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Triple combination of tigecycline-colistin-meropenem against carbapenemase producing Klebsiella pneumoniae isolates in an in vitro PK-PD model

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Background: In absence of effective therapeutic approaches against carbapenamase producing *Klebsiella pneumoniae* (CP-Kp) isolates, combination therapy is often used in order to increase antibacterial activity. Tigecycline has a broad spectrum of *in vitro* activity against a variety of tetracycline-susceptible and tetracycline-resistant bacterial strains. Meropenem possesses some activity against CP-Kp isolates and colistin is often used as the last resort to combat those pathogens. We therefore assessed the triple and double combination of standard dosing regimens of tigecycline, colistin and meropenem against CP-Kp isolates in an *in vitro* PK-PD model.

Material/methods: One wild-type and 2 VIM producing CP-Kp isolates with CLSI MICs 0.125, 1, and 2 mg/l for tigecycline, 0.5, 0.25 and 0.5 mg/l for colistin and 0.06, 16 and 256 mg/l for meropenem were used at 10^7CFU/ml in an *in vitro* PK-PD model against the double and triple combination of tigecycline, colistin and meropemen. Another 4 CP-Kp isolates with various resistance mechanisms (1 KPC, 1 NDM, 1 KPC+VIM and 1 KPC+VIM+SHV-5) and tigecycline/colistin/ meropenem MICs of 0.5/4/64, 4/32/512, 1/2/256, 1/2/128, respectively were tested against the triple combination. The human plasma concentration-time profiles of 100mg q12 tigecycline, 4.5MU q12 colistin and 1g q8 of meropenem dosing regimens were simulated for 48h targeting tigecycline, colistin and meropenem free serum maximum concentrations of 0.3, 1.6 and 60 mg/L with half-lives >14h, 12h and <2h, respectively. Drug levels were determined by a microbiological assay. Bacterial growth was assessed by quantitative cultures estimating the CFU/ml at regular time points and $\log_{10}$CFU/ml reduction (killing) from the initial inoculum was estimated at 48h.

Results: The wild-type isolate were completely killed by meropenem alone or in combination with the other drugs whereas no killing was found for colistin and tigecycline alone or in combination. Against the 2 VIM isolates, no killing was observed with monotherapy regimens despite a 5 and 2 $\log_{10}$CFU reduction observed at 24h with colistin and meropenem, respectively. Among the double combinations, no killing was observed with colistin+tigecycline whereas only 1$\log_{10}$CFU/ml reduction was found with meropenem+tigecycline at 48h. On the contrary, colistin+meropenem decreased by 1 and 5$\log_{10}$ the CFU/ml counts of the isolates with meropenem MIC 256 and 16 mg/l, respectively whereas the triple combination decreased by 5$\log_{10}$ the CFU/ml counts of both isolates. Similarly, a 3 and 5 $\log_{10}$ CFU/ml reduction was observed with the triple combination against the other 3 isolates with mixed resistance mechanisms and MICs 256 (KPC+VIM) and 64-128mg/l (KPC and KPC+VIM+SHV-5), respectively. The triple combination did not kill the NDM isolate with meropenem MIC 512 mg/l.

Conclusions: The double combination colistin+meropenem was effective against CP-Kp isolates with meropenem MICs up to 16 mg/l. Notably, the triple combination colistin+meropenem+tigecycline was effective even for isolates with meropenem MICs up 256 mg/l.