Pharmacodynamic Modeling of the In Vivo Interaction between Cefotaxime and Ofloxacin by Using Serum Ultrafiltrate Inhibitory Titers

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The pharmacokinetics (PK) and pharmacodynamics (PD) of cefotaxime and ofloxacin and of their combination were examined in a three-period randomized crossover study involving 12 healthy adults. The PK of cefotaxime and ofloxacin were modeled. PD was assessed from the predicted concentrations in serum and serum ultrafiltrate inhibitory titers for 10 test organisms. An inhibitory sigmoid Emax model based on the probability of bacterial growth was used, where Emax = 1 and EC50 is the concentration resulting in a 50% probability of growth. The total body clearance (CL T) and volume of distribution at steady state (VSS) for cefotaxime were 0.236 liters/kg/h and 0.207 liters/kg, respectively, for the monotherapy and 0.231 liters/kg/h and 0.208 liters/kg for the combination therapy. Ofloxacin exhibited PK parameters of 0.143 liters/kg/h for CL T and 1.21 liters/kg/for VSS following the monotherapy and of 0.141 liters/kg/h for CL T and 1.16 liters/kg for VSS following combination therapy. For the combination interaction, an interaction term, 0, defined the type and relative extent of interaction. The range of observed 0 values (−0.033 to 0.067) is consistent with an additive PD interaction according to standards similar to those used for the in vitro fractional inhibitory concentration index.

Combinations of antimicrobial agents are often preferred to single agents for the treatment of serious infections (11, 28). These combinations may provide a broader antibacterial spectrum and more-rapid bacterial killing than single agents. Problems with resistance emerging during therapy may be minimized when combinations are used. Resistance may result from the initial presence of a resistant subpopulation or from bacterial mutations. In either case, resistance to two drugs is less common than resistance to a single agent. Although am noglycosides have been traditionally combined with β-lactam agents, fluoroquinolone–β-lactam combinations have been used with increasing frequency (6, 12, 16, 20, 23, 24). These reports have usually involved combinations of ciprofloxacin and extended-spectrum penicillins (6, 12, 23, 24).

Cefotaxime plus ofloxacin was compared to cefotaxime plus tobramycin treatment in cancer patients with fever and symptoms of serious infection (20). A statistically improved cure rate for the cefotaxime-ofloxacin combination (71%) compared to that for the cefotaxime-tobramycin combination (47%) was observed. Synergy or partial synergy was also demonstrated in 89 of 110 gram-negative isolates when a 1:1 ratio of cefotaxime and desacetylcefotaxime was combined with ofloxacin (13). For gram-positive organisms, 81 of 89 isolates showed synergy or partial synergy by the checkerboard method. However, the 1:1 ratio of desacetylcefotaxime to cefotaxime is somewhat higher than the ratio reported in pharmacokinetic (PK) studies.

In this study, serum ultrafiltrate inhibitory titers (uSITs) from healthy volunteers given cefotaxime alone, ofloxacin alone, and the combination of cefotaxime and ofloxacin in a crossover study were measured. The objective of this study was to determine the interactions of pharmacokinetics (PK) and pharmacodynamics (PD) between cefotaxime and ofloxacin.

MATERIALS AND METHODS

A protocol was developed and approved by the institutional review board. Informed consent was obtained from all participants. Twelve healthy subjects were enrolled in this three-period crossover study involving cefotaxime and ofloxacin given alone and in combination. Subjects were male or female and were aged between 18 and 40 years. A serum pregnancy test was performed on all female subjects, and the result was required to be negative. No other drugs were permitted within 1 week of the study, except for previously prescribed oral contraceptives. Barrier contraceptive methods were recommended to all females, including those using oral contraceptives.

Subjects were confined to the research center for 3 days during each of three treatment phases. The treatment phases consisted of 2 g of cefotaxime every 8 h (treatment A), 400 mg of ofloxacin every 12 h (treatment B), and a combination of cefotaxime and ofloxacin with the same dosages (treatment C). Each antimicrobial agent was administered for five doses at times that would provide a wide range of the cefotaxime-ofloxacin concentration ratio. Cefotaxime was administered at 0830 and 1630 on day 2 and at 0630, 0830, and 1630 on day 3 for treatments A and C. Ofloxacin was administered at 1900 on day 1 and at 0700 and 1900 on days 2 and 3 during treatments B and C. All doses were administered by constant rate infusion with intravenous (i.v.) pumps over a period of 0.5 h for cefotaxime and 1 h for ofloxacin. The same dosing times were used for the combination regimen. Administration times were staggered at intervals of 4 min. As a consequence, all infusions were started within 50 min following the stated times and remained constant for a particular subject. The administration times for cefotaxime relative to ofloxacin remained fixed for all subjects.

