Comparable Population Pharmacokinetics and Pharmacodynamic Breakpoints of Cefpirome in Cystic Fibrosis Patients and Healthy Volunteers

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Cystic fibrosis (CF) patients are often reported to have higher clearances and larger volumes of distribution per kilogram of total body weight (WT) for beta-lactams than healthy volunteers. As pharmacokinetic (PK) and pharmacodynamic breakpoints for CF patients are lacking, we systematically compared its population PK and microbiology/pharmacodynamic (PK/PD) breakpoints for cefpirome, a zwitterion with a net charge of zero at physiological pH that penetrates the outer membrane of Gram-negative pathogens more rapidly than ceftazidime (36, 55). Cefpirome is the only other zwitterionic beta-lactam. Its use is further supported by high-performance liquid chromatography (HPLC) and a duration of an unbound plasma concentration above the MIC ≥ 65% of the dosing interval as a pharmacodynamic target. Unscaled clearances for CF patients were similar to those seen with healthy volunteers, and the volume of distribution was 6% lower for CF patients. Linear scaling of total clearance by WT resulted in clearance that was 20% higher (P ≤ 0.001 [nonparametric bootstrap]) in CF patients. Allometric scaling by LBM explained the differences between the two subject groups with respect to average clearance and volume of distribution and reduced the unexplained between-subject variability of renal and nonrenal clearance by 10 to 14%. For the CF patients, robust (>90%) probabilities of target attainment (PTA) were achieved by the administration of a standard dose of 2 g/70 kg WT every 12 h (Q12h) given as 30-min infusions for MICs ≤ 1.5 mg/liter. As alternative dosage regimens, a 5-h infusion of 1.33 g/70 kg WT Q8h achieved robust PTAs for MICs ≤ 8 to 12 mg/liter and a continuous infusion of 4 g/day for MICs ≤ 12 mg/liter. Prolonged infusion of cefpirome is expected to be superior to short-term infusions for MICs between 2 and 12 mg/liter.

Respiratory tract infections in patients with cystic fibrosis (CF) require optimal treatment. Prevention of Pseudomonas aeruginosa chronic lung infections is especially critical for CF patients (26, 34), as these infections are extremely difficult to eradicate. Early efficacious treatment of P. aeruginosa lung infections can delay such infections or prevent them from becoming chronic (37). While P. aeruginosa is one of the most challenging pathogens in infections in CF patients of all ages, lung infections during the first years of life of CF patients are often caused by Staphylococcus aureus and Haemophilus influenzae (26, 66). It seems prudent to treat lung infections by S. aureus and H. influenzae in CF patients with alternative antibiotics that are not commonly used to treat P. aeruginosa infections in CF patients. This approach promises to preserve the effectiveness and limit the emergence of resistance to antipseudomonal antibiotics in CF and other patients for young CF patients who are not yet chronically infected by P. aeruginosa.

Cefpirome can serve as one such alternative agent for treatment of infections by H. influenzae and methicillin-susceptible

Staphylococcus aureus (MSSA) (32, 35). Cefpirome has an MIC90 of 8 to 16 mg/liter (31) for P. aeruginosa. However, higher MICs for P. aeruginosa strains from CF patients with cefpirome MIC90 values of 8 or 128 mg/liter and MIC50 values of 32 or >128 mg/liter (4, 47) and for methicillin-resistant S. aureus do not support its use in empirical monotherapy (20, 33). Optimized dosage regimens of cefpirome are, however, expected to be valuable for treatment of infections by P. aeruginosa when the MIC of the infecting strain has been confirmed to be at or below the susceptibility breakpoint. The British Society for Antimicrobial Chemotherapy (12) defined a susceptibility breakpoint of ≤1 mg/liter for cefpirome against Enterobacteriaceae and Pseudomonas spp. We suspected that optimized dosage regimens might achieve higher pharmacokinetic/pharmacodynamic (PK/PD) breakpoints for cefpirome, as evaluated in the present study.

