Antimicrobial Activity of PZ-601 (SMP-601) Tested Against Selected Wildtype and Resistant Collections of Targeted Species (USA and Europe)

Abstract E-268

Ronald N Jones, Jennifer M. Streit, Douglas J Biedenbach, Thomas R Fritsche, Helio S Sader; JMI Laboratories, North Liberty, IA, USA

Contact information:
Ronald N. Jones, MD
JMI Laboratories

319-665-3370 phone
319-665-3371 fax
ronald-jones@uiowa.edu

Abstract

Background: PZ-601 (SMP-601) is a novel parenteral carbapenem (CARB) with a broad spectrum of activity against MRSA, some VRE and many species of Enterobacteriaceae (ENT). The purpose of this study was to establish PZ-601 wildtype (WT) MIC distributions for *S. aureus* (SA), *E. coli* (EC), *K. pneumoniae* (KPN), *K. oxytoca* (KOXY) as well as potency against resistant (R) subsets.

Methods: 1,500 WT organism strains (4 species) from Europe (EU) and USA were tested by reference both microdilution method against PZ-601 and 24 comparator drugs according to the CLSI M7-A7 (2006) method. An additional 60 R subset strains of CARB-R ENT (serine and metallo enzymes [MβL]), VISA, VRSA, linezolid (LZD)-R and CA-MRSA were compared to WT MIC results.

Results:

Strains	Cum. % inhibited at PZ-601 MIC (μg/ml): ≤0.06	0.12	0.25	0.5	1	2	4	No. tested
MRSA-USA	2	10	40[a]	59	81	99	100	269
MRSA-EU	6	19	39	54	81	98	99	231
CA-MRSA	0	0	100	-	-	-	-	10
VISA, VRSA	0	0	10	20	50	100	-	10
LZD-R SA	20	40	60	70	100	-	-	10
EC	2	20	74	95	98	99	100	500
KPN	1	28	80	94	98	99	100	400
KOXY	2	56	79	90	95	98	100	100

a. Underlined value is modal MIC

WT PZ601 MIC distributions for MRSA were bimodal (0.25 and 1 μg/ml) with different predominant modes for USA (0.25 μg/ml) and EU (1 μg/ml). CA-MRSA USA300 strains had PZ-601 MIC results at 0.25 μg/ml with VISA and VRSA isolates all inhibited at ≤2 μg/ml (see Table). LZD-R did not effect PZ-601 susceptibility. All ENT species tested had a PZ-601 MIC_{90} at 0.5 μg/ml; highest MIC at 4 μg/ml. ENT strains producing serine carbapenemases or MβLs (KPC-2 and 3, Nmc-A, SME-2, VIM-1, IMP1; from 8 species and 6 nations) had non-WT PZ-601 MIC values at ≥16 μg/ml.

Conclusions: PZ-601 was very active against WT MRSA isolated in the USA and EU. PZ-601 was also active against VISA, VRSA, CA-MRSA and LZD-R staphylococci. WT EC, KPN and KOXY strains were very PZ-601-S ($MIC_{50/90}$, 0.12-0.25/0.5 μg/ml), equally potent compared to imipenem. PZ-601 results demonstrate a promising spectrum of activity against targeted WT MRSA and key ENT species on two continents.

Introduction

The emergence of bacterial resistance against many commonly used antimicrobials has created a serious therapeutic concern and resulted in increased utilization of carbapenems for Gram-negative pathogens and vancomycin, daptomycin and linezolid for Gram-positive infecting organisms.The increased resistance has also created a need to produce new antimicrobial options especially agents stable to various emerging β-lactamases (extended spectrum β-lactamases; ESBL). PZ-601 (formerly SMP-601) is a novel parenteral carbapenem with a broad spectrum of activity against methicillin-resistant *Staphylococcus aureus* (MRSA), some vancomycin-resistant enterococci (VRE) and many species of Enterobacteriaceae. PZ-601 has a history of increased activity against MRSA and enterococci compared to existing carbapenems.

The purpose of this study was to establish the PZ-601 MIC distribution for wildtype (WT) *S. aureus, Escherichia coli*, *Klebsiella pneumonia*, and *Klebsiella oxytoca* strains from both North America (United States; USA) and Europe, as well as potency against specific PZ-601-resistant subsets.

Materials and Methods

Bacterial Isolates. A total of 1560 non-duplicate strains were selected to represent a susceptible, WT set of isolates to produce a MIC distribution for PZ-601. Strains were identified as not having unusual resistance patterns to comparable carbapenem agents such as imipenem (examples: metallo β-lactamases, serine carbapenemases, hyper-producing Amp-C enzymes associated with porin alterations, etc.). The WT isolate distribution included MRSA (500), *E. coli* (500), *K. pneumoniae* (400), and *K. oxytoca* (100), with sufficient sample size to assure high confidence (Ordway ICPD, 2007).

