Population Pharmacokinetic Comparison and Pharmacodynamic Breakpoints of Ceftazidime in Cystic Fibrosis Patients and Healthy Volunteers

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Received 7 July 2009/Returned for modification 29 September 2009/Accepted 29 December 2009

Despite the promising activity of ceftazidime against 
Pseudomonas aeruginosa  
and  
Burkholderia cepacia, there has not yet been a study that directly compared the pharmacokinetics (PK) of ceftazidime in cystic fibrosis (CF) patients and healthy volunteers by population PK methodology. We assessed the population PK and PK/pharmacodynamic (PD) breakpoints of ceftazidime in CF patients and healthy volunteers. Eight CF patients (total body weight [WT] [average ± standard deviation] = 42.9 ± 18.4 kg) and seven healthy volunteers (WT = 66.2 ± 4.9 kg) received 2 g ceftazidime as a 5-min intravenous infusion. High-performance liquid chromatography (HPLC) was used for drug analysis, and NONMEM (results reported), S-ADAPT, and NPAG were used for parametric and nonparametric population PK modeling. We considered linear and allometric body size models to scale clearance and volume of distribution. Monte Carlo simulations were based on a target time of non-protein-bound plasma concentration of ceftazidime above MIC of ≥65%, which represents near-maximal killing. Unscaled total clearance was 19% lower in CF patients, and volume of distribution was 36% lower. Total clearance was 7.82 liters/h for CF patients and 6.68 liters/h for healthy volunteers with 53 kg fat-free mass. Allometric scaling by fat-free mass reduced the between-subject variability by 32% for clearance and by 18 to 26% for volume of both peripheral compartments compared to linear scaling by WT. A 30-min ceftazidime infusion of 2 g/70 kg WT every 8 h (q8h) achieved robust (≥90%) probabilities of target attainment (PTAs) for MICs of ≤1 mg/liter in CF patients and ≤3 mg/liter in healthy volunteers. Alternative modes of administration achieved robust PTAs up to markedly higher MICs of ≤8 to 12 mg/liter in CF patients for 5-h infusions of 2 g/70 kg WT q8h and ≤12 mg/liter for continuous infusion of 6 g/70 kg WT daily.

Respiratory tract infections are the primary reason for frequent hospitalization of patients with cystic fibrosis (CF) and the main cause of mortality (4, 60). About 4 of 5 adults with CF (age: 26 to 30 years) are infected by  
Pseudomonas aeruginosa  against species belonging to the  
Burkholderia cepacia  
complex (45, 46, 64). Infections by  
Burkholderia cepacia  are of particular interest to CF patients, since  
Burkholderia cepacia  can cause a rapid deterioration of lung function (29, 71). Efficacious anti-infective therapy against both  
Burkholderia cepacia  and  
Pseudomonas aeruginosa  is critical, in particular as eradication of  
Pseudomonas aeruginosa  in the lungs of CF patients is possible only in the early stage of infection (19, 34).

Two groups compared the pharmacokinetics (PK) in CF patients and healthy volunteers within the same study (33, 44). CF patients had higher clearances (liters/h/kg) and shorter terminal half-lives for ceftazidime. Mouton et al. (53) compared the pharmacodynamic (PD) profiles of CF patients and healthy volunteers based on data from two different studies and found that CF patients required higher doses than healthy volunteers to achieve the same PD target.

For beta-lactams, the duration of non-protein-bound plasma concentration above the MIC (fT>MIC) has been identified as the target for near-maximal bactericidal killing, and an fT>MIC of 65% has been identified as the target for near-maximal bactericidal killing, and an fT>MIC target of 40% best predicts bacteriostasis at 24 h for cephalosporins in mouse infection models (22, 25). Based on these target values the probability of target attainment (PTA) can be predicted via Monte Carlo simulation (MCS). The effect of an altered body composition on PK requires dose adjustment in certain patient populations (21, 31, 49, 55, 71). Therefore, it may be important to use a descriptor that accounts for body size and body composition for dose selection and optimization of the PTA. A lack of adipose tissue in CF patients may require dose adjustments (16, 48, 62, 71).

