Clinical Pharmacodynamics of Antipseudomonal Cephalosporins in Patients with Ventilator-Associated Pneumonia

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Advanced-generation cephalosporins are frequently used for empirical coverage of ventilator-associated pneumonia (VAP) due to their activity against a broad spectrum of Gram-positive and Gram-negative aerobic bacteria, including Pseudomonas aeruginosa and Enterobacteriaceae. Providing optimal antibiotic exposure is essential to achieving successful response in patients with VAP. We evaluated exposures of two antipseudomonal cephalosporins, ceftazidime and cefepime, in patients with VAP due to Gram-negative bacilli to identify the pharmacodynamic parameter predictive of microbiological success. Population pharmacokinetic models were used to estimate individual free drug exposures. Pharmacodynamic indices were determined for each patient using the baseline Gram-negative bacilli with the highest drug MIC. Classification and regression tree analysis was utilized to partition exposure breakpoints, and multivariate logistic regression was conducted to identify predictors of microbiological success. A total of 73 patients (18 receiving ceftazidime therapy and 55 receiving cefepime therapy) were included. MICs ranged widely from 0.047 to 96 μg/ml. The microbiological success rate was 58.9%. Predictive breakpoints were identified for all pharmacodynamic parameters, including a serum \( fT > MIC \) greater than 53% (\( P = 0.02 \)). When controlling for APACHE II (odds ratio [OR], 1.01; 95% confidence interval, 0.93 to 1.09; \( P = 0.85 \)) and combination therapy (OR, 0.74; 95% confidence interval, 0.25 to 2.19; \( P = 0.59 \)), achieving a greater than 53% \( fT > MIC \) remained a significant predictor of success (OR, 10.3; 95% confidence interval, 1.1 to 92.3; \( P = 0.04 \)). In patients with VAP due to Gram-negative bacilli, serum exposure of greater than 53% \( fT > MIC \) was found to be a significant predictor of favorable microbiological response for antipseudomonal cephalosporins. These data are useful when determining dosing regimens for cephalosporin agents under development for pneumonia.

Even with significant enhancements in the management of mechanically ventilated patients, ventilator-associated pneumonia (VAP) remains the most common hospital-acquired infection in intensive care unit (ICU) patients (1, 2). Ceftazidime and cefepime are advanced-generation cephalosporins with activity against a broad spectrum of Gram-positive and Gram-negative aerobic bacteria, including Pseudomonas aeruginosa and Enterobacteriaceae (3, 4, 5, 6, 7). As a result, these agents are routinely prescribed for empirical coverage of many severe infections and are recommended as a backbone empirical therapy in the current VAP guidelines (8). Nevertheless, due to increasing resistance among bacteria often implicated in VAP, new antimicrobial treatments are needed.

Like other \( \beta \)-lactams, cephalosporins exhibit time-dependent bactericidal activity where efficacy is correlated with the percentage of the dosing interval during which free drug concentrations remain above the MIC against the organism (\( fT > MIC \)) (9, 10). For cephalosporins, animal infection models have demonstrated that ~40% and ~60% to ~70% \( fT > MICs \) are necessary for bacteriostatic activity and bactericidal activity, respectively (11). Studies in patients with severe infections have identified similar pharmacodynamic targets in the range of 45% to 60% \( fT > MIC \); however, those studies have had mixed infections or had limited concentration data available for patients when estimating exposure (12, 13).

The paucity of novel agents to treat resistant Gram-negative infections has shifted the focus of development efforts largely toward this public health concern (14, 15). In response, at present, three novel cephalosporins for the treatment of multidrug-resistant (MDR) Gram-negative bacillus infections are under investigation in clinical trials, including plans for study in pneumonia (16). Knowledge of an accurate exposure threshold that would be predictive of microbiological response in VAP would be of significant value when finalizing dosing regimens for study in clinical trials. Here, we evaluated the serum exposure of two antipseudomonal cephalosporins, ceftazidime and cefepime, in patients with VAP due to Gram-negative bacilli, serum exposure of greater than 53% \( fT > MIC \) was found to be a significant predictor of favorable microbiological response for antipseudomonal cephalosporins. These data are useful when determining dosing regimens for cephalosporin agents under development for pneumonia.