The primary outcome measurements included concentrations of cefotaxime and ofloxacin in serum and serum ultrafiltrate inhibitory activity. Blood samples were collected during day 3 for all treatment phases at 0800, 0900, 1000, 1100, 1200, 1600, 1700, 1800, 2000, and 2100. As with dosing times, sampling times for individual subjects were within 50 min following the stated times and were constant relative to dosing times. During treatments A and B, two 7-ml blood samples were obtained, one for drug concentration, and one for uSIT measurement. Three 7-ml samples were obtained at each time for treatment C. Serum was removed and frozen at −70°C.

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Ofloxacin, cefotaxime, and desacetylcefotaxime concentrations in serum were determined by specific reverse-phase high-performance liquid chromatography assays developed and validated at the Clinical Pharmacokinetics Laboratory. Quantitation ranges were defined by the linear region of a standard curve where the minimal quantifiable concentration (MQC) exhibits a peak height of approxi-
mately 10 times the baseline noise amplitude. Minimum detectable concentra-
tions (MDC) were 2 to 2.5 times less than the MQC; however, these concentra-
tions were not used in the PK analysis. Validation was performed over 5 days prior to determining the stability of study samples. The reported assay variability was obtained from quality control samples that were run during the period in which study samples were analyzed and represents a combined intra- and interday coefficient of variation (CV). CVs during the validation phase were similar to and often lower than those obtained during the study. Cefotaxime, desacetylcefotaxime, and ofloxacin concentrations were quantitated from 0.50 to 100 μg/ml. CVs for quality control samples were 6.9% at 2.00 μg/ml, 5.7% at 15.0 μg/ml, 6.9% at 75.0 μg/ml, and 8.6% at 240 μg/ml. For concentrations that were greater than 100 μg/ml, samples were diluted two- to fourfold with buffer and then reassayed. For desacetylcefotaxime, concentrations were quantitated from 0.43 to 17.2 μg/ml. CVs for quality control samples were 6.0% at 1.72 μg/ml, 5.4% at 6.89 μg/ml, and 6.5% at 13.5 μg/ml. Concentrations of ofloxacin were quantitated from 0.10 to 10.0 μg/ml. CVs for quality control samples were 4.4% at 7.00 μg/ml, 4.4% at 1.4 μg/ml, and 5.3% at 0.35 μg/ml.

Sera from 100 patients were stored at −20°C during the study. Serum samples were analyzed by the standard method. A control sample containing cefotaxime or ofloxacin (alternating) in media was included in each assay plate to monitor the sUTT testing. With sterile Mueller-Hinton cation-adjusted broth, serial dilutions were performed to provide serum ultrafiltrate dilutions ranging from 1.2 to 1:1,024. All studies were performed by using 96-well microtiter trays with a final volume of 0.1 ml per well. The test organisms included two strains of Staphylococcus aureus, Streptococcus pneumoniae, Klebsiella pneumoniae, Enterobacter cloacae, and Pseudomonas aeruginosa.

Data analysis. PK-PD analysis was accomplished by a three-step analysis and Adapt II (release 3) software (4a). The first step involved PK analysis of the ofloxacin and cefotaxime data. Models were selected on the basis of prior data (cefotaxime) and goodness of fit. A one-compartment model was clearly inap-
propriate given the concentration-time curve shape. More complex models were not needed based on examination or residuals. In addition, the number of available data points would not support a three-compartment model. For cefo-
taxime and ofloxacin varied in different cases, as did the ratios of con-
centrations of cefotaxime to ofloxacin. The sigmoidicity factor was fixed at 5, which was consistent with the fitted values in this study. Then, for each simu-
lation case, the value of was changed at 0.1 intervals between 4 and −4. For each concentration pair, the probability of growth was calculated and rounded to 0 (no growth) or 1 (growth) if the probability was ≤0.5 or >0.5, respectively. The FIC index was determined for the simulated checkerboard panel and tabulated with corresponding values of . This analysis revealed that values ranging from −0.3 to 0.3 are consistent with additivity. Values of and −0.6 are consistent with synergy, while values ranging from −0.6 to −0.3 represent possible synergy.