The resistance subsets consisted of metallo β-lactamase producing Enterobacteriaceae (IMP-, VIM-series;10), serine β-lactamase-producing Enterobacteriaceae (KPC-, SME-, NmcA- types; 20), MRSA exhibiting elevated vancomycin results (VISA, hVISA, and VRSA; 10), staphylococci with linezolid resistance (10), and community-acquired MRSA (CA-MRSA) clone USA300-0114 and variants (10). Isolates originated from Europe and North America and were cultured in 2005-2006.

Susceptibility Test Methods. Isolates were tested by the reference broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI; formerly the NCCLS) M7-A7 (2006) standard against PZ-601 and 24 comparator antimicrobial drugs depending on the Gram's identification. Interpretive criteria for comparison agents were those published in the current M100-S17 (2007) document. Quality control (QC) applied recently determined PZ-601 ranges, published by an acceptable M23-A2 protocol design (CLSI Agenda Book, January 2007). Concurrently tested comparison agents had all QC results within published (M100-S17, 2007) ranges.

Results

•PZ-601 MIC distributions for all nine tested organism groups are shown in Table 1. PZ-601 had bimodal MICs of 0.25 and 1 μg/ml with a MIC_{90} of 2 μg/ml against all staphylococci.

•Geographical analysis (Figure 1) showed that the two predominant modes for staphylococci were different for the USA (0.25 μg/ml) and Europe (1 μg/ml). CA-MRSA USA 300 strains had PZ-601 MIC results at 0.25 μg/ml which coincides with the modal MIC for all USA WT strains. The highest, reproducible MIC was observed in a WT European *S. aureus* isolate (16 μg/ml).

• All VISA and VRSA isolates were inhibited at ≤2 μg/ml of PZ-601, and linezolid resistance also did not affect PZ-601 susceptibility.

•The comparative activity of PZ-601 and 19 other agents tested against the MRSA is shown in Table 2. PZ-601 was at least four-fold more potent than imipenem against MRSA and showed similar activity to that of vancomycin.

•The WT *E. coli* and *Klebsiella* spp. strains were highly PZ-601-susceptible ($MIC_{50/90}$, 0.25/0.5 μg/ml) with the most elevated value at 4 μg/ml. Only the documented carbapenemase-producing enteric bacilli had PZ-601 MIC values at >4 μg/ml (Table 1).

•Enterobacteriaceae strains producing serine carbapenemases or MβLs (KPC-2 and 3, Nmc-A, SME-2, VIM-1, IMP-1; from 8 species and 6 nations) had non-WT PZ-601 MIC results at ≥16 μg/ml, clearly resistant.

•The activity of PZ-601 and 16 comparator drugs against WT *E. coli* is shown in Table 2. Imipenem was two-fold more active than PZ-601 against both *E. coli* and *Klebsiella* species (not shown).

Results

Table 1. MIC distributions of PZ-601 tested against nine groups of Gram-positive and Gram-negative bacteria (Europe and USA, 2006).

Organism group (no. tested)[a]	Occurrences at MIC (μg/ml): ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
S. aureus													
MRSA (500)	6	6	7	52	127	86	120	91	4	0	1	0	0
CA-MRSA (10)	0	0	0	0	10	0	0	0	0	0	0	0	0
VISA, VRSA (10)	0	0	0	0	1	1	3	5	0	0	0	0	0
Linezolid-resistant (10)	1	0	1	2	2	1	3	0	0	0	0	0	0
E. coli (500)	0	1	10	87	274	101	17	7	3	0	0	0	0
K. pneumoniae (400)	0	0	4	108	207	55	17	8	1	0	0	0	0
K. oxytoca (100)	0	0	2	54	23	11	5	3	2	0	0	0	0
Carbapenemase producers													
Serine-types (20)[b]	0	0	0	0	0	0	0	0	0	0	1	1	18
Metallo-types (10)[c]	0	0	0	0	0	0	0	0	0	0	2	2	6

[a]MRSA = wildtype methicillin-resistant *S. aureus*, CA-MRSA = community-acquired MRSA (USA300), VISA = vancomycin-intermediate *S. aureus*, VRSA = vancomycin-resistant *S.aureus*.
[b]Includes: *C. freundii* (2), *E. cloacae* (3), *E. coli* (2), *K. oxytoca* (4), *K. pneumoniae* (5) and *S. marcescens* (4).
[c]Includes: *E. cloacae* (4), *K. pneumoniae* (3), and one strain each of *E. aerogenes*, *P. mirabilis* and *S. marcescens*.

