Antimicrobial Susceptibility and Pharmacodynamic Comparison of Cefepime and Piperacillin-Tazobactam Against Enterobacteriaceae Producing Extended-Spectrum ß-Lactamase

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AMENDED ABSTRACT

Background: The frequency of resistance to ß-lactams among nosocomial isolates has been increasing due to ESBL-producing enteric bacilli. Although clinical outcome data are highly desirable, assessment of clinical efficacy has been limited due to the lack of a statistically meaningful number of well-documented cases. T>MIC is the PK/PD parameter that best correlates with in vivo activity of ß-lactams, therefore, a stochastic model was used to forecast the PK/PD target hit rates of piperacillin-tazobactam (P-T) and cefepime (PIM) against *E. coli* (EC) and *K pneumoniae* (KP) ESBL phenotypes (NCCLS criteria). **Methods:** Monte Carlo simulation was used to estimate the probability of P-T or PIM obtaining 40% to 70% (P70/40) T>MIC against EC and KP obtained from the SENTRY 2000 Program (N. America). MIC data were used to estimate the probability distribution function (PDF) of EC and KP. PDFs for PK vectors were estimated using mean parameters from subjects with CrCl between 60 and 91 mL/min. The model assumed a regimen of 3.375 g Q4 or 6 hr for P-T and a regimen of 1 or 2 g BID for PIM. A 5000-patient simulation was done for each drug-species combination. **Results:** ESBL phenotype rates were 3.4% among 1909 EC and 5.4% among 743 KP. The P70/40 T>MIC for PIM 2 g BID was 99.0/99.8% and 96.4/99.8% against EC and KP, respectively. The P70/40 T>MIC for PIM 1 g BID was 97.0/99.4% for EC and 92.0/96.6% for KP. For P-T 3.375 g Q4 hrs against EC and KP, the P70/40 T>MIC was 89.6/94.8% and 63.1/74.5%. For P-T 3.375 g Q6 hrs the P70/40 T>MIC was 76.8/91.4% and 46.7/63.1% against EC and KP. **Conclusions:** These data suggest that T>MIC target hit rates are greater for PIM than for P-T against current ESBL stains when contemporary dosing regimens, which minimize failure risk, are used for this IV ß-lactam.

INTRODUCTION

Increasing antimicrobial resistance among extended-spectrum ß-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae* is a growing concern.[1,2] Infection with ESBL-producing *E coli* or *K pneumoniae* has been associated with a significantly longer duration of hospital stay and greater hospital charges. Prior cumulative drug exposure (in terms of number of antimicrobial agents and total duration of treatment) has been demonstrated to be an independent predictor of ESBL-producing *E coli* or *K pneumoniae* infection.[3] Therefore, it is important, especially in the setting of empirical therapy, to identify agents with a relative high probability of *in vivo* efficacy against these pathogens.

Nonclinical (i.e., in vitro and animal) pharmacodynamic models of infection have been used to establish the conditions under which an anti-infective agent is effective.[4,5,6] By manipulating drug pharmacokinetics in these models, mean human serum concentration-time courses have been simulated for many agents. For penicillins and cephalosporins, experiments have shown that antibacterial effects best correlate with the duration of time that drug concentrations exceed the minimum-inhibitory concentration (MIC) of the micro-organism.[7,8]

For enteric Gram-negative bacilli such as *E coli* or *K pneumoniae*, ß-lactam antibacterial effects are observed when free-drug serum concentrations are above the MIC for as little as 35% of the dosing interval and are maximized when concentrations are above the MIC for 60% to 70% of the dosing interval.[9]

The assessment of clinical efficacy of agents used commonly in the critical care unit has been hampered due to the lack of a statistically meaningful number of well-documented cases with ESBL-producing *E coli* and *K pneumoniae*. Monte Carlo simulation is a method that may be used to estimate the probability of obtaining optimal pharmacodynamic targets by incorporating the variability in drug exposure observed in a population of patients and the range of contemporary MIC values encountered clinically into a stochastic model.[10-13] The purpose of this report is 2-fold: First, to compare the resistance rates and patterns of ESBL-producing *E coli* and *K pneumoniae* phenotypes obtained from the 2000 SENTRY Antimicrobial Surveillance Program for piperacillin-tazobactam and cefepime; and second, to estimate the probability of achieving 40% to 70% T>MIC for piperacillin-tazobactam and cefepime against these specified isolates.

MATERIALS AND METHODS

Microbiological data- The SENTRY Antimicrobial Surveillance Program was established in 1997 to monitor the prominent pathogens and antimicrobial resistance patterns of nosocomial and community-acquired infections via a broad network of sentinel hospitals selected according to geographic location and bed capacity. All *E coli* and *K pneumoniae* isolates recovered during 2000 in the North American region (United States and Canada) were analyzed for this study. These isolates were saved on transport swabs and sent to the University of Iowa College of Medicine (Iowa City, IA) for storage and further identification/susceptibility testing. On receipt by the monitor, isolates were subcultured on blood agar to ensure viability and purity. Species identifications were confirmed with the Vitek System (bioMérieux Vitek) or API (bioMérieux Vitek) products and standard reference methods.[14] Isolates were frozen at –70ºC until they were processed.