Antagonism is defined by values of greater than 0.6, and possible antagonism is defined by values ranging from 0.3 to 0.6.

Area under the ultrafiltrate inhibitory activity versus time curve (AUIC) was calculated by the linear trapezoidal rule for the 14-h period when sUTT mea-
surements were made. These values, which were intended to compare combina-
tion treatment with monotherapy, were referred to as the 14-h AUIC. The 24-h AUIC was calculated by model integration with subject-
specific PK parameters. The MIC used was the geometric mean MIC obtained
for the organism. The 14-h AUIC was calculated as the AUIC divided by the MIC for a particular pathogen. The 14-h AUIC was calculated as the AUIC divided by the MIC for a particular pathogen. The 14-h AUIC was calculated by model integration with subject-
specific PK parameters. The MIC used was the geometric mean MIC obtained for the pathogen. The 24-h AUIC was calculated by the linear trapezoidal rule for the 24-h period, with concentrations calculated at 5-min intervals. Percent time above MIC was calculated by dividing the number of cases in which the FIC or C/EC was ≤1 divided by the total number of cases (288) × 100%.
RESULTS

Eleven subjects completed the study. One female subject withdrew after completing two of three phases due to a skin rash. The mean age of all subjects was 27.9 (25.6%) years (26.7 years for males [n = 6] and 29.4 years for females [n = 5]). The body weights were 72.8 (12.8%) kg overall (77.7 kg for males and 66.9 kg for females). The mean height was 172 cm for all subjects. Mean heights were higher for males (179 cm) than for females (164 cm).

Both cefotaxime and ofloxacin were well tolerated by most subjects. There were 12 adverse experiences reported during the three study phases. Headache was the most common, occurring for subjects during treatments A (n = 1), B (n = 2), and C (n = 1). One subject reported myalgia in the neck region during cefotaxime treatment. There were two cases of local venous irritation during treatments B (n = 1) and C (n = 1). One subject reported nausea during the ofloxacin treatment. He also reported contact dermatitis due to adhesive tape during the combination treatment and mild pharyngitis (presumed viral) before and during cefotaxime treatment. Subject no. 8 completed her combination treatment first without difficulty and then developed a generalized pruritic rash during the cefotaxime treatment. She was removed from the study due to presumed allergic reaction to cefotaxime.

Mean concentrations of cefotaxime, desacetylcefotaxime, and ofloxacin in serum for the three treatment phases are shown in Fig. 1A to C. Error bars (SD) were omitted from Fig. 1C to minimize clutter. However, the SDs were similar to those observed for the monotherapy regimens.

Table 1 provides the PK parameters for ofloxacin and cefotaxime. The mean (CV%) CL Ts of cefotaxime were 0.236 (18.2%) liters/kg/h when administered as monotherapy and 0.231 (19.5%) liters/kg/h when administered with ofloxacin. The mean volumes of distribution at steady state (V SS) were 2.07 (16.9%) liters/kg for cefotaxime alone and 0.208 (13.0%) liters/kg for cefotaxime in the combination treatment. There were no differences between the two treatment regimens in terms of CL T for cefotaxime (P = 0.509) or V SS for cefotaxime (P = 0.853). For cefotaxime alone, male subjects had a mean CL T of 0.223 liters/kg/h and a mean V SS of 0.194 liters/kg. These values were not different from those of female subjects, who had a mean CL T of 0.251 liters/kg/h and a mean V SS of 0.221 liters/kg (P = 0.326 and 0.248, respectively). Similar results were seen for cefotaxime during combination treatment. Male subjects had a mean CL T of 0.221 liters/kg/h and a mean V SS of 0.202 liters/kg, while female subjects had a mean CL T of 0.242 liters/kg/h and a mean V SS of 0.216 liters/kg. Desacetylcefotaxime was detected in all subjects with mean minimum concentrations of 0.79 µg/ml (CV, 48.0%) following cefotaxime and desacetylcefotaxime treatment. The mean maximum concentrations of desacetylcefotaxime were 6.59 µg/ml (25.8%) and 7.08 µg/ml (32.1%) for the single and combination treatments, respectively. The AUC(0–8) values of desacetylcefotaxime were 25 ± 22.6% of cefotaxime alone and 26.5 µg · h/ml (26.2%) for cefotaxime plus ofloxacin. There were no significant differences between the two treatments in the above PK parameters for desacetylcefotaxime.

