In Vivo Analysis of AmpC β-lactamase Induction by Tebipenem in Enterobacteriaceae and Pseudomonas aeruginosa

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Introduction

- Urinary tract infections (UTIs) are among the most common bacterial infections and the great majority of these infections are caused by Escherichia coli, followed by Klebsiella pneumoniae and Pseudomonas mirabilis.
- Tebipenem is an investigational fluoropenem that is currently undergoing clinical development for treating complicated UTI and acute pyelonephritis in the US.
- Tebipenem possesses broad-spectrum activity against isolates producing penicillins, cephalosporins, and extended-spectrum β-lactamases, and intrinsic and plasmid-encoded AmpC β-lactamases (see p-values 129, 122, and 125 × 10−6).
- The overall deactivation caused by β-lactamases in peptide accumulation. These peptides bind to AmpC, which negatively regulates AmpC production. The decrease of β-lactamases, and intrinsic and plasmid-encoded AmpC β-lactamases, which negatively regulates AmpC production.

Results

- In general, tebipenem and imipenem increased production of AmpC among all Enterobacteriaceae, except for C. koseri and 3. mcr-4 (Table 1).
- Exposure to cefepime and ofloxacin did not seem to affect production of AmpC among the Enterobacteriaceae species tested (Table 1).
- Exposure to tebipenem and ofloxacin increased the production of AmpC in P. aeruginosa after exposure. The same effect on P. aeruginosa was observed for meropenem, although carbapenems are not AmpC substrates.
- The study investigated the induction properties of tebipenem over the AmpC-encoded gene in Gram-negative organisms.

Materials and Methods

Bacterial organisms

- A total of 8 Enterobacteriaceae species and 2 Pseudomonas aeruginosa isolates were selected for the AmpC induction experiments for tebipenem, imipenem, ertapenem, and cefepime. These isolates were tested for susceptibility as well.
- The organisms used were susceptible control for cefepime, which can withstand hydrolysis. These can be hydrolyzed if enough enzyme gets produced. The exception would be carbapenems, which are not AmpC substrates.
- Enterobacter cloacae species and 1 isolate were selected for the AmpC induction experiments for tebipenem, imipenem, ertapenem, and cefepime. These isolates were tested for susceptibility as well.

Conclusions

- The induction experiments performed showed that exposure to tebipenem promoted increased production of AmpC in Enterobacteriaceae species. Imipenem seemed to be more effective, in general, on AmpC inducer stronger than tebipenem.
- The AmpC induction phenomenon seems to be species-dependent for both tebipenem and theresin, since no negative or insignificant results were obtained for C. koseri and S. mcr-4.
- AmpC induction among Enterobacteriaceae was not observed for the comparator agents cefepime and ofloxacin.
- In general, exposure to tebipenem, followed by ofloxacin and tebipenem, promoted induction production over exposure to cefepime.
- Enterobacteriaceae or if AmpC-negative cells showed increased production of AmpC after drug exposure did not display increased MIC when compared to the respective baseline MIC. This observation may suggest that the production of AmpC induced in these isolates was not sufficient enough to cause a shift in MIC.
- Finally, tebipenem showed potent activity against AmpC-positive isolates with confirmed overproduction of AmpC. The increase in AmpC enzymatic activity was similar to that observed for meropenem, both of which were greater than those noted for imipenem and etrapenem.

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References

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