Investigation of *In Vitro* Antagonistic and Synergistic Effects of Finafloxacin in Combination with Other Antibiotics

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51st ICAAC
Chicago 2011
E-1835

**Revised Abstract**

**Background:**
Finafloxacin (FIN) is a novel member of the fluoroquinolone class of antibiotics. Specifically, FIN belongs to a new 8-cyano subclass that contains a new base component which confers improved antibacterial activity under acidic conditions. Combination antibiotic therapy has been one of the options considered when dealing with multi-drug resistant bacteria infection. The aim of this study was to identify potential antagonistic or synergistic interaction between FIN and other commonly used antibiotics.

**Methods:**
Chequerboard experiments were performed on pH 5.8 and 7.2 under otherwise standard CLSI conditions using FIN in combination with meropenem (MER), cefazolin (CTZ), amikacin (AMK) or clindamycin (CLI) against P. aeruginosa ATCC 27853 and *E. coli* UTI clinical isolate. Time-kill studies were performed at synergetic drug concentrations observed in the chequerboard experiment, and at or combinations of non-synergic concentrations.

**Results:**
In the chequerboard experiments most antibiotic combinations showed additive effect (FICI: ≤ 0.5-0.6) under both acidic and neutral conditions. When tested against *P. aeruginosa* ATCC 27853 and *E. coli* UTI clinical isolate FIN-AMK showed synergy (FICI: ≤ 0.5) at pH 7.2 and pH 5.8, respectively. Borderline synergy (FICI = 0.5) was observed for FIN-MER against *P. aeruginosa* at pH 7.2 for two out of three experiments.

In the time-kill studies no synergy was observed for either FIN-AMK or FIN-MER at the chequerboard synergistic drug concentrations. However, FIN-AMK showed enhanced bactericidal effects at early time points when it was used at a higher drug concentration of 0.5x MIC, as compared to the simple most active agent. The enhanced effect was observed against both *P. aeruginosa* ATCC 27853 and *E. coli* UTI clinical isolate. Increasing the drug concentrations for FIN-MER to 0.5x MIC showed slight improvement in the bactericidal effect.

**Introduction**
Finafloxacin (FIN) is a novel member of the fluoroquinolone class of antibiotics. Specifically, FIN belongs to a new 6-7-zyano subclass. The agent contains a novel base component which confers improved antibacterial activity under acidic conditions1, where the activity of many existing fluoroquinolones is impaired. Combination antibiotic therapy has been one of the options considered when dealing with multi-drug resistant bacteria infection. However, there is a possibility of antagonism arising from the combination of certain antibiotics. Therefore, it is important to ensure that the use of FIN in combination therapy does not cause antagonistic effects.

**Conclusions**
• No antagonism was observed when FIN was used in combination with the antibiotics tested
• FIN-AMK & FIN-MER showed synergistic bacteriostatic effects
• Both combinations at 0.5x MIC showed enhanced bactericidal effects at early time points, compared to the individual drugs at the same concentration
• Further studies at higher concentrations are warranted

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