is adequate for the treatment of infections caused by clinically relevant pathogens in the tissue and plasma of critically ill patients. In agreement with previous studies, the ranges of values of $C_{\text{av,ss}}$ and $T > \text{MIC}$ show that there is a higher interindividual variability in patients. These data support the present thinking that twice-daily dosing of cefpirome may be insufficient (18) and that the administration of a loading dose of cefpirome may be advisable to effectively kill bacteria at the target site in critically ill patients.

When the excellent correlation of the CL$_{\text{CCR}}$ and CL of cefpirome ($p = 0.945$) in septic patients (Fig. 3) is considered, optimization of cefpirome therapy for an individual can easily be performed (18). In the circumstance of substantially impaired renal function, as indicated by a CL$_{\text{CCR}}$ less than 50 ml/min in critically ill patients, the total daily dose of cefpirome should be tailored accordingly. For that purpose, the formula $\text{DR} = \text{DP} \cdot \{1 - [\text{fr} \cdot (1 - \text{RF})]\}$ can be applied, where DR is the dose in the patient with impaired renal function, DP is the daily dose recommended in the present study (6 g), fr is the ratio of the renal clearance to CL, and RF is the ratio of the CL in the patient with renal impairment to the average CL in our critically ill subjects (67 ml/min). As cefpirome is eliminated primarily by glomerular filtration and the CL of cefpirome is approximately equal to CL$_{\text{CCR}}$ (31), the value of fr equals 1. Thus, the previous formula can be simplified to $\text{DR} = 6 \cdot [1 - (1 - \text{RF})]$ and confirms that dose adjustment is exclusively dependent on RF, i.e., the extent of renal function impairment. This may be done only under the assumption that extrarenal CL remains unaffected if the renal clearance of cefpirome decreases.

In conclusion, the present study showed that the concentrations of cefpirome in the subcutaneous adipose tissue of septic patients were lower than those in the subcutaneous adipose tissue of healthy controls. However, on the basis of PK-PD...
calculations, the measured concentrations of cefpirome appeared to be appropriate for the treatment of STIs in septic patients due to the long $t_{1/2}$. Hence, cefpirome dosing should be at 2 g three times daily, to ensure that infections in plasma and subcutaneous adipose tissue caused by susceptible bacterial strains are adequately treated in each patient. Independently of the renal function, an initial loading dose of cefpirome should be administered.

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REFERENCES