Cefpirome is a zwitterion with a net charge of zero at physiological pH that penetrates the outer membrane of Gram-negative pathogens more rapidly than ceftazidime (36, 55). Cefepime is the only other zwitterionic beta-lactam with net charge of zero whose PK has been studied with CF patients (66). However, only noncompartmental methods were applied to assess the PK of cefepime in CF patients. Cefpirome’s stability with respect to beta-lactamases is comparable to that of ceftazidime and cefepime (5, 21, 49). The balance between
Table 1. Demographic data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (median [minimum to maximum])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects (males/females)</td>
<td>12 (8/4) / 12 (6/6)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>22.5 [18–34] / 29 [20–35]</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170 [140–183] / 175 [161–182]</td>
</tr>
<tr>
<td>Total body WT (kg)</td>
<td>53.3 [31.5–66.5] / 63.6 [53.0–85.0]</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>45.7 [26.2–55.9] / 50.0 [41.8–62.7]</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>45.8 [23.0–55.7] / 47.0 [36.6–61.5]</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.0 [13.2–20.3] / 20.6 [17.7–28.4]</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>131 [89.3–164] / 116 [92.3–150]</td>
</tr>
</tbody>
</table>

* Calculated by the formula of Cheyml (22) and James (39).
* Calculated by the formula of Jannahasanat et al. (40).
* Estimated creatinine clearance for a subject with nominal WT of 70 kg calculated as described previously (17).

Materials and Methods

Subjects. We studied a total of 24 Caucasian volunteers (12 CF patients and 12 healthy volunteers) (Table 1) after they had given their written informed consent. The present study followed the same clinical procedures as described previously (16) regarding physical examination, electrocardiography, laboratory tests, and routine monitoring for adverse events as well as regarding food and fluid intake (including the restrictions for intake of alcohol, methylxanthines, and tobacco). The study was approved by the local ethics committee and followed the revised version of the Declaration of Helsinki.

Study design and drug administration. This study had a single-center, open, single-dose, parallel-group design. Each subject received a single 10-min intravenous infusion of 2,000 mg cefpirome dissolved in 20 ml water for injection. Infusions were administered with a Braun Perfusor (Braun, Melsungen, Germany), and those instruments were checked daily by weighing defined volumes delivered by the perfusor.

Blood and urine sampling. All blood samples were drawn from a forearm vein via an intravenous catheter contralateral to the one used for dosing. For all subjects, blood samples were drawn immediately before start of the infusion (0 min), at 5 and 10 min after the start of infusion, and at 5, 10, 15, 20, and 30 min and 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 h after the end of infusion. Samples were cooled in ice water for approximately 10 to 15 min before centrifugation. After centrifugation, all plasma samples were immediately frozen and stored at −70°C. Urine was collected from the start of the infusion until 1 h after the end of infusion and at 1 to 2, 2 to 3, 3 to 4, 4 to 6, 6 to 8, 8 to 10, 10 to 12, 12 to 24, 24 to 36, and 36 to 48 h after the end of infusion. Urine samples were stored at 4°C during the collection interval. Immediately after the end of the collection period, the pH and amount of urine were measured and aliquots were frozen and stored at −70°C.

Drug analysis. We measured total cefpirome concentrations in plasma and urine by reversed-phase high-performance liquid chromatography (HPLC) with an internal standard (desacetyl-cefotaxime). To each plasma sample, an equivalent amount of 0.1 M sodium hydrogen sulfate buffer (pH 5.0) combined with the desacetyl-cefotaxime internal standard (10 mg/liter) was added. Urine samples were diluted by a factor of 100 with distilled water that contained the internal standard. Acetonitrile (400 μl) was used to deproteinize each sample. After centrifugation at 11,000 rpm for 5 min, 1,000 μl of dichloromethane was added to the supernatant for extraction of acetonitrile. After centrifugation for 5 min, 10 to 20 μl of the aqueous phase was injected into the HPLC system.

We ensured that cefpirome was stable under these conditions and used a Spherisorb ODS II column (Waters, Germany; 5 μm particle size; 250 by 8 by 4.6 mm) with a water-acetonitrile mixture at pH 5.5 and tetrasodiumammonium hydrogen sulfate as an ion-pairing reagent. Cefpirome was detected at a wavelength of 254 nm in plasma and 273 nm in urine. Calibration was performed by linear regression. The cefpirome assay was linear between 0.614 and 322 mg/liter in plasma and between 17.1 and 8,000 mg/liter in urine. The interday precision of the spiked quality control standards of cefpirome in plasma ranged from 1.10 to 3.44%, and the analytical recovery ranged from 101.6 to 103.1%. The interday precision of the spiked quality control standards of cefpirome in urine ranged from 2.26 to 2.93%, and the analytical recovery ranged from 96.6 to 101.4%.