Due to the hydrophilic properties of ceftazidime, we believed that fat-free mass (FFM) may better describe body size than total body weight (WT), as FFM but not WT accounts for body composition. In addition to explaining the differences in average PK parameters between lean, “normal,” and obese patients, a useful body size descriptor should reduce the unexplained between-
subject variability (BSV) in PK parameters. Such a body size descriptor can be used to select dosage regimens that achieve target concentrations and target effects more precisely.

Our first objective was to compare the population PK of ceftazidime between CF patients and healthy volunteers within the same study. Second, we assessed whether the difference in average PK parameters and the BSV in clearance and volume of distribution is better described by FFM than by WT. Our third objective was to predict the PK-PD MIC breakpoints for various ceftazidime dosage regimens in CF patients. We applied the latest parametric and nonparametric population PK methodology and evaluated linear and allometric body size models comparing the PK in CF patients and healthy volunteers in order to greatly extend a descriptive noncompartmental analysis of our study reported previously (65–67).

(The population PK modeling work has in part been presented as part of a meta-analysis [14, 15] and in part as a poster [37].)

**MATERIALS AND METHODS**

**Subjects.** A total of 15 Caucasian volunteers (8 CF patients and 7 healthy volunteers) participated in the study after they had given their written informed consent. For the two CF patients 10 and 15 years old, written informed consent was obtained from their legal representative. General clinical procedures were as described previously (16). The study was performed in 1983; the study protocol was approved by the local ethics committee, and the study was conducted by following the revised version of the Declaration of Helsinki.

**Study design and drug administration.** The study was a single-dose, single-center, open, parallel group trial. Subjects received 2 g ceftazidime as a 5-min infusion q6h, and (v) continuous infusion. Concentrations of each dosage regimen for various ceftazidime dosage regimens in CF patients. We applied the latest parametric and nonparametric population PK methodology and evaluated linear and allometric body size models comparing the PK in CF patients and healthy volunteers in order to greatly extend a descriptive noncompartmental analysis of our study reported previously (65–67).

**Population PK analysis.** (i) Structural model. We tested one-, two-, and three-compartment models with linear disposition and evaluated competing models using their predictive performance assessed via visual predictive checks (VPCs), the objective function, and standard diagnostic plots as described previously (16, 18).

**Population PK-PD analysis.** (ii) Body size model. The following body size descriptors and body size models were considered: (i) no body size model, (ii) linear scaling by WT, (iii) allometric scaling by WT (3, 35, 80), (iv) linear scaling by a new equation estimating FFM (39), and (v) allometric scaling by FFM. We assessed the ability of each body size model to describe the differences in average PK parameters between both subject groups and to reduce the unexplained (random) BSV. The exponents for the effect of body size on clearance were fixed to 1.0 for linear scaling and 0.75 for allometric scaling as described previously (16). Exponents were fixed to 1.0 for volumes of distribution for linear and allometric body size models.

(iii) Differences between subject groups. We used scale factors for clearance (FCYF<sub>C</sub>) and volume of distribution at steady state (FCYF<sub>CL</sub>) to describe the difference in average PK parameters after accounting for the effect of body size as described previously (16).

(iv) Between-subject variability and observation model. An exponential model was used to describe the BSV of PK parameters, and a combined additive and proportional residual error model was used to describe the residual unidentified variabil-

**RESULTS**

Demographics and noncompartmental analysis. Our CF patients had a normal renal function and were smaller and leaner than our healthy volunteers (Table 1). Peak concentrations in CF patients were approximately twice as high as those in healthy volunteers (Table 2). We did not scale the noncompartmen-

**Population PK analysis.** The visual predictive check (Fig. 1) indicated highly sufficient predictive performance for the linear three-compartment model, which was slightly better than that for the linear two-compartment model. A one-compartment model had insufficient predictive performance and yielded poor curve fits. As the objective function in NONMEM was
worse by 46 for the two-compartment model than for the three-compartment model, the latter model was selected as the final model. This choice was consistent with results from S-ADAPT and NPAG.

