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In Vitro Activity of Plazomicin and Comparator Agents against Urinary Tract Infection Isolates from the United States and Europe

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Abstract

Background: Plazomicin (PLZ) is a next generation aminoglycoside developed to overcome common aminoglycoside-resistance mechanisms and has completed Phase 3 studies in complicated urinary tract infections and serious infections caused by carbapenem-resistant *Enterobacteriaceae*. We evaluated the activity of PLZ and comparators against isolates collected from urinary tract infections (UTI), including isolates carrying common β-lactamases, in United States (US) and European hospitals.

Methods: Isolates collected from UTIs (n=2,414) in 58 US and 33 European hospitals during 2014–2015 were susceptibility (S) tested by CLSI reference broth microdilution methods. Isolates displaying the CLSI ESBL-screening phenotype were screened by microarray-based assay for the presence of genes encoding CTX-M, TEM, SHV, KPC, NDM, and transferable AmpC enzymes.

Results: PLZ inhibited 95.8% and 99.1% of 2,344 *Enterobacteriaceae* (ENT) isolates collected from UTIs at ≤2 and ≤4 µg/mL, respectively. PLZ was slightly more active against European isolates (96.7% inhibited at ≤2 µg/mL) when compared to US isolates (95.2% inhibited at ≤2 µg/mL). PLZ inhibited 99.5% of the *E. coli* and *K. pneumoniae* isolates at ≤2 µg/mL. *E. aerogenes* (n=44), *E. cloacae* (n=38), *Citrobacter* spp. (n=190), and 112/113 (99.1%) *K. oxytoca* were inhibited by PLZ at ≤2 µg/mL. *Proteus mirabilis* (n=71) and indole-positive Proteeae species (n=260) displayed PLZ MIC values slightly higher than other ENT species ($MIC_{50/90}$, 2/4 µg/mL). Among 268 *E. coli* and *K. pneumoniae* isolates meeting the CLSI ESBL-phenotypic criteria, 209 carried ESBLs (150 CTX-M-15-like, 36 CTX-M-14-like, 27 SHV ESBL, and 1 CTX-M-2-like). PLZ inhibited 99.1% at ≤2 µg/mL, including 186 CTX-M-producing isolates. PLZ MIC results for 21 *P. aeruginosa* ($MIC_{50/90}$, 4/8 µg/mL) ranged from 0.25 to 8 µg/mL. The highest PLZ MIC value for *Staphylococcus* spp. (n=14) was 0.5 µg/mL. PLZ displayed limited activity against *Enterococcus* spp. (n=22; $MIC_{50/90}$, 32/64 µg/mL) and *Acinetobacter* spp. (n=13; MIC50/90, 2/8 µg/mL).

Conclusion: PLZ was active against >95% of the ENT isolates recovered from UTI sources in US and European hospitals, including isolates carrying common ESBLs, such as CTX-M-producing isolates that were detected among >50% of the ESBL-phenotype isolates.

	PLZ MIC50/90 (µg/mL):		
Organism (total no. tested)	**Overall**	**US**	**Europe**
Enterobacteriaceae (2,344)	0.5/2	0.5/2	0.5/2
E. coli (981)	0.5/1	0.5/1	0.5/1
K. pneumoniae (629)	0.25/0.5	0.25/0.5	0.25/0.5
ESBL producers (209)	0.5/1	0.5/1	0.5/1
CTX-M producers (186)	0.5/1	0.5/1	0.5/1

Introduction

- Antimicrobial resistance among gram-negative uropathogens is on the rise, decreasing the utility of numerous antimicrobial agents for treating UTIs
- Among resistant organisms, *Enterobacteriaceae* isolates carrying β-lactamases, including CTX-M enzymes, is a matter of concern
  - Additionally, these isolates carrying β-lactamase genes are often resistant to other antimicrobial classes, such as fluoroquinolones, and aminoglycosides
- Plazomicin is a semi-synthetic aminoglycoside that retains activity against multi-drug resistant *Enterobacteriaceae,* including aminoglycoside resistant isolates
- Plazomicin demonstrates activity against *Enterobacteriaceae* species isolated from urinary tract infections, including organisms producing β-lactamases, *Staphylococcus* spp., and some *P. aeruginosa*
- We evaluated the activity of plazomicin and comparator antimicrobial agents against isolates collected from patients with UTIs in United States (US) and European hospitals, including isolates carrying common β-lactamases