MATERIALS AND METHODS

Study design. This study is a retrospective pharmacokinetic/pharmacodynamic analysis. Demographic, pharmacokinetic, and microbiological data from patients treated for VAP with ceftazidime or cefepime were included. Data corresponding to patient demographics (age, gender, and race) and the following clinical parameters were collected from the medical record: height, weight, creatinine clearance (ClCR) on admission, and Acute Physiology and Chronic Health Evaluation (APACHE) II score (17). Pharmacokinetic models were constructed to estimate pharmacodynamic exposure in each included subject. These pharmacodynamic indices were linked to microbiological response to determine the serum drug exposure predictive of a successful response.

Patients. Patients from previously conducted studies of ceftazidime (18) and cefepime (19) were compiled. The study was approved by the Hartford Hospital Institutional Review Board. A waiver of informed consent was granted because all of the data were already in existence and...
TABLE 1 Patient characteristics and dosing regimens by drug

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%) of males</td>
<td>50 (68.5)</td>
</tr>
<tr>
<td>Mean (SD) age (yr)</td>
<td>52.8 (21.7)</td>
</tr>
<tr>
<td>Mean (SD) wt (kg)</td>
<td>78.4 (19.2)</td>
</tr>
<tr>
<td>Mean (SD) APACHE II score</td>
<td>16.6 (6.5)</td>
</tr>
<tr>
<td>Mean (SD) CLCR (ml/min)</td>
<td>106.6 (30.8)</td>
</tr>
</tbody>
</table>

No. (%) receiving the following cefepime regimen:
- 2 g every 2 h (0.5-h infusion): 18 (24.7)
- 2 g every 12 h (0.5-h infusion): 2 (11.1)
- 4.5 g every 24 h (continuous infusion): 1 (5.5)

No. (%) receiving the following ceftazidime regimen:
- 1 g every 12 h (0.5-h infusion): 55 (75.3)
- 1 g every 8 h (0.5-h infusion): 15 (27.2)
- 2 g every 12 h (0.5-h infusion): 10 (18.2)
- 2 g every 8 h (0.5-h infusion): 2 (3.6)
- 2 g every 8 h (3-h infusion): 20 (36.4)
- 2 g every 8 h (3-h infusion): 8 (14.5)

TABLE 2 Univariate analysis for association with microbiological response

<table>
<thead>
<tr>
<th>Variable</th>
<th>Microbiological failure (n = 30)</th>
<th>Microbiological success (n = 43)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age (yr)</td>
<td>54.4 (22.7)</td>
<td>51.6 (21.2)</td>
<td>0.600</td>
</tr>
<tr>
<td>No. (%) of male patients</td>
<td>19 (63.3)</td>
<td>31 (72.1)</td>
<td>0.592</td>
</tr>
<tr>
<td>Patient wt (kg)</td>
<td>81.3 (25.0)</td>
<td>76.4 (13.8)</td>
<td>0.287</td>
</tr>
<tr>
<td>CLcr (ml/min)</td>
<td>115.5 (51.4)</td>
<td>100.4 (50.0)</td>
<td>0.214</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>16.1 (6.47)</td>
<td>17.0 (6.5)</td>
<td>0.553</td>
</tr>
<tr>
<td>MIV, median (range)</td>
<td>3.1 (5.5–8.0)</td>
<td>1.0 (2.5–5.75)</td>
<td>0.006</td>
</tr>
<tr>
<td>No. (%) of patients with combination therapy</td>
<td>23 (76.7)</td>
<td>29 (67.4)</td>
<td>0.553</td>
</tr>
<tr>
<td>No. (%) of patients with ceftazidime therapy</td>
<td>5 (27.8)</td>
<td>13 (72.2)</td>
<td>0.295</td>
</tr>
<tr>
<td>No. (%) of patients with cefepime therapy</td>
<td>25 (45.5)</td>
<td>30 (54.5)</td>
<td>0.295</td>
</tr>
</tbody>
</table>

*All data are listed as mean (SD) unless otherwise specified.*
**TABLE 3** Population pharmacokinetic estimates for ceftazidime in patients with VAP