The estimates for the final population PK model with allometric scaling by FFM were well comparable between NONMEM, S-ADAPT, and NPAG (Table 3) despite the different estimation algorithms applied. Estimates for volume of the deep peripheral compartment were larger in NPAG, since there were 3 subjects in each group who had large volumes for this compartment. Allometric scaling by FFM explained the differences in average PK parameters better than the other body size models, since it yielded disease-specific scale factors (FCYFCL and FCYF VSS in Table 4) closest to 1.0. A scale factor of 1.0 means that the average clearance or volume of distribution is the same in both patient groups, if the patient groups are matched in body size. These scale factors represent the ratios of group estimates between CF patients and healthy volunteers after adjusting for body size using the respective body size model. The scale factors from NONMEM (Table 4) were well comparable to results from S-ADAPT (data not shown).

Without accounting for body size, clearance and volume of distribution were 14 to 15% lower in CF patients (Table 4). The linear body size models yielded 45% or 30% higher clearances in CF patients. The allometric body size models explained the differences between CF patients and healthy volunteers better than linear models. The allometric model based on FFM yielded a 17% higher clearance in CF patients (Table 4). Allometric body size models also reduced the unexplained BSV in clearance and volume of distribution more than the linear body size models. Allometric scaling by FFM reduced the unexplained BSV by 32% for total clearance and by approximately 18 to 26% for volume of distribution for the peripheral compartments (Table 5). As the allometric body size model based on FFM explained most of the differences in clearance and volume of distribution between both subject groups, we did not seek to include other potentially confounding variables in the covariate model.

Monte Carlo simulation. CF patients had lower PTAs than healthy volunteers, which resulted in 1.5- to 3-times-lower PK-PD MIC breakpoints for the studied dosage regimens (Fig. 2). Continuous infusion of 6 g/70 kg WT per day had a PK-PD breakpoint of 12 mg/liter in CF patients and 16 mg/liter in healthy volunteers for both targets. For the near-maximal kill target \((f_{T/\text{MIC}} > 0.65\%\)) PK-PD MIC breakpoints were 8 to 12 mg/liter in CF patients and 16 mg/liter in healthy volunteers for both prolonged-infusion regimens. For the near-maximal kill target, CF patients had breakpoints of 2 mg/liter for short-term

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**TABLE 2. Unscaled PK parameters from noncompartmental analysis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median [minimum–maximum] for:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CF patients</td>
</tr>
<tr>
<td>Total clearance (liters/h)</td>
<td>5.37 [3.35–12.8]</td>
</tr>
<tr>
<td>at steady state (liters)</td>
<td>20 [148–397]</td>
</tr>
<tr>
<td>Peak concn (mg/liter)</td>
<td>445 [151–1200](^a)</td>
</tr>
<tr>
<td>Terminal half-life (h)</td>
<td>1.48 [0.49–1.78]</td>
</tr>
<tr>
<td>Mean residence time (h)</td>
<td>1.54 [0.62–2.35]</td>
</tr>
</tbody>
</table>

\(^a\) Normalized to a dose of 2 g ceftazidime, since three CF patients received a slightly higher or slightly lower dose.

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**FIG. 1.** Visual predictive check based on 8,000 CF patients and 7,000 healthy volunteers simulated from the three-compartment model based on FFM (see Table 3; based on results from NONMEM). The plots show the observed data, the 80% prediction intervals (10 to 90% percentile), and the interquartile ranges (25 to 75% percentile). Ideally, 50% of the observed data points should fall inside the interquartile range and 80% of the observed data should fall inside the 80% prediction interval.
TABLE 3. Estimates from the population PK model based on allometric scaling by fat-free mass