The mean CL Ts of ofloxacin were 0.143 (14.7%) liters/kg/h when administered alone and 0.141 (16.3%) liters/kg/h when administered with cefotaxime. The mean V SS of ofloxacin was 1.20 (24.9%) liters/kg for the cefotaxime treatment and 1.16 (6.6%) liters/kg for the ofloxacin-cefotaxime treatment. No statistical differences in the CL T (P = 0.782) or V SS (P = 0.684) of ofloxacin were observed when comparing ofloxacin administered with and without cefotaxime. For ofloxacin alone, male subjects had a mean CL T of 0.144 liters/kg/h and a mean V SS of 1.15 liters/kg. These values were not different from those of female subjects, who had a mean CL T of 0.142 liters/kg/h and a mean V SS of 1.25 liters/kg (P = 0.901 and 0.629, respectively). During the combination treatment, male subjects had a mean CL T of 0.145 liters/kg/h and a mean V SS of 1.19 liters/kg, while female subjects had a mean CL T of 0.137 liters/kg/h and a mean V SS of 1.12 liters/kg. There were no differences in CL T and V SS with regard to sex (P = 0.612 and 0.133, respectively). The test organisms exhibited geometric mean MICs ranging from 0.239 to 18.4 µg/ml for cefotaxime and 0.122 to 1.66

FIG. 1. Mean concentrations of cefotaxime (■), desacetylcefotaxime (■), and ofloxacin (○) in serum by treatment period. Mean concentrations (±SD) of cefotaxime and desacetylcefotaxime during cefotaxime monotherapy (A) and ofloxacin monotherapy (B) are shown, along with concentrations of cefotaxime, desacetylcefotaxime, and ofloxacin during the combination regimen (C). Time zero corresponds to 0700.


\[ y = 0.987 \times x - 0.096 \ (r^2 = 0.946) \]

For ofloxacin, the regression line was 0.941 \times x - 0.169 \ (r^2 = 0.88)

The measured uSITs were summarized for the individual drugs and the combination by using a 14-h AUIC. Fourteen hours was used, since this was the period of time when assessments for inhibitory activity were made. These AUIC values can be used to compare the monotherapies to the combination therapy. Table 3 shows the mean (CV\%) AUIC values for cefotaxime, ofloxacin, and the combination of cefotaxime and ofloxacin. In this study, cefotaxime and ofloxacin were administered every 8 h and 12 h, respectively. The administration times were designed to provide a broad range of cefotaxime-ofloxacin concentration ratios, thus improving the ability to evaluate the type of interaction.

Differences between measured and predicted 14-h AUICs were evaluated by using a log ratio, ln [AUIC/(AUC/MIC)] by subject and organism. The overall log ratios were 1.03 for cefotaxime (P = 0.01), 0.899 for ofloxacin (P < 0.001), and 0.94 for the combination (P < 0.001). Although these values are statistically different from 1.0, this difference is not practically important. The correlations between AUIC and predicted AUC/MIC values are shown in Fig. 2A to C. This analysis supports the hypothesis that AUIC can be predicted from pharmacokinetic and bacterial susceptibility data.

The study design did not allow determination of 24-h AUC/MIC ratios directly; however, simulations were used to evaluate 24-h AUC/MIC and time above \( EC_{50} \) values, as shown in Table 4. Time above \( EC_{50} \) was less than 50% for cefotaxime against the two \textit{Pseudomonas} test isolates and one isolate of \textit{S. aureus}. These isolates also were associated with comparatively low AUC/MIC. Further research is needed to refine time above MIC and AUC/MIC targets for ofloxacin and cefotaxime for a variety of infections. At present, optimizing AUC/MIC appears most important for fluoroquinolones and optimizing time above MIC appears most important for \( \beta \)-lactam agents (2, 3, 7). Figure 3 shows the mean and range of \( \theta \) values for the 10 test isolates. The mean \( \theta \) values ranged from -0.033 to 0.067, and all values were consistent with additivity.

