Activity of Plazomicin in Combination with Other Antibiotics Against Multidrug Resistant Enterobacteriaceae

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Objectives

To evaluate the potential for antiinfectious interactions between plazomicin and other available agents when used in combination against a panel of MDR Enterobacteriaceae, including isolates with characterized beta-lactam and aminoglycoside resistance mechanisms.

Methods

- **In-vitro Testing**
  - Enterobacteriaceae isolates were chosen based on their resistance to available antibiotics. Isolates were provided by Chris M. Pillar (University of California, San Francisco, CA, USA) for funding the study described herein.
  - The isolates included E. coli, K. pneumoniae, K. oxytoca, E. cloacae, and D. vulgaris.

- **Drug Susceptibility Testing**
  - The drugs used for testing included plazomicin (PLZ), tigecycline (TIG), gentamicin (GEN), aztreonam (AZM), imipenem (MEM), and colistin (COL).

- **Fractional Inhibitory Concentration Index (FICI)**
  - The fraction inhibitory concentration index (FICI) was calculated as follows: FICI = (MICagent alone/MICagent in combination) x (MICother agent alone/MICother agent in combination).

- **Synergy, Antagonism, and World Health Organization (WHO) Classifications**
  - Synergy was defined as an FICI < 0.50, while antagonism was defined as an FICI > 5.0.
  - WHO classification was used to determine the potential for synergy with a score of 1: synergy, 2: indifference, and 3: antagonism.

- **Additional Testing**
  - The potential for synergy with other agents was evaluated in checkerboard assays against Enterobacter cloacae ECO1151 and K. oxytoca ECO1143.

Results

- **Table 1**
  - Summary of Activity of Plazomicin Alone and in Combination Against Enterobacteriaceae.

- **Table 2**
  - Summary of Activity of Plazomicin Alone and in Combination Against Entero-Bacteriaceae spp.

- **Table 3**
  - Summary of Activity of Plazomicin Alone and in Combination Against Klebsiella spp.

- **Table 4**
  - Summary of Activity of Plazomicin Alone and in Combination Against Enterobacteriaceae spp.

- **Table 5**
  - Summary of Activity of Plazomicin Alone and in Combination Against Proteus spp.

Conclusions

- **Plazomicin maintained potent activity against the MDR Enterobacteriaceae evaluated and, as shown by checkerboard analysis and time-kill analysis, was synergistic with both piperacillin/tazobactam and ceftazidime.
- There was no apparent interaction (synergy or antagonism) for PLZ in combination with the remaining evaluated agents, aside from occasional isolates where FICI values indicated of synergistic interactions.

These results illustrate the potential for plazomicin as both a monotherapy and combination therapy for the treatment of serious infections caused by MDR Enterobacteriaceae.

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References