Population PK analysis. (i) Population model. Linear one-, two-, and three-compartment models with a time-delimit zero order input into the central compartment were considered. Models were discriminated based on their predictive performance determined by visual predictive checks (VPCs) (16) and normalized prediction distribution errors (NPDE) (11), their objective function value, and standard diagnostic plots as previously described (19). Renal clearance (CLR) and nonrenal clearance (CLNR) were estimated by simultaneously estimating the mean PK parameter values determined for CF patients and healthy volunteers. A scale factor of 1.0 indicates the mean PK parameter values determined for CF patients and healthy volunteers of the same body size for the respective body size models are identical. A scale factor above (or below) 1.0 indicates that the estimated value for the respective PK parameter for CF patients was higher (or lower) than that determined for healthy volunteers of the same body size.

(ii) Body size. The following models to describe body size and body composition were evaluated: (a) no size model, (b) linear scaling by WT, (c) allometric scaling by WT (2), (d) linear scaling by LBM (22, 39), and (e) allometric scaling by LBM. We set the allometric exponents to 0.75 for all clearance terms and 1.0 for all volumes. All exponents were set at 1.0 for models with linear scaling. A standard WT of 70 kg and standard LBM of 53 kg were used. Further details on these body size models have been presented previously (16–18).

(iii) Between-subject-variability model. Between-subject variability (BSV) of PK parameters was estimated using an exponential parameter variability model. Disease-specific scale factors for renal clearance (FCYF_CLR) and nonrenal clearance (FCYF_CLNR) and volume of distribution at steady state (FCYF_VSS) were estimated to account for differences between CF patients and healthy volunteers. These scale factors represent the PK parameter ratios of the values obtained with CF patients to those obtained with healthy volunteers. A scale factor of 1.0 indicates the mean PK parameter values determined for CF patients and healthy volunteers of the same body size for the respective body size models are identical. A scale factor above (or below) 1.0 indicates that the estimated value for the respective PK parameter for CF patients was higher (or lower) than that determined for healthy volunteers of the same body size.

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(iv) Observation model and computation. The residual unidentified variability was modeled by a combined additive and proportional error model for plasma concentrations and amounts in urine. We applied first-order conditional estimation using the interaction option in NONMEM VI level 1.2 software (8) and the importance sampling Monte-Carlo Parametric Expectation-Maximization method (method=4) in S-ADAPT software (version 1.57 beta) (6) for population PK modeling as reported previously (16, 18, 19). The SADAPT-TRAN translator tool (14) was used to facilitate S-ADAPT analyses. Initial analyses were performed using NONMEM V level 1.1 software. The Beal M3 method (7) was applied in S-ADAPT analyses to account for observations below the quantification limit. No compartmental analysis was performed using WinNonlin Pro software (version 4.0.1; Pharsight Corp., Mountain View, CA).

Nonparametric bootstrap methods with 1,000 replicates for each body size model were applied using NONMEM software to determine the 90% confidence intervals (5 to 95% percentile) of estimated PK parameters (17). The bootstrap analysis was stratified by patient group.

Monte Carlo simulation. For β-lactam antibiotics such as cefpirome, the time determined for non-protein-bound plasma concentrations above the MIC (\(C_{\text{MIC}}\)) best predicts bacterial killing at 24 h in animal infection models (24, 27). For cephalosporins, a PK/PD target of 40% \(f_{\text{T}_{\text{MIC}}}\) best correlates with bactericidal activity at 24 h and a target of 65% \(f_{\text{T}_{\text{MIC}}}\) best predicts near-maximal bactericidal activity at 24 h in animal models. An MIC range of 0.125 to 64 mg/liter was evaluated, and a protein binding value of 10% was used for cefpirome (53, 63).

Various dosage regimens at a daily cefpirome dose of 4 g/70 kg WT were compared: (i) 30-min infusion of 2 g/70 kg WT Q12h, (ii) 5-h infusion of 2 g/70 kg WT Q12h, (iii) 30-min infusion of 1.33 g/70 kg WT Q8h, (iv) 5-h infusion of 1.33 g/70 kg WT Q8h, and (v) continuous infusion of 4 g/70 kg WT per day. For each dosage regimen, the time course of plasma concentrations was simulated for 1,080 CF patients and 1,080 healthy volunteers by the use of the same demographic parameters used in the clinical data. The PK/PD breakpoint was defined as the highest MIC at each dosage regimen, the time course of plasma concentrations was simulated for 10,800 CF patients and 10,800 healthy volunteers by the use of the same demographic characteristics as were observed with the subjects in this study. These profiles were simulated at steady state without residual error. The PTA was calculated as the fraction of CF patients and healthy volunteers who achieved the PK/PD target at each MIC. The PK/PD breakpoint was defined as the highest MIC with a PTA of at least 90%.

