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Evaluation of Tebipenem Activity Tested against a Collection of Isogenic *Escherichia coli* Strains Producing Various Clinically Relevant β-Lactamases

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Introduction

- β-lactamases are important β-lactam resistance mechanisms in *Enterobacteriaceae*
- Carbapenems are widely used and potent antimicrobial agents with broad spectrum of activity, including against isolates producing extended-spectrum β-lactamases (ESBLs) and AmpC enzymes
- The high prevalence of fluoroquinolone- and extended-spectrum β-lactam-resistance among gram-negative pathogens in the hospital and community settings highlights the need for more effective therapies
- Tebipenem, the active metabolite of tebipenem-pivoxil, is an oral carbapenem introduced in Japan (2009) for pediatric respiratory and otolaryngologic infections and is under clinical development for treatment of complicated urinary tract infections (cUTIs) where it is administered as a prodrug, tebipenem pivoxil hydrobromide (SPR994)
- This study evaluates the *in vitro* antimicrobial activity of tebipenem and comparators when tested against a collection of isogenic *Escherichia coli* strains carrying clinically relevant and diverse β-lactamase-encoding genes

Materials and Methods

- Fifty *E. coli* isogenic strains carrying either native or recombinant plasmids containing narrow-spectrum β-lactamase (NSBL)-, ESBL-, AmpC-, or carbapenemase-encoding genes were included
- Isolates carrying engineered vectors providing different expression levels or combinations of β-lactamase genes were included, as well as genes encoding for mutations in the Ω loop of KPC-2
- *E. coli* laboratorial strains absent of β-lactamase genes were also included and tested to provide the respective baseline profile
- Susceptibility testing was performed by a reference broth microdilution method against tebipenem and comparators
  - 96-well frozen-form broth microdilution panels with cation-adjusted Mueller-Hinton broth were manufactured by JMI Laboratories (North Liberty, Iowa, USA) per the Clinical and Laboratory Standards Institute (CLSI) specifications described in the M07 (2018) document
  - Quality control strains that included *E. coli* ATCC 25922, *Klebsiella pneumoniae* ATCC BAA 1705, and *Pseudomonas aeruginosa* ATCC 27853 were tested before and concomitantly with selected isolates, and bacterial inoculum density was monitored by counting the number of colony-forming units present in the inoculum material
- Differences in fold MIC results for each antimicrobial agent tested against the baseline *E. coli* and respective isogenic strain carrying a β-lactamase-encoding gene were plotted in bar graphs (Figures 1 through 8)

Results

- Similar baseline MIC values for tebipenem (≤0.004–0.015 mg/L) and ertapenem (0.008–0.015 mg/L) were obtained against baseline laboratorial *E. coli* strains
- Tebipenem MIC results against strains producing narrow-spectrum SHV and TEM variants were similar to those obtained against isogenic baseline strains (≤4-fold differences; Figures 1 and 2)
  - MIC values for carbapenems other than tebipenem were generally also not affected by these NSBL enzymes, except for ertapenem (MIC, 0.06 mg/L) against SHV-1, for which the MIC was 8-fold higher than the baseline strain MIC (MIC, 0.008 mg/L) (Figure 1)
  - Cefazolin MIC values increased 64-, 16-, and 32-fold when tested against *E. coli* strains producing SHV-154, SHV-161, and TEM-2, respectively (Figure 1)
- Tebipenem MIC values against ESBLs were similar to those from baseline isogenic isolates regardless of ESBL variants (TEM, SHV, or CTX-M), transcription levels, or gene combinations (Figures 2 to 4)
  - Ertapenem MIC values increased 2- to 16-fold against isolates carrying TEM and SHV ESBL-encoding genes
- Tebipenem MIC values obtained against strains producing GES ESBL variants, PER-5, OXA-1, OXA-2, OXA-10, or plasmid-encoded AmpC enzymes remained similar to the respective baseline strain (Figures 5 and 6)
  - Ertapenem MIC values increased 16-fold when tested against a recombinant *E. coli* expressing OXA-10 (Figure 5)
- Tebipenem, ertapenem, and ceftazidime MIC values increased 8-fold against a strain producing the K1 *Klebsiella oxytoca* intrinsic enzyme compared to the baseline strain (Figure 5)
- Carbapenem MIC values were affected by NDM-1, KPC-2, KPC-3, SME-2, SME-4, OXA-48, and GES-11 (Figures 7 and 8)
  - The KPC-2 variants containing D179Y (KPC-33) or D176Y alterations had an effect over the MIC of carbapenem agents much lower than that observed for KPC-2 (Figure 7)

Conclusions

- The *in vitro* data presented here confirmed the activity of tebipenem against *E. coli* strains producing class A, C, or D non-carbapenemase enzymes, including ESBLs and plasmid-encoded AmpC enzymes
- Similar to other carbapenems, the tebipenem activity was adversely affected when tested against isolates expressing class A, B, and D carbapenemases
- Amino acids alterations (D176 or D179) in the Ω loop of KPC-2 restored the activity of carbapenem agents, including tebipenem
- These results confirm the stability of tebipenem against an array of β-lactamases and support its clinical development as an oral alternative for treating infections caused by isolates resistant to narrow- and extended-spectrum β-lactam agents