**DISCUSSION**

Cefotaxime PK characteristics were similar to those previously reported (27). The mean CL\(_T\) of cefotaxime was reported to be 0.229 liters/kg/h. In our study, the CL\(_T\) of cefotaxime was 0.236 liters/kg/h. The mean CL\(_T\) of ofloxacin in our study was 0.143 liters/kg/h. Previous studies have reported more rapid CL\(_T\)s for ofloxacin, ranging from 0.187 to 0.217 liters/kg/h for a 400-mg intravenous dose (9, 10). Unlike the previous studies, the present study included female subjects. However, after correction for body weight, CL\(_T\) was similar in males and females.

In this study, the \( EC_{50} \) for both cefotaxime and ofloxacin were highly correlated with MICs against the test organisms. This finding is expected, since the uSIT measurement is similar to a MIC test when the starting concentration of the serum ultrafiltrate sample is known (18, 26). The only difference is that the medium consists of as much as 50% serum ultrafiltrate, which contains only free drug. Serum ultrafiltrate was used in the present study to avoid the inhibitory effects of serum due to complement and other factors. In order to inactivate complement, serum may also be heated to 50°C for 0.5 to 2 h. This procedure was not feasible in our study, since cefotaxime is unstable under these temperature conditions. Although ultrafiltration removes most of the serum factors that affect these tests, some factors that enhance (17) or inhibit antimicrobial effects remain present.

Several factors contribute to the predictability of uSIT and AUIC. The mean log ratio of AUIC to predicted AUC/MIC was 1.03, showing excellent agreement. Cefotaxime exhibits protein binding ranging from 27 to 38% (22). This binding would tend to reduce the measured AUIC, since only free drug is active. In contrast, the active metabolite desacetylcefotaxime may contribute to the activity of cefotaxime (14), thereby increasing the AUIC. Ofloxacin has slightly higher protein binding, 47 to 50% (19), and this may account for the lower mean log ratio (0.899) of AUIC to predicted AUC/MIC. Ofloxacin does not have any active metabolites to offset the effect of protein binding. As expected, the mean log ratio of the combination was between the values found for ofloxacin and cefotaxime. The log ratio of 0.94 for the combination supports an additive antimicrobial interaction.

Areas under the bactericidal curve and AUICs have been previously used to compare different antimicrobial agents (1). This comparison is logical for fluoroquinolones, because the primary parameter that predicts efficacy is AUC/MIC (2, 7). AUC/MIC is theoretically similar to AUIC (25). For cefotaxime and other \( \beta \)-lactam agents, time above MIC is the primary parameter that predicts efficacy (2, 7).  

### Table 1. Mean PK parameters for ofloxacin and cefotaxime when administered alone and in combination

<table>
<thead>
<tr>
<th>Drug treatment</th>
<th>CL(_T) (liters/kg/h)</th>
<th>CL(_D) (liters/kg/h)</th>
<th>V(_p) (liters/kg)</th>
<th>V(_p) (liters/kg)</th>
<th>V(_\infty) (liters/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefotaxime monotherapy</td>
<td>0.236 (18.2)</td>
<td>0.265 (64.9)</td>
<td>0.089 (51.7)</td>
<td>0.118 (38.1)</td>
<td>0.207 (16.9)</td>
</tr>
<tr>
<td>Cefotaxime combination</td>
<td>0.231 (19.5)</td>
<td>0.265 (72.5)</td>
<td>0.099 (50.5)</td>
<td>0.110 (36.4)</td>
<td>0.208 (13.0)</td>
</tr>
<tr>
<td>Ofloxacin monotherapy</td>
<td>0.143 (14.7)</td>
<td>0.853 (57.3)</td>
<td>0.381 (42.8)</td>
<td>0.820 (24.9)</td>
<td>1.20 (24.9)</td>
</tr>
<tr>
<td>Ofloxacin combination</td>
<td>0.141 (16.3)</td>
<td>1.12 (46.0)</td>
<td>0.370 (41.9)</td>
<td>0.792 (15.3)</td>
<td>1.16 (6.65)</td>
</tr>
</tbody>
</table>

* Values in parentheses are CV\%s.