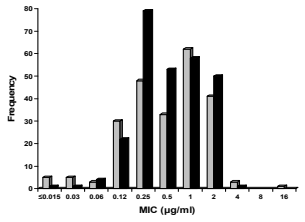
Table 2. Activity of PZ-601 and selected antimicrobial agents tested against MRSA and *E. coli* (500 strains each).

Organism (no. tested)/Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/resistant[a]
MRSA (500)				
PZ-601	0.5	2	≤0.015-16	- / -
Imipenem[a]	2	>32	≤0.03->32	56.2 / 37.6
Cefepime[a]	16	>16	0.25->16	43.4 / 49.0
Ceftazidime[a]	>16	>16	8->16	2.2 / 76.0
Ceftriaxone[a]	>32	>32	2->32	4.8 / 52.2
Ciprofloxacin	>4	>4	0.06->4	15.0 / 84.4
Clindamycin	≤0.25	>2	≤0.25->2	59.6 / 40.0
Daptomycin	0.25	0.5	0.12-2	99.8 / -
Ertapenem[a]	>1	>1	≤0.25->1	84.2 / 14.4
Erythromycin	>2	>2	≤0.25->2	19.8 / 1.8
Gentamicin	≤2	>8	≤2->8	86.4 / 13.2
Linezolid	1	2	0.25-2	100.0 / -
Ampicillin[a]	>16	>16	≤1->16	0.0 / 100.0
Oxacillin[a]	>2	>2	>2	0.0 / 100.0
Piperacillin-tazobactam[a]	32	>64	2->64	18.8 / 81.2
Quinupristin-dalfopristin	0.5	1	≤0.25->2	99.4 / 0.6
Rifampin	≤0.25	-	≤0.25->2	88.9 / 11.1
Tetracycline	≤2	>8	≤2->8	87.8 / 10.8
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	95.8 / 4.2
Vancomycin	1	1	0.25-2	100.0 / 0.0
E. coli (500)				
PZ-601	0.25	0.5	0.03-4	- / -
Imipenem	0.12	0.25	0.06-1	100.0 / 0.0
Amoxicillin-clavulanic acid	8	16	≤1->16	84.0 / 4.2
Ampicillin	>16	>16	≤1->16	48.8 / 50.4
Cefazolin	≤2	8	≤2->16	92.2 / 4.6
Cefepime	≤0.12	≤0.12	≤0.12->16	99.4 / 0.4
Cefoxitin	≤2	8	≤2->16	95.2 / 0.8
Ceftazidime	≤1	≤1	≤1->16	99.2 / 0.6 (1.2)[b]
Ceftriaxone	≤0.25	≤0.25	≤0.25->32	99.4 / 0.6 (0.8)[b]
Ciprofloxacin	≤0.03	>4	≤0.03->4	78.4 / 21.6
Ertapenem	≤0.06	≤0.06	≤0.06-0.25	100.0 / 0.0
Gentamicin	≤2	≤2	≤2->8	93.0 / 6.6
Meropenem	≤0.12	≤0.12	≤0.12	100.0 / 0.0
Piperacillin-tazobactam	1	4	≤0.5->64	95.2 / 2.2
Polymyxin B	≤0.5	≤0.5	≤0.5-2	100.0 / 0.0
Tetracycline	≤2	>8	≤2->8	71.0 / 28.6
Trimethoprim-sulfamethoxazole	≤0.5	>2	≤0.5->2	70.4 / 29.6

[a] Criteria as published by the CLSI [2007], β-lactam susceptibility should be directed by the oxacillin test results.
[b] Percentage of isolates with ESBL phenotypes (CLSI, M100-S17 [2007])

Results

Figure 1. MRSA MIC distributions for PZ-601 comparing USA and European isolates.



Conclusions

▪PZ-601 was very active against WT MRSA in both the USA and Europe. A bimodal MIC population was discovered between the USA (0.25 μg/ml) and Europe (1 μg/ml). PZ-601 was also active against VISA, VRSA, CA-MRSA and linezolid-resistant staphylococci.

▪WT *E. coli* (500 strains), *K. pneumoniae* (400 strains) and *K. oxytoca* (100 strains) isolated in Europe and the USA were all susceptible to PZ-601 at ≤4 μg/ml (99.4% inhibited at ≤2 μg/ml).

▪Carbapenemases (serine- or metallo-types) in Enterobacteriaceae were associated with markedly elevated PZ-601 MIC results (≥16 μg/ml), approximately two-fold greater than the highest PZ-601 MIC detected in the WT distribution.

▪PZ-601 results show a promising spectrum of activity against contemporary WT MRSA and key species members of the Enterobacteriaceae. These results can be valuable for the determination of optimal dosing via PK/PD target attainment models.

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