Acknowledgements

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Figure 1 Increase in fold MIC of antimicrobial agents tested against *E. coli* carrying narrow-spectrum β-lactamase-encoding genes compared to the respective baseline strain

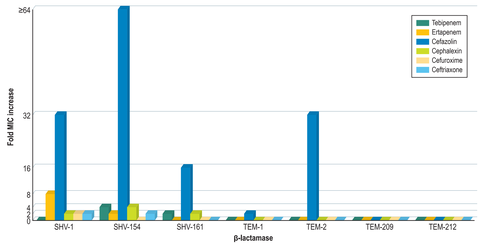


Figure 2 Increase in fold MIC of antimicrobial agents tested against *E. coli* carrying TEM ESBL-encoding genes compared to the respective baseline strain

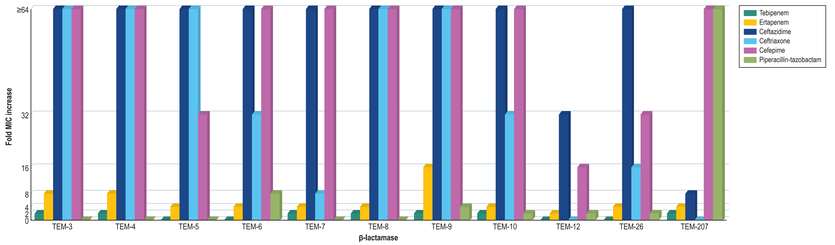


Figure 3 Increase in fold MIC of antimicrobial agents tested against *E. coli* carrying SHV- and CTX-M-encoding genes compared to the respective baseline strain

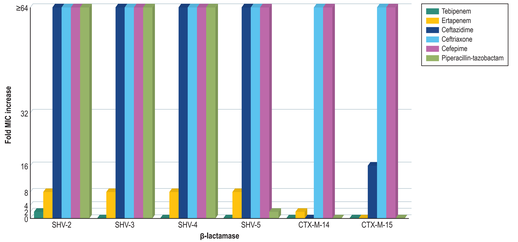


Figure 4 Increase in fold MIC of antimicrobial agents tested against *E. coli* carrying combinations of β-lactamase-encoding genes compared to the respective baseline strain

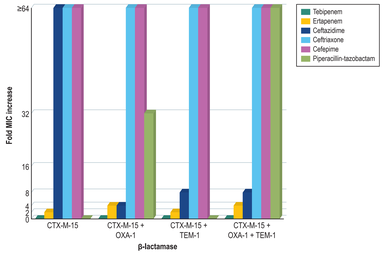


Figure 5 Increase in fold MIC of antimicrobial agents tested against *E. coli* carrying β-lactamase-encoding genes compared to the respective baseline strain

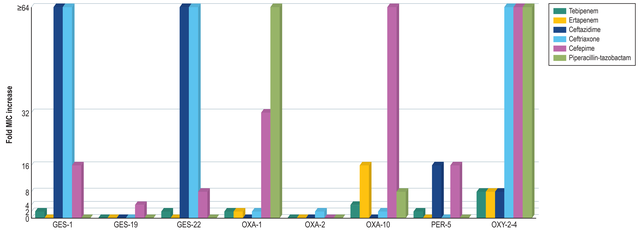


Figure 6 Increase in fold MIC of antimicrobial agents tested against *E. coli* carrying plasmid- and chromosomal (SRT, *Serratia marcescens*)-encoded AmpC genes compared to the respective baseline strain

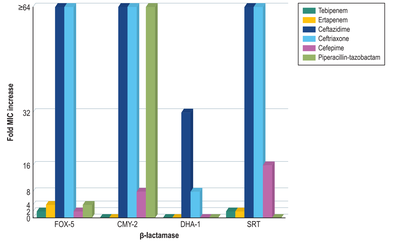


Figure 7 Increase in fold MIC of antimicrobial agents tested against *E. coli* carrying class A and B carbapenemase-encoding genes compared to the respective baseline strain

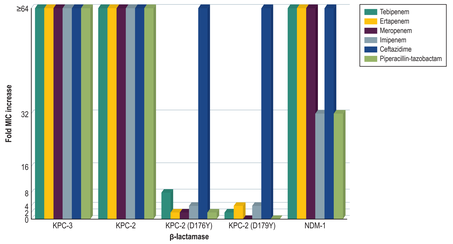
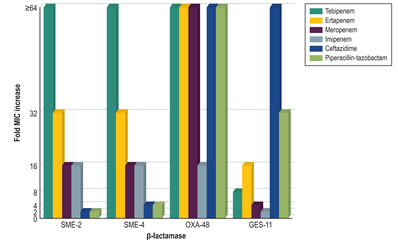


Figure 8 Increase in fold MIC of antimicrobial agents tested against *E. coli* carrying other carbapenemase-encoding genes compared to the respective baseline strain



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