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NONMEM</th>
<th>S-ADAPT</th>
<th>NPAG</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF patients</td>
<td>Healthy volunteers</td>
<td>CF patients</td>
<td>Healthy volunteers</td>
</tr>
<tr>
<td>CL (liters h(^{-1}))</td>
<td>7.82(^{\text{a}}) (28)</td>
<td>6.68 (28)</td>
<td>7.70 (30)</td>
</tr>
<tr>
<td>Vse(^{\text{g}}) (liters)</td>
<td>12.2</td>
<td>12.7</td>
<td>12.5</td>
</tr>
<tr>
<td>V1 (liters)</td>
<td>5.73 (45)(^{\text{c}})</td>
<td>5.67 (45)</td>
<td>5.43 (40)</td>
</tr>
<tr>
<td>V2 (liters)</td>
<td>3.92 (25)</td>
<td>3.88 (25)</td>
<td>4.34 (43)</td>
</tr>
<tr>
<td>V3 (liters)</td>
<td>3.16 (29)</td>
<td>3.13 (29)</td>
<td>2.75 (33)</td>
</tr>
<tr>
<td>CL(_{\text{Cinf}}) (liters h(^{-1}))</td>
<td>27.9</td>
<td>27.9</td>
<td>19.2 (68)</td>
</tr>
<tr>
<td>CL(_{\text{Cdeep}}) (liters h(^{-1}))</td>
<td>2.57</td>
<td>2.57</td>
<td>1.05 (60)</td>
</tr>
<tr>
<td>CVc</td>
<td>0.122</td>
<td>0.122</td>
<td>0.119</td>
</tr>
<tr>
<td>SDc (mg/liter)</td>
<td>0.059</td>
<td>0.059</td>
<td>0.057</td>
</tr>
</tbody>
</table>

\(^{\text{a}}\) CL, total clearance; Vss, volume of distribution at steady state; V1, volume of distribution for the central compartment; V2, volume of distribution for the shallow peripheral compartment; V3, volume of distribution for the deep peripheral compartment; CL\(_{\text{Cinf}}\), intercompartmental clearance between the central and the shallow peripheral compartment; CL\(_{\text{Cdeep}}\), intercompartmental clearance between the central and the deep peripheral compartment; CVc, proportional residual error component for the plasma concentrations; SDc, additive residual error component for the plasma concentrations. The duration of zero order input was fixed to 5 min and not estimated.

\(^{\text{b}}\) All clearance and volume estimates are group estimates of the respective PK parameter for subjects of standard size (fat-free mass: 53 kg).

\(^{\text{c}}\) Apparent coefficients of variation describing the between-subject variability. As sample size was small, one joint variance was estimated for CF patients and healthy volunteers for each parameter.

\(^{\text{d}}\) Derived from the group means of V1, V2, and V3, not an estimated parameter.

\(^{\text{e}}\) Coefficients of correlation for the random variability between pairs of random effects are as follows: r(V1,V2) = −0.67, r(V1,V3) = 0.56, r(V2,V3) = −0.59.

\(^{\text{f}}\) Estimates reported for NPAG are geometric means of the support points for each subject group.

\(^{\text{g}}\) The nonparametric estimation algorithm in NPAG yielded large volumes of the deep peripheral compartment (between 20 and 50 liters) for three CF patients and three healthy volunteers. Therefore, the geometric means for V3 in NPAG are larger than those in NONMEM and S-ADAPT.

infusion q6h and of 1 mg/liter for short-term infusion q8h at a daily dose of 6 g/70 kg WT. Healthy volunteers had breakpoints of 4 mg/liter for short-term infusion q6h and of 3 mg/liter for short-term infusion q8h at a daily dose of 6 g/70 kg WT.

For the bacteriostasis target (FT\(_{\text{MIC}}\) \(\approx 40\%\)), the PK-PD MIC breakpoints were 16 mg/liter in CF patients and 24 mg/liter in healthy volunteers for both prolonged-infusion regimens. For this target, CF patients had breakpoints of 6 mg/liter for short-term infusion q6h and of 4 mg/liter for short-term infusion q8h at a daily dose of 6 g/70 kg WT. Healthy volunteers had breakpoints of 12 mg/liter for short-term infusion q6h and of 8 mg/liter for short-term infusion q8h at a daily dose of 6 g/70 kg WT.