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_l$ (liters/h)</td>
<td>3.84</td>
<td>4.22</td>
<td>2.71</td>
</tr>
<tr>
<td>$V_c$ (liters)</td>
<td>0.05</td>
<td>0.04</td>
<td>0.036</td>
</tr>
<tr>
<td>$V_t$ (liters)</td>
<td>10.86</td>
<td>11.65</td>
<td>6.08</td>
</tr>
<tr>
<td>$K_{12}$ (h$^{-1}$)</td>
<td>3.35</td>
<td>1.57</td>
<td>4.29</td>
</tr>
<tr>
<td>$K_{21}$ (h$^{-1}$)</td>
<td>2.4</td>
<td>1.34</td>
<td>2.6</td>
</tr>
</tbody>
</table>

* $C_l$, renal clearance; $V_c$, proportion of creatinine clearance estimate contributing to renal clearance; $V_t$, volume of distribution of the central compartment; $K_{12}$, microtransfer rate constant from the central to the peripheral compartment; $K_{21}$, microtransfer rate constant from the peripheral compartment to the central compartment.

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**RESULTS**

**Patient characteristics and microbiological response.** Seventy-three patients with VAP were evaluable for microbiological outcome; 18 patients received ceftazidime and 55 patients were treated with cefepime. Patient characteristics and the frequency of each dosing regimen are presented in Table 1. Combination therapy was common but did not appear to have any impact on microbiological response. *Pseudomonas aeruginosa* was the most common infecting pathogen (63.0%; $n = 46$) followed by *Klebsiella pneumoniae* (8.2%; $n = 6$), *Enterobacter cloacae* (8.2%; $n = 6$), *Escherichia coli* (4.1%; $n = 3$), *Haemophilus influenzae* (4.1%; $n = 3$), *Serratia marcescens* (4.1%; $n = 3$), and *Acinetobacter baumannii* (2.7%; $n = 2$).

Microbiological response was classified as successful in 58.9% of patients. When stratified by microbiological response, the demographics of the populations were similar (Table 2). Additionally, there was no difference in microbiological response rates between ceftazidime-treated patients and cefepime-treated patients. However, the MIC (median [range]) was significantly higher in patients with microbiological failure ($3 [0.094 to 96]$ versus $1 [0.047 to 32]$ μg/ml; $P = 0.006$).

**Population pharmacokinetic model.** Thirty-two patients with serum ceftazidime concentrations were used to develop the population pharmacokinetic model for this agent. An average of five serum samples (range, 2 to 7) were collected for each patient. Seventeen patients received CI and 15 received II ceftazidime, with the dosage adjusted based on renal function. The final population pharmacokinetic parameters derived from ceftazidime-treated patients are shown in Table 3. The predicted versus observed (pre-Bayesian) population plot for the model fit the population well (Fig. 1A), with $r^2$, bias, and precision values of 0.72, 0.36, and 20.31 μg/ml, respectively. The individual predicted maximum $a$ posteriori (MAP) Bayesian versus observed concentration plot (Fig. 1B) had $r^2$, bias, and precision values of 0.99, −0.011, and 0.96 μg/ml, respectively.

**Pharmacodynamic indices.** Of the 18 ceftazidime patients, 15 (83.3%) achieved serum $fT > MIC$ exposures of 100%. The median (range) $%fT > MIC, fC_{max}/MIC, fC_{min}/MIC$, and $fAUC/MIC$ values were 100 (31.3 to 100), 42.5 (1.8 to 351.4), 6.26 (0.1 to 62.8), and 483.6 (19.8 to 3,030). Forty-two (76.3%) of the 55 cefepime patients had 100% $fT > MIC$. The median (range) $%fT > MIC, fC_{max}/MIC, fC_{min}/MIC$, and $fAUC/MIC$ values were 100 (0.8 to 100), 29.5 (1.1 to 2,318), 6.14 (0.03 to 318.1), and 293.3 (4.2 to 17,399).

When the populations were combined, most patients (78.1%) achieved serum $fT > MIC$ exposures of 100%, presumably because of the high-dose regimes recommended for patients on the VAP clinical pathway at our institution and low MICs in many situations. As a result, the median (range) $fT > MIC$ for the total study population was 100 (0.8 to 100). Modest collinearity

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**FIG 1** (A) Population predicted versus observed ceftazidime concentrations using the mean parameter estimates from the population pharmacokinetic model. (B) Individual predicted versus observed ceftazidime concentrations with mean population parameters as the maximum $a$ posteriori Bayesian estimates.
colinearity between %\( T > \text{MIC} \) and \( \frac{C_{\text{max}}}{\text{MIC}} \) (A), \( \frac{C_{\text{min}}}{\text{MIC}} \) (B), and \( \frac{AUC}{\text{MIC}} \) (C) for the 73 patients with VAP treated with ceftazidime (open triangles) and cefepime (closed circles).