Materials and Methods

- A total of 2,414 isolates recovered from UTI in 58 hospitals located in the US and 33 hospitals in Europe during 2014 and 2015 were analyzed
- Susceptibility was assessed using the reference broth microdilution method described by the Clinical and Laboratory Standards Institute
- Categorical interpretations for all comparator agents were those found in CLSI criteria in M100-S27 (2017), EUCAST breakpoint tables (version 7.0, January 2017), and/or United States Food and Drug Administration (US FDA) package inserts
- Quality control (QC) was performed according to CLSI guidelines (M7-A9), and all QC MIC results were within acceptable ranges as published in CLSI documents
- Isolates displaying an extended-spectrum beta-lactamase (ESBL) phenotype (MIC, >1 µg/mL for aztreonam, ceftazidime, and/or ceftriaxone) according to CLSI guidelines were screened for the presence of β-lactamase-encoding genes
  - Check-MDR CT101 kit (Check-Points, Wageningen, Netherlands) was used to identify the presence of specific beta-lactamases according to the manufacturer's instructions
- Genes encoding CTX-M groups 1, 2, 8+25, and 9; TEM wild type (WT) and ESBL; SHV WT and ESBL; ACC; ACT/MIR; CMYII; DHA; FOX; KPC; and NDM-1 were screened

Results

- Plazomicin ($MIC_{50/90}$, 0.5/2 µg/mL) was active against 2,344 *Enterobacteriaceae* UTI isolates (Table 1)
  - Plazomicin inhibited 95.8% and 99.1% of *Enterobacteriaceae* isolates at ≤2 and ≤4 µg/mL, respectively (Figure 1)
  - Plazomicin displayed slightly greater activity against European isolates when compared to US isolates (96.7% and 95.2% inhibited at ≤2 µg/mL, respectively)
- Plazomicin was active against *E. coli* ($MIC_{50/90}$, 0.5/1 µg/mL), *K. pneumoniae* ($MIC_{50/90}$, 0.25/0.5 µg/mL), and other *Enterobacteriaceae* species associated with UTI (Table 1)
  - *P. mirabilis* isolates displayed slightly higher plazomicin MIC values when compared to other species ($MIC_{50/90}$, 2/4 µg/mL), which is consistent with the activity of this species against the aminoglycoside class
- Against 21 *P. aeruginosa* isolates, plazomicin ($MIC_{50/90}$, 4/8 µg/mL) displayed activity 2-fold lower than amikacin ($MIC_{50/90}$, 2/4 µg/mL)
- Plazomicin ($MIC_{50/90}$, ≤0.06/0.25 µg/mL) was active against 14 *Staphylococcus* spp. isolates from UTI
- Plazomicin displayed limited activity against *Enterococcus* spp. (n=22; $MIC_{50/90}$, 32/64 µg/mL) and *Acinetobacter* spp. (n=13; $MIC_{50/90}$, 2/8 µg/mL; data not shown)
- Among 268 *E. coli* and *K. pneumoniae* UTI isolates meeting the CLSI ESBL-phenotypic criteria, 209 carried ESBLs,including 150 $bla_{CTX\text{-}M\text{-}15\text{-}like}$, 36 $bla_{CTX\text{-}M\text{-}14\text{-}like}$, 27 bla_{SHV} ESBL, and 1 $bla_{CTX\text{-}M\text{-}2\text{-}like}$ (Table 2)
  - A total of 26 isolates carried genes encoding transferrable cephalosporinases (AmpC), and $bla_{CMY\text{-}2\text{-}like}$ was the most common (16 isolates), followed by bla_{DHA} (9) and bla_{FOX} (1)
  - Genes encoding KPC enzymes were detected among 27 isolates and 1 isolate harbored $bla_{NDM\text{-}1}$
- Plazomicin inhibited 99.0% of the isolates carrying ESBL-encoding genes at ≤2 µg/mL, and all but 1 isolate (99.5%) was inhibited at ≤4 µg/mL
  - All isolates harboring genes encoding transferrable AmpCs or carbapenemases were inhibited by plazomicin at ≤2 µg/mL (Figure 1)
- Plazomicin activity (MIC_{50} and MIC_{90} ranges, 0.25 to 0.5 and 1 µg/mL) was not affected by the presence of β-lactamases
  - The activity of clinically available aminoglycosides and some other comparator agents was diminished against isolates carrying β-lactamase-encoding genes (Table 1)

Table 1 Activity of plazomicin and comparator antimicrobial agents tested against UTI isolates