### Table 2. Median MICs and mean \( EC_{50} \) for the 10 test organisms

<table>
<thead>
<tr>
<th>Organism(^a)</th>
<th>Cefotaxime value</th>
<th>Ofloxacin value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC (\mu g/ml)</td>
<td>( EC_{50} ) (\mu g/ml)</td>
</tr>
<tr>
<td>\textit{S. aureus} (51)</td>
<td>2</td>
<td>2.14 (24.0)</td>
</tr>
<tr>
<td>\textit{S. aureus} (63)</td>
<td>2</td>
<td>3.62 (17.8)</td>
</tr>
<tr>
<td>\textit{S. pneumoniae} (82)</td>
<td>1</td>
<td>1.32 (26.7)</td>
</tr>
<tr>
<td>\textit{S. pneumoniae} (86)</td>
<td>2</td>
<td>1.29 (29.6)</td>
</tr>
<tr>
<td>\textit{E. cloacae} (142)</td>
<td>0.25</td>
<td>0.33 (35.4)</td>
</tr>
<tr>
<td>\textit{E. cloacae} (193)</td>
<td>0.5</td>
<td>0.88 (23.8)</td>
</tr>
<tr>
<td>\textit{K. pneumoniae} (208)</td>
<td>0.25</td>
<td>0.54 (28.7)</td>
</tr>
<tr>
<td>\textit{K. pneumoniae} (247)</td>
<td>0.25</td>
<td>0.20 (60.6)</td>
</tr>
<tr>
<td>\textit{P. aeruginosa} (46)</td>
<td>16</td>
<td>21.1 (42.6)</td>
</tr>
<tr>
<td>\textit{P. aeruginosa} (159)</td>
<td>16</td>
<td>18.0 (26.0)</td>
</tr>
</tbody>
</table>

* Values in parentheses are CV\%s.

\(^a\) Numbers in parenthesis following organisms are culture stock numbers.
primary PD parameter of interest (2, 3). Time above MIC evolved from in vitro studies and animal studies in which dosage intervals varied widely. However, if dosage intervals are designed rationally, and time above MIC is sufficient, the AUC/MIC or AUIC also becomes an important predictor of efficacy. In subsets of patients for whom time above MIC exceeds 80%, AUC/MIC still predicts efficacy (8).

In previous studies, 24-h AUC/MIC was shown to be predictive of antibacterial efficacy for ciprofloxacin in the treatment of nosocomial lower respiratory tract infections (7). The present study was primarily designed to study the type of PD interaction between ofloxacin and cefotaxime. The range of cefotaxime-ofloxacin concentration ratios was maximized by collecting blood samples over a 14-h period. usITs were collected during two dosing intervals, but the times selected were not sufficient to allow determination of AUIC for one full dosing interval. Consequently, the measured 24-h AUIC could not be determined. Table 3 provides the 14-h AUICs for the three drug regimens. These data can be used to compare relative activities, since cefotaxime and ofloxacin were administered with identical time schedules for the single and combination regimens.

Predicted 24-h AUC/MIC was calculated by the PK-PD parameter estimates and assuming an additive PD interaction. These data can be used to demonstrate the strengths and weaknesses of the single drugs and of the combination regimen. Based on retrospective analysis, an AUC/MIC of 125 to 250 was associated with good clinical and microbiologic outcomes of patients with suspected nosocomial pneumonia treated with ciprofloxacin (7). This AUC/MIC range corresponds to an average concentration of 5 to 10 times that of the MIC. Similar targets have not been established for cefotaxime and ofloxacin or for other infections in humans. Moreover, AUC/MIC breakpoints have not been evaluated for any combination antimicrobial regimen in a clinical trial.