**DISCUSSION**

The life expectancy and quality of life of CF patients have improved impressively during the last 70 years. Optimal treatment of infections by *P. aeruginosa* (28) is crucially important, as it is almost impossible to eradicate chronic lung infections by this pathogen in CF patients. Ceftazidime is still the cephalosporin with the best activity against *P. aeruginosa* (45) and is a valuable treatment option in antipseudomonal therapy in CF patients (6, 12, 61, 69).

MCS can identify dosage regimens that achieve a high PTA for treatment of a specific patient population (26). To better understand the potentially altered PK in CF patients compared to healthy volunteers, differences in body size and body composition should be considered for an MCS. We assessed the effect of these factors on the PK of ceftazidime within the same study. While this assures that the clinical and bioanalytical procedures are standardized, one limitation of our study is that the demographic characteristics of CF patients and healthy volunteers were not matched. The resulting larger range in body composition in our study is likely to support a distinction between different body size models. Another potential limita-

TABLE 4. Ratios\(^{\text{a}}\) of group estimates for clearance and volume of distribution for different body size models (based on results from NONMEM)

<table>
<thead>
<tr>
<th>Body size model</th>
<th>FCYF(_{\text{CL}})</th>
<th>FCYF(_{\text{Vss}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>No body size model</td>
<td>0.861</td>
<td>0.853</td>
</tr>
<tr>
<td>WT (linear scaling)</td>
<td>1.45</td>
<td>1.13</td>
</tr>
<tr>
<td>WT (allometric scaling)</td>
<td>1.27</td>
<td>1.13</td>
</tr>
<tr>
<td>FFM (linear scaling)</td>
<td>1.30</td>
<td>1.01</td>
</tr>
<tr>
<td>FFM (allometric scaling)</td>
<td>1.17</td>
<td>1.01</td>
</tr>
</tbody>
</table>

\(^{\text{a}}\) FCYF\(_{\text{CL}}\), ratio of group estimates for total clearance in CF patients divided by total clearance in healthy volunteers; FCYF\(_{\text{Vss}}\), ratio of group estimates for volume of distribution at steady state in CF patients divided by volume of distribution at steady state in healthy volunteers.

TABLE 5. Between-subject variability (variances) for different body size models\(^{\text{b}}\)

<table>
<thead>
<tr>
<th>Body size model</th>
<th>Relative between-subject variance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL</td>
<td>V1</td>
</tr>
<tr>
<td>WT (linear scaling)</td>
<td>100(^{\text{b}})</td>
</tr>
<tr>
<td>WT (allometric scaling)</td>
<td>75(^{\text{c}})</td>
</tr>
<tr>
<td>FFM (linear scaling)</td>
<td>85(^{\text{c}})</td>
</tr>
<tr>
<td>FFM (allometric scaling)</td>
<td>68(^{\text{c}})</td>
</tr>
</tbody>
</table>

\(^{\text{b}}\) Shown are relative between-subject variances for the respective PK parameter and body size models (see Table 3 for parameter explanations) based on results from NONMEM.

\(^{\text{c}}\) The between-subject variance for linear scaling by WT was used as the reference.

\(^{\text{c}}\) The lower this number, the more variability was explained by the respective body size model. These values indicate that the between-subject variability (variance) for total clearance was reduced by 25% for allometric scaling by WT, by 15% for linear scaling by FFM, and by 32% for allometric scaling by FFM, all compared to linear scaling by WT.
tion of our study from 1983 is that our results for relatively lean CF patients may not be directly applicable to therapy of CF patients with normal body composition nowadays. However, our results may be very valuable for CF patients in economically challenged countries and potentially for other patient groups with lean body composition. A population PK analysis with lean CF patients seems important to put PK studies of (relatively) lean CF patients from the 1970s and 1980s in perspective with more recent studies of CF patients of normal body size and body composition that are matched to healthy volunteers, as in the aztreonam study by Vinks et al. (77).