Antimicrobial susceptibility testing of isolates was performed by reference broth microdilution methods as described by the National Committee for Clinical Laboratory Standards (NCCLS).[15,16] Interpretive criteria were those published by the NCCLS. *K pneumoniae* and *E coli* isolates expressing an ESBL phenotype, as defined by a ceftazidime or ceftriaxone, or aztreonam MIC ≥ 2.0 mg/L, were further characterized with ESBL Etest (AB Biodisk, Solna, Sweden) strips containing antimicrobial gradients ranging from 0.016 to 256 mg/L, paired with strips containing the same cephalosporin gradient in the presence of 2 mg/L of clavulanic acid, or with commercial ESBL Etest strips that contain a stable gradient of ceftazidime (1-32 mg/L) on one half and ceftazidime plus clavulanic acid (2 mg/L) on the other half. An 8-fold or greater reduction in MIC with clavulanate acid in comparison with the MIC with the substrate oxyimino cephalosporin alone was considered evidence of a positive ESBL test.[17]

Pharmacokinetic data- Serum pharmacokinetic data following intravenous (IV) dosing of piperacillin-tazobactam and cefepime were obtained from the medical literature.[18,19] In these studies, 3.375 g piperacillin-tazobactam (3.0 and 0.375 g, respectively) and cefepime 1 g were administered over a 30-minute period in patients with estimated creatinine clearances of 60 to 91 mL/min.

For piperacillin-tazobactam, the elimination $T_{1/2}$ was 1.1 ± 0.23 hours and the peak serum concentration was 228 ± 25 mg/L. Plasma clearance was 159 ± 19 mL/min. Renal clearance accounted for 48.4 ± 5.8% of drug removal. The average volume of distribution at steady state was 13.0 ± 1.4 L. For cefepime, the elimination $T_{1/2}$ was 3.33 ± 0.74 hours and the peak serum concentration was 70.5 ± 20.8 mg/L. Total body clearance was 75.5 ± 12.9 mL/min. Renal clearance accounted for 80.3 ± 10.6% of drug removal. The average volume of distribution at steady state was 19.6 ± 2.99 L.

Complete details of the pharmacokinetic modeling methods and results are available from the aforementioned sources. The fraction of unbound drug for piperacillin-tazobactam and cefepime assumed in these analyses were 70% and 84% respectively.

Pharmacodynamic model- Pharmacodynamic analyses were made using Monte Carlo simulation. A 5000-patient population simulation was performed with Crystal Ball 2000.1 (Decisionerring, Inc. Denver, Colorado) using the aforementioned pharmacokinetic data in conjunction with the following pharmacokinetic model:

$$\text{T>MIC (hours)} = \frac{\text{Ln Dose}/(V_{SS}/\text{fu})\text{-Ln MIC}}{0.693/\ T_{1/2}} \qquad (1)$$

where V_{SS} is the volume of distribution at steady-state, $T_{1/2}$ is the serum elimination half-life, and fu is the fraction of unbound drug. The random number generator routine (multiplicative congruential generator) used the following iterative formula:

$$r \leftarrow (630{,}360{,}016 \cdot r) \bmod (2^{31} - 1) \qquad (2)$$

The generator has a period length of 2,147,483,646, meaning that the cycle of random numbers repeats after approximately 2.15 billion trials.

For piperacillin-tazobactam, a dosage regimen of 3.375 g IV every 4 or 6 hours was modeled. For cefepime, a dosage regimen of 1 or 2 g IV every 12 hours was modeled. The probability of obtaining T>MIC equal to 40%, 50%, 60%, and 70% of the dosing interval was estimated for each dosage regimen and microorganism.

RESULTS

Microbiological- During the SENTRY study period (2000), 1909 *E coli* and 743 *K pneumoniae* blood stream isolates were tested. Of these, 65 (3.4%) *E coli* and 40 (5.4%) *K pneumoniae* were ESBL phenotypes (i.e., ceftazidime and/or ceftriaxone and/or aztreonam MIC ≥ 2 mg/L).

The activity of piperacillin-tazobactam for the 105 ESBL phenotype strains is shown in Table 1. Piperacillin-tazobactam was significantly more active against *E coli* isolates (MIC_{50}, 4 mg/L) compared with *K pneumoniae* strains (MIC_{50}, 16 mg/L). Also at the NCCLS breakpoint for susceptibility (≤16 mg/mL), 89.1% and 62.5% of *E coli* and *K pneumoniae* strains were inhibited, respectively. For cefepime (Table 2), the ESBL phenotypes were 16-fold more susceptible to cefepime than to piperacillin-tazobactam, using MIC_{50} values as a comparison value. This greater potency for cefepime indicated that 92.5% to 98.5% of strains were inhibited at ≤8 mg/mL, which is the NCCLS breakpoint for cefepime when testing Enterobacteriaceae.