To illustrate the benefits of prolonged and continuous infusion compared to short-term infusions, we calculated the expected PTA for specific MIC distributions (referred to here as the “PTA expectation value”) as described previously (16, 18). We used eight previously published MIC distributions for cefpirome activity against P. aeruginosa from non-CF patients (1, 9, 31, 35, 42, 43, 62, 64), with MIC90 values of 8, 16, 16, 16, 12, 16, and 16 mg/liter.

### RESULTS

Our CF patients had 16% lower WT, 9% lower LBM, and 8% lower body mass index (Table 1) than the healthy volunteers. All subjects had a normal renal function. The average creatinine clearances estimated by the Cockcroft and Gault (23) formula for a nominal subject with 70 kg WT (for details, see Matthews et al. [51] and Bulitta et al. [17]) were comparable in the two subject groups but more variable in the CF patient group (average ± standard deviation [SD], 124 ± 24 ml/min in CF patients versus 118 ± 15 ml/min in healthy volunteers).

Noncompartmental analysis. The median CF patient PK parameter estimates divided by the respective median estimates for healthy volunteers ranged from 92.7 to 107.3% for all noncompartmental PK parameters (Table 2). One CF patient and one healthy volunteer gave an outlier value for the amount of cefpirome in urine during one sampling interval. For the CF patient with the outlier value, a total of 2.8 g of cefpirome was recovered from urine, most likely because this patient had a 3.5-fold-larger amount of cefpirome in urine during the 1- to 2-h sampling interval compared to all other subjects (Fig. 1). This potential outlier was probably the result of a recorded urine volume that was incorrectly large. One healthy volunteer had a 15-fold-smaller amount recovered from urine during the 0- to 1-h interval compared to all other subjects (Fig. 1).

Both of those subjects had normal renal function, and the amounts excreted in urine during all other sampling intervals were consistent with all other patient results. Reanalysis of these samples by HPLC confirmed the originally measured concentrations. Inclusion of either of these two potential outliers altered at least one population mean by more than 3% and BSV (variance) by more than 5% and caused a notable disadvantage in the objective function (\(-2 \cdot \log \text{likelihood}\)) by 23 or 115 points. Therefore, population PK analysis identified these two values as outliers that were excluded for all subsequent modeling. As we had used the amounts of urine excreted during each dosing interval and not cumulative urinary excretion, our NONMEM and S-ADAPT population PK analyses could appropriately handle the exclusion of these two outliers.

### Population PK analysis

The VPC exhibited highly sufficient predictive performance for the two-compartment models (results not shown) and three-compartment models (Fig. 1). A one-compartment model had insufficient predictive performance. The objective function of the three-compartment model was 273 points better than that of the two-compartment model and 1,205 points better than that of the one-compartment model. As was consistent with the VPC, the NPDE for the three-compartment model showed a slightly larger variability of the model predictions compared to the variability of the observations for healthy volunteers.

Population PK parameter estimates from NONMEM and S-ADAPT analyses were in excellent agreement (Table 3) for every parameter except for a slightly larger variability for volume of the deep peripheral compartment in S-ADAPT. Compared to the VPC in NONMEM, the final model in S-ADAPT yielded a similar VPC with a very slightly worse predictive performance during the terminal phase of plasma concentrations. Therefore, estimates from NONMEM (Table 3) were used for MCS.

We distinguished the different size models (i) by their estimates for the FCYF disease-specific scale factors (Table 4) and (ii) by their estimates for the unexplained random BSV in clearance and volume of distribution (Table 5). CF patients

### TABLE 2. Unscaled PK parameters from noncompartmental analysis (median [minimum to maximum])

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (median [minimum to maximum])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total clearance (liters/h)</td>
<td>6.52 [4.05–8.51]</td>
</tr>
<tr>
<td>Renal clearance (liters/h)</td>
<td>5.59 [3.18–9.98]</td>
</tr>
<tr>
<td>Nonrenal clearance (liters/h)</td>
<td>0.842 [0.0–1.77]</td>
</tr>
<tr>
<td>Volume of distribution at steady state (liters)</td>
<td>14.4 [7.32–25.3]</td>
</tr>
<tr>
<td>Fraction excreted unchanged in urine (%)</td>
<td>84.4 [78.6–100]</td>
</tr>
<tr>
<td>Peak concn (mg/liter)</td>
<td>221 [135–560]</td>
</tr>
<tr>
<td>Terminal half-life (h)</td>
<td>2.07 [1.95–3.29]</td>
</tr>
<tr>
<td>Mean residence time (h)</td>
<td>2.16 [1.38–3.03]</td>
</tr>
</tbody>
</table>