Our final population PK model (Table 3) had highly sufficient predictive performance (Fig. 1) for CF patients, whereas predictions for healthy volunteers were slightly too variable. This results in slightly more-conservative predictions for the PTA in healthy volunteers. One limitation of our MCS is that it was based only on 15 subjects for whom we had frequent plasma samples. However, our results for the PK parameters of ceftazidime in healthy volunteers were in good agreement with those from other authors (5, 27, 40, 52, 57, 70, 78). We are aware of only two studies on the PK of ceftazidime in CF patients which included a healthy volunteer control group. Leeder et al. (44) found a total clearance of 8.5 ± 1.0 liters/h/1.73 m² and Hedman et al. (33) found 7.6 ± 0.7 liters/h/1.73 m² in CF patients. Although some authors report (47, 56, 72) higher clearances of 0.23 to 0.36 liters/h/kg (equivalent to 16 to 25 liters/h/70 kg WT) for ceftazidime in CF patients, most studies (41, 50, 53, 58, 75, 76) of juvenile to adult CF patients find an average total clearance of 8 to 11 liters/h for CF patients of standard body size (i.e., 70 kg WT or 1.73 m² body surface area) and a coefficient of variation (CV) of 9 to 26% for the BSV of total clearance. Our geometric mean of 7.82

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FIG. 2. Probability of target attainment for different dosage regimens of 6 g ceftazidime per 70 kg WT daily at steady state (based on results from NONMEM).
liters/h (CV, 28.3%; from NONMEM) for total clearance in CF patients with 53 kg FFM (Table 3) was in good agreement with the clearances for CF patients in the literature.

The reported average volume of distribution ranges between 0.237 and 0.46 liters/kg WT (equivalent to 16.6 and 32 liters/70 kg WT), with coefficients of variation between 14 and 53% in CF patients (41, 44, 47, 50, 53, 56, 58, 76). Our geometric mean of 12.8 liters (from NONMEM) for CF patients with 53 kg FFM and coefficients of variation between 25 and 45% for the individual volumes (Table 3) was at the lower end of the arithmetic means reported in the literature. The nonparametric estimation algorithm in NPAG yielded larger volumes of distribution at steady state (Table 3), which were well comparable with literature estimates. Our results on terminal half-life (Table 2) were in good agreement with the shorter terminal half-life of 1.5 ± 0.2 h in CF patients compared to 1.76 ± 0.2 h in healthy volunteers reported by Leeder et al. (44). The reported average half-lives in juvenile to adult CF patients range between 1 and 2 h (41, 47, 50, 56, 58, 68, 72, 76).

As our CF patients were smaller and leaner than our healthy volunteers (Table 1), we evaluated various body size models to describe differences in average PK parameters using population PK modeling. The differences in average PK parameters were better explained by FFM than by WT (Table 4), most likely since FFM accounts for body composition whereas WT does not. Lean body mass calculated by the Cheymol and James formula (21, 38) yielded results very similar to those of FFM (results not shown). In agreement with theoretical considerations (79) and other studies (3), allometric scaling explained the difference in average clearance between both patient groups better than linear scaling of clearance (Table 4). Furthermore, allometric scaling by FFM reduced the unexplained BSV of clearance and of both peripheral volumes of distribution most (Table 5). This allows one to design dosing regimens based on FFM that achieve target concentrations and target effects more precisely.

These results are in agreement with studies on the PK of beta-lactams in CF patients and healthy volunteers (16, 17, 62, 71, 77) and are comparable to results from Leeder et al. (44) on ceftazidime. Leeder et al. found a 42% increased total clearance (142 ± 17 ml/min/1.73 m² in CF patients versus 101 ± 10 ml/min/1.73 m² in healthy volunteers) and Hedman et al. (33) found a 25% increased renal clearance (125 ± 20 ml/min/1.73 m² in CF patients and 100 ± 9 ml/min/1.73 m² in healthy volunteers) for ceftazidime. Hedman et al. explained this increased renal clearance primarily by an increased glomerular filtration rate in CF patients determined via inulin clearance. This might have been in part caused by an altered glomerulotubular balance due to a primary tubular transport defect (7, 11) or by a 16% higher resting energy expenditure in CF patients (73) due to a higher energy need secondary to chronic lung infection. A potential limitation of our model is that it did not account for renal function.