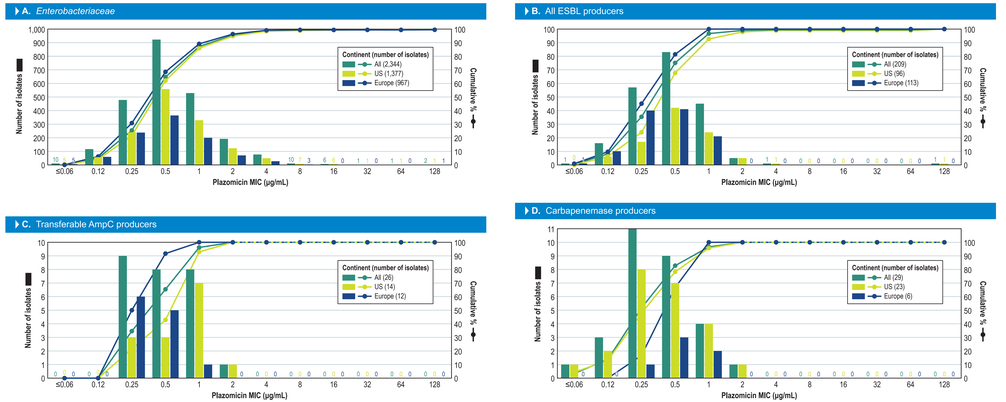
	MIC_{50}/MIC_{90} (µg/mL)							
Organism group (no. tested)	**Plazomicin**	**Amikacin**	**Gentamicin**	**Tobramycin**	**Meropenem**	**Piperacillin-tazobactam**	**Colistin**	**Tigecycline**
Enterobacteriaceae (2,344)	0.5 / 2	2 / 4	0.5 / >8	0.5 / 8	0.03 / 0.06	2 / 16	≤0.5 / >8	0.12 / 1
Escherichia coli (981)	0.5 / 1	2 / 4	0.5 / >8	1 / 8	≤0.015 / 0.03	2 / 8	≤0.5 / ≤0.5	0.12 / 0.25
Klebsiella pneumoniae (629)	0.25 / 0.5	1 / 8	0.5 / >8	0.5 / >8	0.03 / 1	4 / >64	≤0.5 / 1	0.25 / 0.5
Klebsiella oxytoca (113)	0.5 / 0.5	1 / 2	0.5 / 1	0.5 / 1	0.03 / 0.03	2 / >64	≤0.5 / ≤0.5	0.25 / 0.25
Enterobacter cloacae species complex (38)	0.5 / 0.5	1 / 2	0.5 / >8	0.5 / >8	0.03 / 0.12	2 / 64	≤0.5 / >8	0.25 / 1
Citrobacter freundii species complex (95)	0.5 / 0.5	2 / 2	0.5 / 8	0.5 / 8	0.03 / 0.06	2 / >64	≤0.5 / 1	0.25 / 0.5
Proteus mirabilis (71)	2 / 4	2 / 4	0.5 / 2	0.5 / 2	0.06 / 0.12	≤0.5 / ≤0.5	>8 / >8	1 / 4
Staphylococcus spp. (14)	≤0.06 / 0.25		≤1 / 4			1 / 16		0.06 / 0.12
Pseudomonas aeruginosa (21)	4 / 8	2 / 4	2 / 16	0.5 / >8	0.5 / 8	4 / 32	1 / 2	4 / 8
All ESBL producers (209)	0.5 / 1	2 / 16	2 / >8	8 / >8	0.03 / 2	8 / >64	≤0.5 / 1	0.25 / 0.5
CTX-M producers (186)	0.5 / 1	2 / 16	8 / >8	8 / >8	0.03 / 0.5	8 / >64	≤0.5 / 1	0.12 / 0.5
CTX-M-15-like producers (150)	0.5 / 1	4 / 16	>8 / >8	>8 / >8	0.03 / 0.5	16 / >64	≤0.5 / 1	0.25 / 0.5
CTX-M-14-like producers (36)	0.5 / 1	2 / 4	1 / >8	1 / 8	≤0.015 / 0.03	2 / 8	≤0.5 / ≤0.5	0.12 / 0.25
Transferrable AmpC producers (26)	0.5 / 1	2 / 16	2 / >8	4 / >8	0.03 / 1	8 / >64	≤0.5 / >8	0.12 / 0.5
Carbapenemase producers (29)	0.25 / 1	16 / 32	8 / >8	>8 / >8	16 / >32	>64 / >64	≤0.5 / >8	0.25 / 1

Table 2 Results of β-lactamase screening for 268 *E. coli* and *K. pneumoniae* isolates recovered from UTI

	No. of positive results*				
β-lactamase	**Overall (268)**	***E. coli* (137)**	***K. pneumoniae* (131)**	**US (142)**	**Europe (126)**
Carbapenemases					
KPC	27		27	22	5
NDM-1	1		1		1
ESBLs					
CTX-M-15-like	150	76	74	58	92
CTX-M-2-like	1	1		1	
CTX-M-14-like	36	29	7	21	15
SHV ESBL	27	1	26	20	7
Transferable AmpC					
CMY-2-like	16	14	2	12	4
DHA	9	2	7	1	8
FOX	1		1	1	
Non-ESBLs					
SHV WT	125	1	124	60	65
TEM WT	143	67	78	72	71

* Isolates might be positive for multiple genes screened

Figure 1 Antimicrobial activity of plazomicin against UTI isolates collected in US and Europe during 2014 and 2015



Conclusions

- Plazomicin displayed activity against *Enterobacteriaceae* UTI isolates recovered in US and European hospitals during 2014–2015
  - The activity of this new aminoglycoside was not affected by the presence of widespread β-lactamase genes among *E. coli* and *K. pneumoniae* isolates, which differs from other agents
- Plazomicin also displayed activity against *Staphylococcus* spp. recovered from UTI, but the activity of this compound was modest against *P. aeruginosa* and limited against enterococci and *Acinetobacter* spp.
- The continued increase of multidrug-resistant isolates among UTI, mainly complicated infections, requires the use of agents that are effective against these organisms, and plazomicin displayed activity against a large collection of these isolates

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