*a* The amount excreted unchanged in urine was larger than the nominal dose for one CF patient. This would cause the nonrenal clearance to be negative, which is physiologically impossible. We therefore instead report 0.0 liters/h for the lowest nonrenal clearance and 100% for the highest fraction excreted unchanged in urine.

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had slightly lower estimates for clearance and volume of distribution than healthy volunteers when body size is ignored (size model 1; Table 4). Estimates for FCYFvss were close to 1.0 (range, 0.96 to 1.03) for size models 2 to 5. Linear scaling by WT resulted in 20% higher (P \leq 0.001) total clearance values for CF patients compared to healthy volunteers (Table 4). This difference was much (8% on average) smaller and not significantly different from 1.0 for allometric scaling by LBM. Allometric scaling by WT and LBM resulted in a 10 to 21% reduction of the unexplained BSV values for renal and nonrenal clearance (Table 5) compared to linear scaling by WT. This reduction was not statistically significant at the relatively small sample size of this study.

Monte Carlo simulation. Fig. 2 shows the slightly lower PTAs for CF patients compared to healthy volunteers. This was primarily due to dose selection by milligram per kilogram of WT, since CF patients had higher total clearance per kilogram of WT. The PK/PD breakpoints determined for CF pa-
Patients were approximately 1.5 times lower than those determined for the healthy volunteers (Table 6).

Standard short-term infusions of 2 g of cefpirome/70 kg WT Q12h achieved a PK/PD breakpoint for CF patients of 4 to 6 mg/liter for bacteriostasis and of 1.5 mg/liter for near-maximal killing. These PK/PD breakpoints increased by a factor of 1.5 to 2 when the same daily dose was given in the form of short-term infusions Q8h instead of Q12h (Table 6). As an alternative mode of administration for CF patients, prolonged (5-h) infusion of 2 g/70 kg WT Q12h achieved a bacteriostasis breakpoint of 16 mg/liter and a near-maximal kill breakpoint of 4 mg/liter. Prolonged infusion of 1.33 g/70 kg WT Q8h for CF patients yielded a breakpoint of 8 to 12 mg/liter (PTA = 82% at an MIC of 12 mg/liter), and continuous infusion of 4 g/70 kg WT per day achieved a breakpoint of 12 mg/liter for near-maximal killing.

Using the CF patient PK values and the near-maximal kill target, PTA expectation values of the 8 previously published clinical MIC distributions had a median of 28% (range, 9 to 55%) for 2 g/70 kg WT when administered as 30-min infusions Q12h, 48% (range, 21 to 76%) for 1.33 g/70 kg WT as 30-min infusions Q8h, 63% (range, 29 to 84%) for 2 g/70 kg WT as 5-h infusions Q12h, 80% (range, 48 to 92%) for 1.33 g/70 kg WT as 5-h infusions Q8h, and 84% (range, 62 to 94%) for continuous infusions of 4 g/70 kg WT per day. Depending on the MIC distribution, prolonged or continuous infusions achieved 20 to 64% higher PTA expectation values than 30-min infusions administered Q12h.

**DISCUSSION**

The armamentarium of clinically available antibiotics against critical Gram-negative pathogens such as *P. aeruginosa* is unlikely to be enriched by a new antibiotic for the next 5 to 10 years.
TABLE 4. Ratios of group estimates (CF patients/healthy volunteers) for clearance and volume of distribution for different body size models