Our MCS used an allometric body size model based on FFM and predicted lower PTAs for CF patients than for healthy volunteers (Fig. 2). The PK-PD MIC breakpoint was 1 mg/liter in CF patients and 3 mg/liter in healthy volunteers for short-term infusion of 2 g/70 kg WT q8h for the near-maximal kill target. The proposed allometric body size model provides an explanation why our CF patients, who were smaller than our healthy volunteers, had shorter drug half-lives (Table 2) and required higher beta-lactam doses to achieve similar PK-PD MIC breakpoints, in particular for short-term infusions. This prediction matches with the higher clinically recommended doses (in mg/kg of total body weight) of beta-lactams for pediatric CF patients than for adult CF patients (30). Mouton et al. (53) found a PTA of ≥90% for MICs of ≤4 mg/liter in CF patients and for MICs of ≥8 mg/liter in healthy volunteers for a fixed dose of 2 g q8h and the target fT > MIC of ≥60%. When we used this target and a fixed dose of 2 g q8h as a 30-min infusion, we obtained a comparable breakpoint of 3 mg/liter in CF patients. Daily doses of up to 12 g ceftazidime split into 3 or 4 intermittent doses have been recommended for CF patients (24), whereas other authors recommend lower daily doses of 6 g in adult CF patients (30). To increase the PK-PD MIC breakpoints and clinical outcome, continuous infusion of ceftazidime has been proposed and studied in CF patients (8, 13, 23, 36, 42, 59, 74–76).

Our MCS assessed the benefit of continuous and prolonged infusion in comparison to short-term infusions, all at a daily dose of 6 g/70 kg WT. Both prolonged infusion regimens achieved PK-PD MIC breakpoints of 8 to 12 mg/liter in CF patients, which were approximately 10 times higher than the breakpoint for short-term infusions q8h at the same daily dose. Giving the same daily dose as a short-term infusion q6h instead of q8h achieved only a PK-PD MIC breakpoint of 2 mg/liter in CF patients. This prediction is in excellent agreement with the better outcome for CF patients with resistant or intermediate isolates when they received continuous ceftazidime infusion compared to when they received short-term infusion (both coadministered with tobramycin) (36, 63) and with results from in vitro PD models (1, 20, 51).

In conclusion, we found a 19% lower unscaled total clearance and a 36% lower volume of distribution at steady state in CF patients than in healthy volunteers, because our CF patients were smaller and leaner. Allometric scaling by FFM explained the differences in average PK parameters better than linear scaling by WT, probably because WT does not account for body composition. Additionally, allometric scaling by FFM reduced the unexplained BSV by 32% for clearance and by 18 to 26% for volume of the peripheral compartments relative to linear scaling by WT. Dosage regimens based on FFM can therefore achieve target concentrations more precisely. The PK-PD MIC breakpoint for near-maximal bactericidal activity was 1 mg/liter in CF patients for short-term infusions of 2 g/70 kg WT q8h. As alternative modes of administration, prolonged (5-h) infusion of 2 g/70 kg WT q8h or continuous infusion of 6 g/70 kg WT/day achieved a PK-PD MIC breakpoint of 8 to 12 mg/liter in CF patients. More large clinical trials are warranted to compare the time course of clinical responses to prolonged or continuous infusion with short-term infusion of beta-lactams in CF patients and to compare clinical responses for dose selection via an allometric body size model based on FFM with standard dosing of CF patients as mg/kg WT.

ACKNOWLEDGMENTS

This work is dedicated to Klaus-Jürgen Hess at the Gymnasium Scheinfeld, Germany, who inspired this work by his continuous support of one of us (J.B.B.). There are no conflicts of interest for any of the authors.
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