In vitro Activity of Fosfomycin, Alone and Combined with Cefepime and Meropenem, Against Carbapenemase-Producing Gram-Negative Bacteria

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Background: Multi-drug resistant (MDR) gram-negative bacteria are serious clinical threats. Fosfomycin (FOF) is an epoxide antibiotic that causes bacterial cell death via disruption of cell wall synthesis. The addition of fosfomycin has been shown to restore susceptibility to other agents against MDR *P. aeruginosa*. We evaluated the in vitro activity of the new IV fosfomycin formulation, alone and combined with cefepime (FEP) and meropenem (MEM), against carbapenemase-producing *Enterobacteriaceae.*

Methods: 80 carbapenemase-producing isolates, including 31 metallo beta-lactamase producing isolates (29 NDMs and 1 each IMP & VIM), 48 KPCs, and 1 OXA-48, were used. The in vitro susceptibility of FOF, FEP and MEM were tested by agar dilution with glucose-6 phosphate by CLSI methods. Combination testing was then performed against 25 representative isolates using fixed concentrations of FOF (8, 16, 32, & 64 mg/ml) at 0.25X the MIC of FOF alone with doubling dilutions of FEP and MEM.

Results: Reduced activity was observed for FEP and MEM against the carbapenemase-producing isolates (Table). 36.2% of the isolates were NDM1 and 60% were KPCs. A total of 92.5% of the isolates were resistant to either FEP or MEM. FOF plus MEM resulted in synergistic activity (4-fold reduction in MEM MIC at 0.25X FOF MIC) against 12 of 25 isolates used for combination testing, with no antagonism observed. For these 12 isolates, MEM MICs ranged from 2 - 16 mg/ml when combined with FOF versus 16 - 128 mg/ml when tested alone. When combined with FEP, synergistic activity was also observed against 6 of the 25 isolates. However, antagonism was observed against 3 isolates with this combination.

Conclusion: The combination of FOF plus MEM resulted in synergistic activity against approximately half of the KPCs and metallo beta-lactamase producing bacteria. Synergistic activity was observed less often with FOF plus FEP, although antagonism was uncommon. Further studies are warranted to determine the in vivo efficacy of FOF combinations. Table: MICs Alone

Drug	Parameter	Metallos	KPC2	KPC3, 4, 7
FOF	MIC Range	1 - 512	8 - >512	8 - >512
	MIC 50/90	32 / 256	32 / 128	32 / 128
FEP	MIC Range	4 - >128	1 - >128	8 - >128
	MIC 50/90	>128 / >128	>128 / >128	>128 / >128
MEM	MIC Range	4 - >128	8 - >128	8 - >128
	MIC 50/90	64 / 128	32 / 64	32 / 64