<table>
<thead>
<tr>
<th>Size model</th>
<th>FCYF&lt;sub&gt;CLR&lt;/sub&gt;</th>
<th>FCYF&lt;sub&gt;CLNR&lt;/sub&gt;</th>
<th>FCYF&lt;sub&gt;CLTOT&lt;/sub&gt;</th>
<th>FCYF&lt;sub&gt;VSS&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No size model</td>
<td>0.96 (0.85–1.09)</td>
<td>1.02 (0.71–1.40)</td>
<td>0.97 (0.87–1.07)</td>
<td>0.84 (0.76–0.95)</td>
</tr>
<tr>
<td>WT (linear scaling)</td>
<td>1.19 (1.08–1.33)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.24 (0.87–1.74)</td>
<td>1.20 (1.11–1.32)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.01 (0.94–1.09)</td>
</tr>
<tr>
<td>WT (allometric)</td>
<td>1.13 (1.03–1.26)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.18 (0.83–1.66)</td>
<td>1.14 (1.06–1.24)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.03 (0.96–1.11)</td>
</tr>
<tr>
<td>LBM (linear scaling)</td>
<td>1.12 (1.00–1.25)</td>
<td>1.16 (0.82–1.63)</td>
<td>1.12 (1.03–1.23)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.96 (0.89–1.04)</td>
</tr>
<tr>
<td>LBM (allometric)</td>
<td>1.07 (0.97–1.20)</td>
<td>1.13 (0.79–1.57)</td>
<td>1.08 (1.00–1.18)</td>
<td>0.98 (0.90–1.06)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data represent median (5% to 95% percentile) values determined using 1,000 nonparametric bootstrap replicates for each body size model. FCYF<sub>NNN</sub> ratio of group estimates for parameter NNN (group estimate for CF patients divided by group estimate for healthy volunteers).

<sup>b</sup> Values were calculated as weighted FCYF<sub>CLR</sub> and FCYF<sub>CLNR</sub> averages by the following equation: FCYF<sub>CLTOT</sub> = (FCYF<sub>CLR</sub> x CL<sub>POP,R</sub> + FCYF<sub>CLNR</sub> x CL<sub>POP,NR</sub>) / CL<sub>POP,R</sub> + CL<sub>POP,NR</sub>, where CL<sub>POP,R</sub> represents the population mean renal clearance and CL<sub>POP,NR</sub> the population mean nonrenal clearance in healthy volunteers.

<sup>c</sup> P ≤ 0.001 for the results of a two-sided nonparametric test (based on 1,000 bootstrap replicate determinations that FCYF was significantly different from 1).

<sup>d</sup> P = 0.002.

<sup>e</sup> P = 0.006.

<sup>f</sup> P = 0.02.

<sup>g</sup> P = 0.03.

<sup>h</sup> P = 0.04.

10 years (10, 28, 56). Therefore, it is vital to optimally use the available antibiotics and preserve their effectiveness by prudent use in the treatment of CF patients (34). MSSA and H. influenzae are often the first pathogens infecting the lungs of young CF patients. To limit the emergence of resistance to antibiotics against P. aeruginosa, one may treat MSSA or H. influenzae infections by the administration of antibiotics such as cefpirome that are not primarily used against P. aeruginosa.

As we are not aware of any data on the PK of cefpirome in CF patients or on its effectiveness in the treatment of CF patients, we evaluated the PK of cefpirome for CF patients and healthy volunteers by population PK and MCS (29). The estimates from our NONMEM and S-ADAPT population PK analyses agreed excellently (Table 3) and were consistent with PK data on cefpirome in the treatment of healthy volunteers in other studies (3, 25, 41, 46, 48, 54, 59). Our population PK model exhibited a highly sufficient predictive performance for cefpirome in plasma and urine (Fig. 1). The prediction inter-

TABLE 5. Between-subject variability (variances) for various body size models relative to linear scaling by WT (see Table 3 and Table 4 for parameter explanations)

<table>
<thead>
<tr>
<th>Size model</th>
<th>CL&lt;sub&gt;L&lt;/sub&gt; (%)</th>
<th>CL&lt;sub&gt;NR&lt;/sub&gt; (%)</th>
<th>V1 (%)</th>
<th>V2 (%)</th>
<th>V3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT linear scaling</td>
<td>100 100 100</td>
<td>95 100 95</td>
<td>100 100 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT allometric</td>
<td>79&lt;sup&gt;a&lt;/sup&gt; 90 90</td>
<td>97 97 97</td>
<td>95 96 96</td>
<td>133&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>LBM linear scaling</td>
<td>115&lt;sup&gt;b&lt;/sup&gt; 96 96</td>
<td>97 97 97</td>
<td>105 105 105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBM allometric</td>
<td>90&lt;sup&gt;c&lt;/sup&gt; 86 86</td>
<td>92 92 92</td>
<td>142&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Data represent median values determined using 1,000 nonparametric bootstrap replicates for each body size model. For each bootstrap replicate, the differences in variance between size models relative to linear scaling by WT were calculated. The individual differences were divided by the median variance of linear scaling by WT for the respective PK parameter. The reported data represent the median values determined using 1,000 bootstrap replicates according to the following equation: [(variance of test size model – variance of linear scaling by WT)/median variance of linear scaling by WT] × 100%.

