1553
ECCMID 2006
JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370,
fax 319.665.3371
ronald-jones@jmilabs.com

Re-evaluation of the Role of Broad-Spectrum Cephalosporins against Staphylococci Applying Contemporary In Vitro Results and Pharmacokinetic-Pharmacodynamic (PK-PD) Principles

H SADER, SM BHAVNANI, PG AMBROSE, RN JONES
JMI Laboratories, North Liberty, IA; ICPD/Ordway Research Institute, Albany, NY

SENTRY ANTIMICROBIAL SURVEILLANCE

AMENDED ABSTRACT

Objectives: To re-evaluate the current in vitro activity and to assess the PK-PD target attainment of cefepime (CPM), ceftriaxone (CRO) and ceftazidime (CAZ) against *Staphylococcus* spp.

Methods: The potency of CPM, CRO and CAZ against staphylococci was accessed through the SENTRY Antimicrobial Surveillance Program database, worldwide. During the 1998-2004 period 41,664 *S. aureus* (SA; 63% oxacillin [OXA]-susceptible [S]) and 14,299 coagulase-negative staphylococci (CoNS; 22% OXA-S) were tested for susceptibility against CPM, CRO, CAZ and numerous comparators by CLSI broth microdilution methods. Using volunteer PK data and a linear intermittent intravenous infusion model, and an animal-derived PK-PD target of 30% time above MIC, expected probabilities of target attainment (PTA) for cephems were evaluated using Monte Carlo simulation. PTA were determined for the following dosing regimens: CPM 1gm q12 and q8 hours, CAZ 1 gm q8 hours and CRO 1 gm q24 hours, each representing the most common dosing patterns applied clinically. Cephem susceptibility (%S) was calculated based on the current CLSI (2006) breakpoints (BKPs) and also on BKPs derived from a PTA > 90%.

Results: Against OXA-S SA, $MIC_{50/90}$ values were (in mg/L): 2 / 4 for CPM, 4 / 4 for CRO and 8 / 16 for CAZ, respectively; and against OXA-S CoNS $MIC_{50/90}$ values were (in mg/L) 0.5 / 2 for CPM, 2 / 4 for CRO, and 4 / 8 for CAZ, respectively. The calculated %S of these cephems are summarized in the Table:

	% susceptible						
	CLSI BKPs (mg/L)			BKPs (mg/L) based on PK-PD PTA [regimen]			
Organism (no. tested)	CPM (≤8)	CRO (≤8)	CAZ (≤8)	CPM (≤8) [1gm q12]	CPM (≤16) [1gm q8]	CRO (≤2) [1gm q24]	CAZ (≤16) [1gm q8]
OXA-S SA (26,339)	100.0	99.7	89.4	100.0	100.0	33.9	99.6
OXA-S CoNS (3,166)	100.0	99.4	95.3	100.0	100.0	77.3	99.5

Twenty year-old CLSI BKPs would rank the tested agents CPM ≥ CRO > CAZ and by PK-PD PTA CPM ≥ CAZ > CRO. CPM has a potency advantage over CAZ (4- to 8-fold) and superiority at the usual dosing over CRO (22.7 – 66.1%) for OXA-S staphylococci. CAZ PK overcomes by-weight activity disadvantages, while a low proportion (<5%) of active free-drug penalizes CRO in the PTA calculations. PTA remained at >90% to a BKP of 16 mg/L for CPM (1 gm q8) and CAZ and to a BKP of 2 mg/L for CRO.

Conclusions: Regardless of applied BKP (CLSI or PK-PD), CPM has the widest and more potent anti-staphylococcal activity among commonly used "third- or fourth-generation" cephems. When used at doses ≥ 3 gm/day, CPM assures maximal coverage of OXA-S staphylococci whether using existing (CLSI) or modified (PK/PD) BKPs. CRO should be used with caution.

INTRODUCTION

Non-clinical pharmacokinetic-pharmacodynamic (PK-PD) models of infection (i.e., in vitro and animal) have been used to establish the conditions under which an anti-infective agent is efficacious and to assess the activity of such an agent when human serum concentration time profiles are simulated. For cephalosporins and other ß-lactam agents, experiments have shown that antibacterial effects best correlate with the duration of time (T) within a given dosing interval that free-drug concentrations exceed the MIC of the microorganism (T > MIC). For staphylococci, antibacterial effects were observed for cephalosporins when free-drug concentrations in serum were above the MIC for ~30% of the dosing interval.

In the present study, we employ the global SENTRY Antimicrobial Surveillance Program MIC database for the years 1998-2004 to assess the potency of the cephems cefepime, ceftriaxone, and ceftazidime against staphylococci. In addition, we use volunteer PK data, a linear intermittent intravenous infusion model, a PK-PD target of ≥ 30% time above MIC and Monte Carlo simulation to compare probabilities of target attainment (PTA) for the three cephems and different dosing regimens.