was observed between %\( T > \text{MIC} \) and the other pharmacodynamic parameters despite significant plateaus at 100% \( T > \text{MIC} \) (Fig. 2). However, due to the range of MICs (ceftazidime MICs, 0.25 to 32 \( \mu \)g/ml; cefepime MICs, 0.047 to 96 \( \mu \)g/ml), \( \frac{C_{\text{max}}}{\text{MIC}} \), \( \frac{C_{\text{min}}}{\text{MIC}} \), and \( \frac{AUC}{\text{MIC}} \) exposures differed widely, resulting in median (range) values of 32.7 (1.1 to 2,318.3), 6.14 (0.03 to 318.1), and 299.6 (4.2 to 17,398.6).

Pharmacodynamic breakpoint. The CART-derived pharmacodynamic parameters values partitioning microbiological success versus failure are included in Table 4. These identified break-
study, population pharmacokinetic models were used to derive the pharmacokinetic parameters in serum of patients with VAP treated with either ceftazidime or cefepime in order to predict individual exposures and their correlation with microbiological response.

With the increased prevalence of MDR Gram-negative organisms in VAP, ceftazidime’s and cefepime’s spectrum of activity has sparked renewed interest in understanding their pharmacodynamics. Furthermore, such data are paramount in decision support for the development of dosing regimens for new antimicrobials. Target pharmacodynamic exposures are traditionally derived from in vitro and in vivo animal infections models, with limited human data to validate these findings. Human studies with cephalosporins have produced variable fT > MIC exposure data for microbiological success (12, 13, 37). Others have suggested enhanced β-lactam activity by maintaining a fCmin/MIC > 4 to 6 (37, 38). In the current study of VAP patients, attainment of specific pharmacodynamic exposures was associated with favorable microbiological response for antipseudomonal cephalosporins, including a serum fT > MIC value compatible with animal infection models (9–11). While all pharmacodynamic indices displayed predictive relationships, our observations are consistent with findings from other studies in that microbiological success was significantly associated with achieving free drug exposures of greater than 53% fT > MIC.

Muller and colleagues saw favorable clinical and microbiological outcomes with ceftazidime in nosocomial pneumonia when patients had a greater than 45% fT > MIC (13). Their population pharmacokinetic model was derived from 75 patients with nosocomial pneumonia, 8 healthy volunteers, and 6 additional ICU patients. We developed a ceftazidime model specifically in the VAP population to accurately estimate drug exposures for all 18 included ceftazidime patients. The cefepime model used here is the same utilized in a pharmacodynamic analysis of cefepime in patients infected with P. aeruginosa performed at our institution by Crandon and colleagues (12). All sites of infection were in- between fT > MIC > 4 to 6 (12, 13). In the current study of VAP patients, attainment of specific pharmacodynamic exposures was associated with 100% fT > MIC uniformly distributed across the population, resulting in a major-

This study is not without limitations. Although this is a retrospective study of data from two different time periods, the mainstay of treatment for VAP is antibiotic chemotherapy. Therefore, we employed microbiological response as an endpoint, instead of clinical response or mortality, to alleviate any concerns surrounding changes in the standard of care for VAP patients. Second, while ceftazidime concentration data were available for each patient, cefepime exposures were estimated using a validated population pharmacokinetic model based on patient covariates. This model was derived from cefepime-treated patients with VAP at the same institution and with the drugs used in dosages similar to those used in the current analysis, and many of these patients contributed concentrations to the original model. Last, assessing patients who were treated with two different agents allowed for a larger sample size but did introduce a potential confounder, which should be considered when interpreting these findings. However, given the similarity between the two agents, it is not unreasonable to predict they would have similar pharmacodynamic targets.

In patients with VAP, a significant relationship between antibiotic exposure and microbiological outcome was observed with antipseudomonal cefepime therapy. Notably, a serum fT > MIC greater than 53% was associated with microbiological success. In addition to these cephalosporins, these data may have application in the design of optimal dosing regimens for future cephalosporins under development for the treatment of VAP.

REFERENCES


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