Pharmacodynamic- Piperacillin-tazobactam and cefepime pharmacodynamic target attainment rates, stratified by micro-organism and dosage regimen, are presented in Table 3. For the piperacillin-tazobactam regimen of 3.375 g IV every 4 hours,target attainment rates against ESBL-producing *E coli* phenotypes approached or exceeded 90% regardless of pharmacodynamic target. For the piperacillin-tazobactam regimen of 3.375 g IV every 6 hours,target attainment rates were somewhat less, ranging between 76.8% and 91.4%.

Similarly, against ESBL-producing *K pneumoniae* phenotypes, the target attainment rate for piperacillin-tazobactam 3.375 g IV every 4 hours ranged from 63.1% to 74.5%, depending on the pharmacodynamic target. As would be expected, target attainment rates were less for 3.375 g IV dosed every 6 hours. For instance, if the pharmacodynamic target was T>MIC of ≥ 70% of the dosing interval, the attainment rate was less than 50%.

In general, PK/PD targets were more likely to be achieved by cefepime than piperacillin-tazobactam regardless of the dosing regimen modeled, PK/PD target, or microorganism considered. One exception was against *E coli* ESBL-producing phenotypes when piperacillin-tazobactam was dosed every 4 hours. In this instance, PK/PD target attainment rates for both agents were approximately 90% or greater. Cefepime achieved desired PK/PD targets at a >90% probability regardless of dosing regimen modeled, PK/PD target selected, or micro-organism considered.

Table 1. *In vitro* activity of piperacillin-tazobactam tested against 105 ESBL phenotype (NCCLS criteria) strains of *E coli* and *K pneumoniae* (SENTRY Antimicrobial Surveillance Program, 2000).

Organism	Cumulative Percent Inhibited at MIC (mg/mL) of :								
	< 0.5	1	2	4	8	16	32	64	Susceptible[a]
E coli (65)	3.1	6.3	26.6	62.5	81.3	89.1	89.1	92.2	89.1
K pneumoniae (40)	0.0	2.5	12.5	35.0	47.5	62.5	72.5	80.0	62.5

[a]Susceptibility criteria of the NCCLS [15,16]

Table 2. *In vitro* activity of cefepime tested against 105 ESBL phenotype (NCCLS criteria) strains of *E coli* and *K pneumoniae* (SENTRY Antimicrobial Surveillance Program, 2000).

Organism	Cumulative Percent Inhibited at MIC (mg/mL) of :								
	<0.12	0.25	0.5	1	2	4	8	16	Susceptible[a]
E coli (65)	49.2	63.1	78.5	84.6	89.2	93.8	98.5	100	98.5
K pneumoniae (40)	7.5	12.5	37.5	62.5	82.5	92.5	92.5	95.0	92.5

[a]Susceptibility criteria of the NCCLS [15,16]

Table 3. Probability of attaining T>MIC targets following standard dosage regimens of piperacillin-tazobactam and cefepime against *E coli* and *K pneumoniae* ESBL-producing phenotypes

Organism	Drug/Regimen	Pharmacodynamic Target[a] 40%	50%	60%	70%
E coli	Piperacillin-tazobactam 3.375 g every 4 hours	94.8	92.7	91.4	89.6
	Piperacillin-tazobactam 3.375 g every 6 hours	91.4	88.5	83.7	76.8
	Cefepime 2 g every 12 hours	99.8	99.8	99.6	99.0
	Cefepime 1 g every 12 hours	99.4	98.8	98.0	97.0
K pneumoniae	Piperacillin-tazobactam 3.375 g every 4 hours	74.5	71.3	67.3	63.1
	Piperacillin-tazobactam 3.375 g every 6 hours	63.1	60.2	53.7	46.7
	Cefepime 2 g every 12 hour	99.8	99.4	98.0	96.4
	Cefepime 1 g every 12 hour	96.6	95.1	93.6	92.0

[a]Percentage of the dosing interval that serum concentrations remain above the MIC

CONCLUSIONS

- *In vitro* susceptibility results show that cefepime is 16 times more potent than piperacillin-tazobactam against ESBL-producing *E coli* and *K pneumoniae* bloodstream isolates
- PK/PD targets associated with favorable clinical outcomes against ESBL-producing *E coli* and *K pneumoniae* isolates were more likely to be achieved with cefepime than with piperacillin-tazobactam, regardless of dosing regimen, PK/PD target, or micro-organism
- PK/PD targets were more likely to be achieved with piperacillin-tazobactam by dosing every 4 hours compared with dosing every 6 hours

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