<sup>b</sup> The lower this value, the more variability was explained by the respective body size model results. A value below 100% indicates that a size model reduced the between-subject variance compared to linear scaling by WT. These values indicate that the between-subject variability (variance) for renal clearance was reduced by 21% for allometric scaling by WT, increased by 15% for linear scaling by LBM, and reduced by 10% for allometric scaling by LBM (all relative to linear scaling by WT).

<sup>c</sup> Results from S-ADAPT analyses did not show this increase in variance in V3 for the allometric size models. Other than this minor difference, results from the NONMEM and S-ADAPT analyses agreed well.
We studied the influence of body size on clearance and volume of distribution by population PK. In the absence of a size descriptor (size model 1; Table 4), CF patients had slightly lower volumes of distribution and clearances, probably because the patients were slightly smaller than the healthy volunteers. Size models 2 to 5 estimated FCYFVSS as a value close to 1.0 (Table 4). We found significantly higher (20%; \( P < 0.001 \)) total clearance in CF patients when clearance was scaled linearly by WT (Table 4). Allometric scaling by LBM resulted in similar total clearance values for the two subject groups. Therefore, the average values for clearance and volume of distribution were quite comparable between CF patients and healthy volunteers when body size was represented by allometric scaling with LBM. It seems likely that earlier PK studies analyzing CF patients that were conducted from the 1960s to the 1980s found notably higher clearances and larger volumes per kilogram of WT for CF patients compared to healthy volunteers (58, 66), as the earlier studies included more severely ill CF patients without access to optimal nutrition and nonantibiotic therapy.

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patients and as some studies did not match CF patients and healthy volunteers by LBM or by another measure of body size that accounts for body composition as proposed previously (66, 67).

In addition to explaining the differences in mean clearance and mean volume of distribution, we compared the abilities of the body size models to reduce the unexplained random BSV. When a size descriptor reduces the unexplained BSV in clearance and volume of distribution, one can predict clearance and volume of distribution for an individual patient more accurately and therefore achieve target concentrations more precisely. The allometric size models based on WT or LBM reduced the unexplained BSV in renal and nonrenal clearance by 10 to 21% relative to linear scaling by WT (Table 5). However, the 90% confidence intervals for this reduction in BSV included 0%; therefore, none of the allometric size models reduced the unexplained BSV significantly better than linear scaling by WT. A larger study would be required to assess whether this reduction in BSV is significant.

Monte Carlo simulations using the final population PK model based on allometric scaling by LBM showed that CF patients achieved slightly lower PTAs than healthy volunteers (Fig. 2). This primarily resulted from CF patients having 20% higher clearance per kg WT (Table 3) and from dose selection as milligrams per kilogram of WT. The PK/PD breakpoints for a given dosage regimen and target were slightly lower for CF patients than for healthy volunteers (Table 6). Our PK/PD breakpoints for near-maximal killing in the treatment of CF patients were in excellent agreement with the breakpoints identified by Roos et al. (59) for cefpirome in the treatment of critically ill patients. To achieve higher PTAs at the same daily dose, we assessed alternative modes of administration via MCS. Continuous infusion (30) or shorter dosage intervals (61) have also been previously proposed for cefpirome use.

The British Society for Antimicrobial Chemotherapy (12) deems isolates with a drug MIC of ≤1 mg/liter as susceptible to cefpirome. Other authors have used ≤4 mg/liter (20) or ≤8 mg/liter (33, 38, 50) as representing susceptibility to cefpirome. Our MCS suggested that 30-min infusions Q12h at a daily dose of 4 g/70 kg WT achieved breakpoints of 1.5 to 3 mg/liter for near-maximal killing and of 4 to 8 mg/liter for bacteriostasis (Table 6). Prolonged and continuous infusion regimens achieved approximately 6- to 8-fold-higher PK/PD breakpoints for near-maximal killing compared to 30-min infusions Q12h at the same daily dose (Table 6). Whether the higher breakpoints result in a higher probability of successful treatment depends on the MIC distribution. Prolonged or continuous infusion is especially superior to 30-min infusion Q12h when the MIC50 and MIC90 fall between 2 and 12 mg/liter (Table 6). For MIC90 values of 1 mg/liter and below, prolonged or continuous infusion is expected to provide only a small benefit compared to short-term infusion, as 30-min infusions of 2 g Q12h had a breakpoint of 1.5 mg/liter for near-maximal killing in CF patients.