MATERIALS AND METHODS

Microbiological data. Susceptibility data for *S. aureus* and CoNS isolates recovered during the period 1998-2004 (SENTRY Program) in the Asia-Pacific (17 sites), European (24 sites), Latin American (10 sites) and North American (38 sites) regions were included in this analysis. Antimicrobial susceptibility testing was performed using reference broth microdilution methods as described by the Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS). Sensititre microdilution trays were obtained from TREK Diagnostics (Cleveland, Ohio, USA). Each strain was tested against more than 30 antimicrobial agents; only results for cefepime, ceftriaxone and ceftazidime are reported here. Interpretation of quantitative MIC results was in accordance with CLSI methods and criteria (2006).

Pharmacokinetic (PK) data. Serum PK parameters estimates for intravenous (IV) dosing of cefepime, ceftriaxone, and ceftazidime were obtained from the medical literature. The fraction of unbound drug for cefepime, ceftazidime and ceftriaxone was 84%, 84% and 7%, respectively.

PK-PD target attainment analysis. PK-PD target attainment analyses were carried out by using a linear intermittent intravenous infusion model and Monte Carlo simulation. Dosing regimen modeled included cefepime (1 gm IV administered every 8 hours and every 12 hours), ceftazidime (1 gm IV administered every 8 hours) and ceftriaxone (1 gm IV administered every 24 hours). Ten thousand patient simulations were carried out in order to estimate the probability of attaining free drug T > MIC targets of ≥ 30% of the dosing interval by fixed MIC values ranging from 0.12 - 32 mg/L for each drug regimen.

RESULTS

- A total of 41,644 isolates of *S. aureus* and 14,299 isolates of CoNS were tested as part of the SENTRY Program during the period from 1998 through 2004. These included 26,339 OSSA (63.2% of total) and 3,166 OS-CoNS (22.2% of total) (Table 1).

Table 1. Comparative antimicrobial activity of cephalosporins tested against 29,505 strains of oxacillin-susceptible staphylococci isolated in the SENTRY Program participating centers, 1998-2004.

		MIC (mg/L)		% by category[a]	
Organism (no. tested)	Cephalosporin	50%	90%	S	R
Staphylococcus aureus (26,339)					
	Cefepime	2	4	100.0	0.0
	Ceftriaxone	4	4	99.7	0.0
	Ceftazidime	8	16	89.4	0.4
coagulase-negative staphylococci (3,166)					
	Cefepime	0.5	2	100.0	0.0
	Ceftriaxone	2	4	99.4	0.0
	Ceftazidime	4	8	95.3	0.5

a. Categories defined by CLSI (2006): S, susceptible (≤ 8 mg/L for all three agents); R, resistant (≥ 32 mg/L for cefepime and ceftazidime, ≥ 64 mg/L for ceftriaxone).

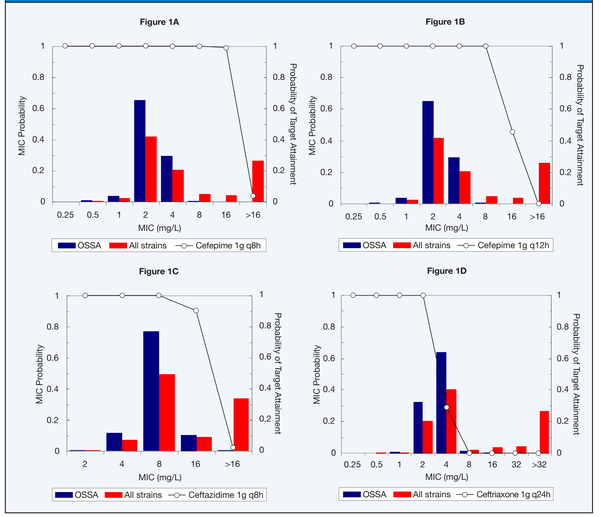
Table 2. Comparison of the in vitro susceptibilities of oxacillin-susceptible staphylococci to three cephalosporins using CLSI breakpoints and breakpoints derived from a probability of target attainment (PTA) of ≥ 90%.

	% Susceptible at MIC breakpoint					
	CLSI (mg/L)			PK-PD PTA (mg/L)[a]		
Organism (no. tested)	Cefepime (≤8)	Ceftriaxone (≤8)	Ceftazidime (≤8)	Cefepime (≤8/≤16)[b]	Ceftriaxone (≤2)[c]	Ceftazidime (≤16)[d]
Staphylococcus aureus (26,339)	100.0	99.7	89.4	100.0/100.0	33.9	99.6
coagulase-negative staphylococci (3,166)	100.0	99.4	95.3	100.0/100.0	77.3	99.5

a. Breakpoints derived from a probability of target attainment (PTA) ≥ 90% (see Figures 1 and 2).
b. Breakpoints for cefepime dosing regimen of 1 gm IV every 8 hours (≤ 16 mg/L) or every 12 hours (≤ 8 mg/L).
c. Breakpoint for ceftriaxone dosing regimen of 1 gm IV every 24 hours (≤ 2 mg/L).
d. Breakpoint for ceftazidime dosing regiment of 1 gm every 8 hours (≤ 16 mg/L).

