Pharmacokinetic-Pharmacodynamic Basis for CLSI Carbapenem Susceptibility Breakpoint Changes

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ABSTRACT

Background: Emerging Enterobacteriaceae (ENT) resistance to carbapenem (CARBs) has called for a change in treatment paradigms and review of CLSI CARB interpretive criteria. Current CLSI breakpoints for ertapenem, imipenem, and meropenem against ENT are 2, 4, and 4 µg/mL, respectively. CLSI susceptible interpretive criteria decisions can be supported using pharmacokinetic-pharmacodynamic (PK-PD) models to predict *in vivo* efficacy.

Methods: Monte Carlo simulation (MCS) was conducted to determine PK-PD target attainment (TA) probabilities by MIC for labeled CARB dosing regimens. For each CARB, MCS (n=5,000 simulated patients) inputs included: 1) parameter estimates from published population PK models using healthy subject data, 2) protein binding point estimates from product labels, 3) murine infection model-derived PK-PD targets, and 4) contemporary ENT MIC distributions. Sensitivity analyses were conducted by inflating the between-subject variability in population PK parameter estimates to approximate variances expected for infected patient populations (%CV ≥ 40%).

Results: PK-PD breakpoints based on actual and inflated variance are shown (table).

Conclusions: PK-PD TA analysis results suggest that CARB interpretive criteria for ENT (M100-S19) may be at least 1 to 2 doubling dilutions too high. The probabilities of standard dosing regimens resulting in exposures consistent with efficacy in pre-clinical infection models do not appear sufficient using the current breakpoints. These data provided decision-support for CLSI CARB interpretive criteria changes scheduled for publication in 2010.

Agent	Dosing regimen	PK-PD breakpoint based on Monte Carlo simulations with actual/inflated variance[1]		
		f %T>MIC ≥ 35	*f* %T>MIC ≥ 40	*f* %T>MIC ≥ 45
Ertapenem	1000 mg Q24h	0.25/0.25	0.25/0.125	0.125/0.06
Doripenem	500 mg Q8h	2/1	1/0.5	1/0.5
Meropenem	500 mg Q8h	1/0.5	0.5/0.25	0.25/0.125
	1000 mg Q8h	2/1	1/0.5	0.5/0.25
Imipenem	500 mg Q6h	1/1	1/1	1/0.5
	1000 mg Q8h	2/2	1/1	0.5/0.5

1. MIC breakpoint associated with achieving ≥ 90% probability of PK-PD target attainment based on achieving free-drug % time > MIC (*f* % T > MIC) ≥ 35, ≥ 40 and ≥ 45 in the circumstance of actual and inflated between-subject variance in population PK parameter estimates.

INTRODUCTION

- The Food and Drug Administration (FDA) and other organizations including the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are systematically re-evaluating susceptibility breakpoints for many classes of antibacterial agents.
- This re-evaluation is necessary since many of the current susceptibility breakpoints were established using old technologies and/or without pathogen-specific data supporting such decisions.
- Emerging *Enterobacteriaceae* (ENT) resistance to carbapenem (CARB) agents has necessitated a change in treatment paradigms and review of CLSI CARB interpretive criteria. At the time these analyses were conducted, CLSI susceptible breakpoints for ertapenem, imipenem, and meropenem against ENT were 2, 4, and 4 µg/mL, respectively.
- The analyses described herein were conducted in support of changes to current CLSI CARB susceptibility breakpoints.

OBJECTIVES

- In support of the evaluation of susceptibility breakpoints for CARBs against ENT, pharmacokinetic-pharmacodynamic (PK-PD) target attainment analyses and accuracy of detecting resistant organisms with defined carbapenemases were determined.

METHODS

PK-PD Target Attainment Analyses

- Using Monte Carlo simulation, the probability of achieving free-drug % time above minimum inhibitory concentration (MIC) values (*f* % T>MIC) associated with efficacy was assessed by MIC value for various *f* % T>MIC targets and labeled CARBs dosing regimens. These labeled dosing regimens included the following eratapenem 1000 mg administered once daily, doripenem 500 mg administered three times daily (Q8h), meropenem 500 mg Q8h, and meropenem 1000 mg Q8h.
- Monte Carlo simulation (n=5,000 simulated patients) inputs included the following:
  - Parameter estimates were obtained from published population pharmacokinetic (PK) models using healthy subject data doripenem [1]; ertapenem [2], imipenem [3] and meropenem [4].
  - Point estimates of protein binding for each agent (8.1, 95, 20, and 2% for doripenem, ertapenem, imipenem, and meropenem, respectively) were obtained from the product package inserts.
  - Murine infection model-derived PK-PD targets
    - *f* % T>MIC values for CARBs against Gram-negative organisms associated with net bacterial stasis have been shown to range from 25-35% with that for 1-2 $\log_{10}$ colony forming unit (CFU) reductions being associated with 35-45% [1]. Given this data, the probability of PK-PD target attainment for *f* % T>MIC values of 30 to 45% were examined.
- The probability of PK-PD target attainment for each CARB dosing regimen evaluated was assessed for the MIC range of 0.015 to 16 µg/mL. Probabilities of PK-PD target attainment were assessed relative to contemporary (2007-2009) MIC distributions for CARBs for ENT species (SENTRY Antimicrobial Surveillance Program, JMI Laboratories, North Liberty, IA).