The MIC90 for cefpirome has been previously reported (31, 45, 57) to be below 1 mg/liter against H. influenzae and about 0.5 to 1 mg/liter against MSSA. More recently, MIC90 values of 1.5 to 4 mg/liter were reported for MSSA (38, 44, 50). Patients infected with MSSA strains that are less susceptible are expected to benefit from prolonged infusion of cefpirome in empirical therapy. The MIC90 of P. aeruginosa is often above 32 mg/liter for cefpirome, which precludes the use of cefpirome in empirical monotherapy. We are not aware of published cefpirome MIC distributions for CF patients. Therefore, we compared the PTA expectation values for continuous and prolonged versus short-term infusion using eight MIC distributions for P. aeruginosa isolates from non-CF patients. The median values over these eight MIC distributions were 6 (range, 2 to 16) mg/liter for MIC50 and 24 (range, 8 to 128) mg/liter for MIC90. As the PK/PD breakpoints shown in Table 6 are higher than several of these MIC90 values, cefpirome is expected to be a useful treatment option for non-CF patients with infections by P. aeruginosa and with a confirmed cefpirome MIC at or below the PK/PD breakpoint.

Continuous and prolonged (5-h) infusions administered Q12h achieved PTA expectation values between 20 and 64% higher than those determined for 30-min infusions of 2 g/70 kg Q12h for near-maximal killing in CF patients. The range of improvement was 18 to 56% when we used the population PK for healthy volunteers. This highlights the potential benefit of prolonged and continuous infusions compared to short-term infusions Q12h when a significant fraction of the MICs falls between 2 and 12 mg/liter. To achieve higher PK/PD breakpoints by the use of intermittent short-term infusions, one might consider cefpirome doses of 6 or 8 g/day, which would lead to 1.5- or 2-times-higher PK/PD breakpoints (i.e., up to 32 mg/liter) compared to the breakpoints for 4 g/day shown in Table 6.

Importantly, the present MCS rely on PK/PD targets from murine infection models, since we are not aware of "validated" β-lactam PK/PD targets for lung infections in CF patients. The phenotypic state of bacteria such as P. aeruginosa in the lungs of CF patients is likely to differ from the phenotypic state of bacteria in these murine infection models. Such potential differences in phenotypic states represent a limitation of the applicability of the present MCS results and may entail a need for CF patients to achieve higher PK/PD targets. A target of 100% fT>MIC is best achieved by a continuous infusion (Fig. 2). Breakpoints for 65% free time above 4 times the MIC, for example, can be calculated by dividing the PK/PD breakpoints for the 65% fT>MIC target (Table 4) by a factor of 4. It is also a limitation of the present MCS for CF patients that the extent of penetration of cefpirome into the site of action in the lungs of CF patients is unknown.

In conclusion, we found similar to slightly lower unscaled clearances and volumes of distribution for CF patients compared to healthy volunteers. Allometric scaling by LBM explained the differences in average PK parameters better than linear scaling by WT. The latter body size model predicted total clearance to be 20% higher (P = 0.001) in CF patients compared to healthy volunteers. Allometric scaling by WT or LBM reduced the unexplained BSV in renal and nonrenal clearance by 10 to 21%. While this reduction in BSV was not statistically significant at the relatively small sample size of this study, dose selection based on LBM may be important to achieve target concentrations more precisely in empirical therapy. A standard dosage regimen of 2 g/70 kg WT Q12h given as 30-min infusions achieved a PK/PD breakpoint of 1.5 mg/liter for near-maximal killing in CF patients. Administering the same dose of 4 g/70 kg WT as 5-h infusions Q8h or as contin-
uous infusions achieved a PK/PD breakpoint of 5 to 12 mg/liter for near-maximal killing. The superiority of prolonged and continuous infusions compared to intermittent short-term infusions is most pronounced when the MIC falls between 2 and 12 mg/liter. Future clinical trials are warranted to achieve a higher probability of successful clinical outcomes for dose selection for CF patients on the basis of LBM instead of WT and superior effectiveness for prolonged or continuous infusion compared to short-term intermittent infusion.

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