- Cefepime (100.0% S) and ceftriaxone (99.7% S) showed excellent activity against OSSA. Ceftazidime was four-fold less active against OSSA (MIC_{90}, 16 mg/L; 89.4% S) than either cefepime (MIC_{90}, 4 mg/L) or ceftriaxone (MIC_{90}, 4 mg/L). All three cephems exhibited consistently acceptable activity (100.0, 99.4 and 95.3%, respectively) against OS-CoNS (Table 1; CLSI breakpoints).
- For the regimen of 1 gm of cefepime IV every 8 or 12 hours the PTA exceeded 90% for strains of *S. aureus* for which MIC values were ≤ 16 mg/L and ≤ 8 mg/L, respectively (Figures 1a and b). Likewise, for ceftazidime 1 gm IV every 8 hours, the PTA was ≥ 90% for strains for which MIC results were ≤ 16 mg/L (Figure 1c) and for ceftriaxone 1 gm IV every 24 hours, the PTA was ≥ 90% for strains for which MIC values were only ≤ 2 mg/L (Figure 1d). The data for CoNS were similar to that seen with *S. aureus* (Table 2).
- When one recalculates the susceptibility of the OSSA in the SENTRY Program database to the three cephems using the data shown in Figures 1 and the assumption that a suitable MIC susceptibility breakpoint should provide at least a 90% probability of attaining the target PK-PD parameter (i.e. free-drug T > MIC of ≥ 30% with correspondent breakpoints of ≤ 8-16 mg/L for cefepime and ceftazidime and to ≤ 2 mg/L for ceftriaxone), the resulting susceptibility rank-order is cefepime (100.0%S) > ceftazidime (99.5-99.6%S) > ceftriaxone (33.9-77.3%S; Table 2).
- Among the three agents studied, two (cefepime and ceftazidime) exhibit a low degree of protein binding (~16), whereas ceftriaxone is well known to exhibit a very high-level of protein binding (~93%). When examined using Monte Carlo simulation, the probabilities of attaining a PK-PD target of free drug time > MIC of ≥ 30% were significantly lower for ceftriaxone compared to both cefepime and ceftazidime (Figures 1).

Figure 1. Probability of PK-PD target attainment for three cephalosporins versus *S. aureus*. Figure 1A, cefepime at 1 gm IV every 8 hours; Figure 1B, cefepime at 1 gm every 12 hours; Figure 1C, ceftazidime at 1 gm IV every 8 hours; Figure 1D, ceftriaxone at 1 gm IV every 24 hours. A total of 41,644 *S. aureus* strains (26,339 oxacillin-susceptible) were included in the analysis.



CONCLUSIONS

- The data presented herein confirms the four- to eight-fold anti-staphylococcal potency advantage of cefepime over ceftazidime. Furthermore, cefepime is shown to have a clear superiority (22.7-66.1% greater susceptibility) at usual dosing over ceftriaxone for OS-staphylococci.
- Based on the results of the present study, a breakpoint requirement of PTA ≥ 90% suggests that staphylococcal breakpoints for cefepime and ceftazidime should remain unchanged or be increased from ≤ 8 mg/L to ≤ 16 mg/L and that for ceftriaxone be decreased to ≤ 2 mg/L.
- When PK-PD target attainment information is used to reassess MIC breakpoints, the CLSI breakpoints vastly overestimate the potentially useful activity of ceftriaxone, especially with a resistant breakpoint at ≥ 64 mg/L.
- The results of the present study emphasize the importance taking into account the differences in protein binding and PK among these three agents when assessing their comparative efficacy in the treatment of staphylococcal infections.
- Regardless of the applied breakpoints (CLSI or PK-PD), cefepime has the broadest and most potent anti-staphylococcal activity among the commonly used "third- or fourth-generation" cephems.

SELECTED REFERENCES

Ambrose PG, Bhavnani SM, Jones RN (2003). Pharmacokinetics-pharmacodynamics of cefepime and piperacillin-tazobactam against *Escherichia coli* and *Klebsiella pneumoniae* strains producing extended-spectrum beta-lactamases: Report from the ARREST program. *Antimicrob Agents Chemother* 47: 1643-1646.

Clinical and Laboratory Standards Institute. (2006). *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 7th ed. Approved Standard M7-A7*. Wayne, PA: CLSI, 2006.

Craig WA (1995). Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins. *Diagn Microbiol Infect Dis* 22: 89-96.

Dudley MN, Ambrose PG. (2000) Pharmacodynamics in the study of drug resistance and setting of in vitro susceptibility breakpoints: Ready for prime time. *Curr Opin Microbiol* 3:515-521.

Sader HS, Fritsche TR, Jones RN (2005). Potency and spectrum trends for cefepime tested against 65,746 clinical bacterial isolates collected in North American medical centers: Results from the SENTRY Antimicrobial Surveillance Program (1998-2003). *Diagn Microbiol Infect Dis* 52: 265-273.