Sensitivity Analyses

- In addition to conducting the simulations using the actual reported between normal subject variability (BSV) in population PK parameters, sensitivity analyses were conducted by inflating the BSV in population PK parameter estimates to approximate that expected in patient populations.
  - BSV in PK was inflated to 40 % CV in the cases in which the actual BSV was lower.
  - For those PK parameters for which BSV was already higher than 40 % CV in healthy volunteers, it was left unchanged.
  - The above-described Monte Carlo simulations described were carried out using both the actual reported and inflated BSV in population PK parameters.

Categorical Breakpoints to Detect Carbapenemase-Producing *Enterobacteriaceae*

- 474 ENT isolates were tested in duplicate, 328 of which were *Klebsiella pneumoniae* carbapenemase (KPC) or metalo-β-lactamase (MβL) producers. All isolates were tested by CLSI M07-A8 and M02-A9 (2009 methods).
- Populations of MIC results were analyzed for accuracy in capturing KPC or MβL strains in the non-susceptible categories (intermediate and resistant).

RESULTS

- **Table 1** provides a summary of the population PK parameter estimates and associated BSV obtained from the literature [2-5]. For agents where the published models did not include a variance covariance matrix (ertapenem and imipenem), population means and BSV (%CV) are reported. For agents where the published models included a full or partial variance covariance matrix (meropenem and doripenem, respectively), the population means and the variance covariance matrices are reported.
- **Figures 1** to **4** show the probability of PK-PD target attainment by MIC value for doripenem, ertapenem, imipenem, and meropenem based on the actual or inflated variance overlaid on MIC distributions for USA ENT isolates (SENTRY Antimicrobial Surveillance Program, 2007-2009).

Table 1. Summary of population PK parameters utilized[a]

Parameter (unit)	Population mean (between subject variability expressed as %CV)			
	Doripenem (n=24)	Ertapenem (n=10[b])	Imipenem (n=18)	Meropenem (n=16)
CL (L/h)	14.5 (13.2%)	1.61 (14%)	11.82 (13.3%)	16.3 (18.9%)
Vc (L)	9.43 (14.4%)	5.15 (55%)	7.37 (21.8%)	12.4 (28.3%)
Vp (L)	5.88 (10.4%)	0.52 (30%)	8.0 (30.5%)	1.21 (148%)
Clic (L/h)	9.69 (-)	0.96 (37%)	5.06 (46.3%)	4.03 (203%)

CL: elimination clearance; Vc: Volume of distribution of central compartment; Vp: Volume of distribution of peripheral compartment; and Clic: Intercompartmental distribution clearance;
a. Based on references 2-5. b. Population PK parameters are based on the normal weight group.

RESULTS

Figure 1. Probability of PK-PD target attainment by MIC value for doripenem based on actual (A) and inflated (B) variance and overlaid on MIC distributions for USA ENT isolates

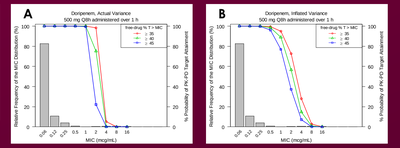


Figure 2. Probability of PK-PD target attainment by MIC value for ertapenem based on actual (A) and inflated (B) variance and overlaid on MIC distributions for USA ENT isolates

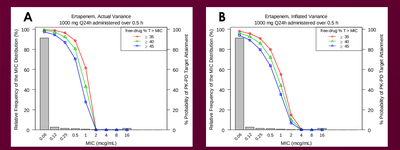


Figure 3. Probability of PK-PD target attainment by MIC value for imipenem based on actual (A and C) and inflated (B and D) variance and overlaid on MIC distributions for USA ENT isolates

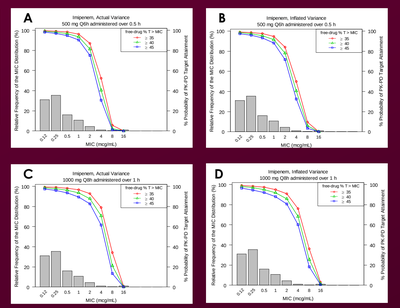
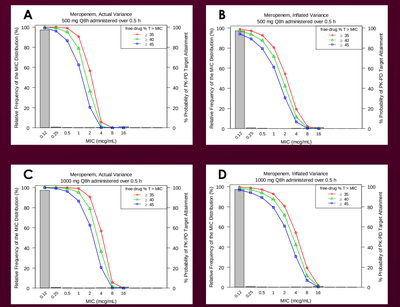