Desacetylcefotaxime was not considered in our PD model. If this metabolite had contributed significantly to the activity of cefotaxime, a lower EC₅₀ estimate for cefotaxime monotherapy would be expected. In fact, there was excellent agreement between the EC₅₀s estimated from the model and the MIC of cefotaxime for each pathogen. Since desacetylcefotaxime did not appear to explain a substantial portion of the activity, we chose not to continue the analysis with a more complex model. A three-drug model would introduce additional problems that were not encountered with the two-drug model. We used predicted drug concentrations rather than

![Table 3](image)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Value for cefotaxime</th>
<th>Value for ofloxacin</th>
<th>Value for cefotaxime-ofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus (51)</td>
<td>118 (25.4)</td>
<td>77 (26.0)</td>
<td>186 (25.3)</td>
</tr>
<tr>
<td>S. aureus (63)</td>
<td>72 (23.6)</td>
<td>167 (38.3)</td>
<td>234 (21.4)</td>
</tr>
<tr>
<td>S. pneumoniae (82)</td>
<td>190 (27.9)</td>
<td>54 (172)</td>
<td>207 (40.6)</td>
</tr>
<tr>
<td>S. pneumoniae (86)</td>
<td>170 (29.4)</td>
<td>26 (19.2)</td>
<td>188 (34.6)</td>
</tr>
<tr>
<td>E. cloacae (142)</td>
<td>795 (43.5)</td>
<td>435 (34.7)</td>
<td>1,140 (42.6)</td>
</tr>
<tr>
<td>E. cloacae (193)</td>
<td>244 (23.4)</td>
<td>276 (28.3)</td>
<td>506 (29.4)</td>
</tr>
<tr>
<td>K. pneumoniae (208)</td>
<td>385 (40.3)</td>
<td>41 (22.0)</td>
<td>398 (22.1)</td>
</tr>
<tr>
<td>K. pneumoniae (247)</td>
<td>1,102 (51.1)</td>
<td>159 (47.8)</td>
<td>1,290 (35.6)</td>
</tr>
<tr>
<td>P. aeruginosa (46)</td>
<td>24 (20.8)</td>
<td>23 (34.8)</td>
<td>38 (34.2)</td>
</tr>
<tr>
<td>P. aeruginosa (159)</td>
<td>23 (17.4)</td>
<td>45 (24.4)</td>
<td>54 (18.5)</td>
</tr>
</tbody>
</table>

*a Values are inverse titer $\times$ time, with CV%$s$ given in parentheses.

*b Numbers in parenthesis following the organisms are culture stock numbers.

FIG. 2. Relationships between measured and predicted 14-h AUICs for cefotaxime (A), ofloxacin (B), and the combination of cefotaxime and ofloxacin (C). Solid lines, lines of identity; dashed lines, best-fit lines from log-transformed linear regression.
observed concentrations to smooth random errors. Desacetylcefotaxime cannot be modeled with the available data. The FIC index, on which our model was based, has not been used extensively for more than two drugs in combination, and such use would be complicated by any interaction between cefotaxime and desacetylcefotaxime. The same limitations would apply to any model that we would have chosen. Considering the problems that would result from a more-complex three-drug model and the lack of evidence supporting a contribution of desacetylcefotaxime to the overall activity, we used the simpler two-drug model.

In this study, the combination of ofloxacin and cefotaxime was found to exhibit additive antibacterial effects. Previous reports for patients and in vitro results have suggested that this was found to exhibit additive antibacterial effects. Previous studies have assessed as follows: FIC = [A]/MIC + [B]/MIC + [C]/MIC, where A is a 1:1 ratio of desacetylcefotaxime to cefotaxime. Our results show that this ratio occurs around 4 to 5 h following a cefotaxime dose.

At 4.5 h, the mean concentration of cefotaxime was only 2.12 μg/mL. Moreover, the ratios of desacetylcefotaxime to cefotaxime varied from 0.01 to 1.8 throughout the dosing interval. It is unclear how the addition of desacetylcefotaxime would affect the FIC determination. Traditionally, three drugs have been assessed as follows: FIC = [A]/MIC + [B]/MIC + [C]/MIC, rather than [A]/MIC + [D]/MIC, where D is a 1:1 combination of drugs B and C and concentrations are expressed in terms of drug B only.

In conclusion, the combination of cefotaxime and ofloxacin did not exhibit any PK interactions, and the PD interaction was additive. This combination exhibited excellent activity against representative isolates of S. aureus, S. pneumoniae, E. cloacae, and K. pneumoniae. In contrast, the activity of this combination against representative strains of P. aeruginosa was suboptimal, primarily because the two agents had minimal activity against the selected strains of P. aeruginosa.

REFERENCES