Figure 4. Probability of PK-PD target attainment by MIC value for meropenem based on actual (A and C) and inflated (B and D) variance and overlaid on MIC distributions for USA ENT isolates



RESULTS

- **Table 2** provides a summary of the PK-PD breakpoints based on actual and inflated variance utilized for the Monte Carlo simulations. PK-PD breakpoints based on inflated variance were the same or varied by one doubling dilution in MIC.
- **Table 3** summarizes the probability of PK-PD target attainment (using inflated PK parameter variances) and the detection of KPC-producing ENT with the new breakpoints. The new breakpoints provide good sensitivity for detecting KPC-producing isolates.

Table 2. Summary of PK-PD breakpoints based on actual and inflated variance

Agent	Dosing regimen	PK-PD breakpoint based on Monte Carlo simulations with actual/inflated variance[a, b]		
		f %T>MIC ≥ 35	*f* %T>MIC ≥ 40	*f* %T>MIC ≥ 45
Doripenem	500 mg Q8h	**2/1**	1/0.5	1/0.5
Ertapenem	1000 mg Q24h	**0.25/0.25**	**0.25**/0.12	0.12/0.06
Meropenem	500 mg Q8h	1/0.5	0.5/0.25	0.25/0.12
	1000 mg Q8h	**2/1**	1/0.5	0.5/0.25
Imipenem	500 mg Q6h	**1/1**	1/1	1/0.5
	1000 mg Q8h	**2/2**	1/1	0.5/0.5

a. MIC breakpoint associated with achieving ≥90% probability of PK-PD target attainment based on achieving *f*%T>MIC ≥35, ≥40, and ≥45 in the circumstance of actual and inflated between-subject variance in population PK parameter estimates.
b. The blue bolded PK-PD breakpoints represent the new CLSI susceptible breakpoints for CARBs against ENT; the red bolded PK-PD breakpoints represent the new intermediate breakpoints.

Table 3. Probability of PK-PD target attainment (*f* % T > MIC ≥ 35%) and capture of KPC-producing *Enterobactericeae* according to new CLSI breakpoints for carbepenems

Drug	New CLSI susceptibility breakpoints (µg/mL)			Comments
	Susceptible	Intermediate	Resistant	
Meropenem	**≤1**	**2**	**≥4**	**Previous BPs: ≤4/8/≥16**
KPC capture (%)	1.2	15	84	Data source = a
PK-PD target attainment % probability	**93**	81	54	1000 mg Q8h
Imipenem	**≤1**	**2**	**≥4**	**Previous BPs: ≤4/8/≥16**
KPC capture (%)	0	14	86	Data source = a
PK-PD target attainment % probability	**95/95**	84/**91**	50/76	500 mg Q6h/1000 mg Q8h
Ertapenem	**≤0.25**	**0.5**	**≥1**	**Previous BPs: ≤2/4/≥8**
KPC capture (%)	0	0.3	99.7	Data source = a
PK-PD target attainment % probability	**91**	80	55	1000 mg Q24h
Doripenem	**≤1**	**2**	**≥4**	**Previous BPs: None**
KPC capture (%)	0	2.2	97.8	Data source = b
PK-PD target attainment % probability	**95**	73	28	500 mg Q8h

a. Data from Jones, et al. (SENTRY Program). CLSI published agenda contents, Jones. 2008. b. Data from Johnson and Johnson presentation. CLSI published agenda contents. January 2010.
BPs = Breakpoints

DISCUSSION/CONCLUSIONS

- PK-PD analysis based on FDA-approved and standard dosing regimens of CARBs and animals models of infection show that previous susceptibility breakpoints for ENT of 4 µg/mL for imipenem and meropenem, and 2 µg/mL for ertapenem do not provide optimal PK-PD exposures, and that lower values should be considered.
- Simulation results based on PK data from healthy subjects and inflated variance were consistent with separate simulations for doripenem and meropenem patient population PK analysis [data not shown], indicating the appropriateness of utilizing inflated PK parameter variances derived from healthy subjects.
- Studies with a panel of confirmed KPC-producing strains ENT show that the new breakpoints would classify over 98% of strains as intermediate or resistant to CARBs.
- While providing improved sensitivity for detecting KPC carbapenemase-producing strains and PK-PD exposures in target ranges, the new CARB breakpoints do not result in major shifts in the susceptibility of the entire population ENT.
- These data provided the decision-support for CLSI CARB interpretive criteria changes published in June 2010.

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