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In vitro synergy and postantibiotic effect of colistin combined with meropenem against Enterobacteriaceae with multiple carbapenem-resistance mechanisms

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Background:

Carbapenemases involved in acquired resistance in Enterobacteriaceae belong to Ambler class A serin β -lactamases, class B metallo- β -lactamases (MBL) or class D (OXA-48-like β -lactamases). Clinical studies have found out that combination antibiotic therapy is associated with better therapeutic outcome than monotherapy in severe infection caused by carbapenemase positive strains. Persistent suppression of bacterial growth after short antimicrobial exposure is called the postantibiotic effect (PAE). The aim of the study was to determine in vitro synergy and postantibiotic effect of colistin alone and combined with meropenem against Enterobacteriaceae producing multiple carbapenemases.

Material/methods:

The study was performed on three strains with multiple carbapenem resistance mechanisms but susceptible to colistin and one positive for OXA-48 but resistant to colistin. The study included: *Citrobacter freundii* strain 132452 positive for VIM-1, NDM-1, TEM-1 and CMY-4, *Enterobacter cloacae* 209377 strain positive for VIM-1, NDM-1, OXA-48, TEM-1 and CTX-M-15, *Klebsiella pneumoniae* strain 145846 positive for VIM-1, NDM-1, TEM1 and SHV-11 all of them being susceptible to colistin and the strain 609815 resistant to colistin and positive for OXA-48.

Antibiotic susceptibility to a wide range of antibiotics was tested by disk-diffusion and broth microdilution method. The synergy of colistin with meropenem was tested by checkerboard and time-kill method. PAE was determined as previously described. Antibiotic concentrations used during time-kill experiments and PAE studies represented mean steady-state concentrations of non-protein bound drug in human body fluids according to the bibliographic data. The following concentrations were used: 4 mg/L for colistin, 7 mg/l for meropenem and 9 mg/L for vancomycin.

Results:

All strains were resistant to amoxicillin alone and combined with clavulanic acid, piperacillin alone and combined with tazobactam, cefuroxime, ceftazidime, cefotaxime, ceftriaxone, cefepime, gentamicin and ciprofloxacin and all except 609815 susceptible colistin.

All strains showed synergy between colistin and meropenem in checkerboard technique with FICI ranging between 0.12 and 0.24 and in time-kill studies with 3-4 log₁₀ difference in CFU reduction between colistin alone and combined with meropenem after 24 h.

None of the strains displayed synergy between colistin and vancomycin in the checkerboard technique with FICI ranging between 2 and 3.5, but the significant reduction of CFU of combination compared to colistin alone was reported in time-kill studies with *C. freundii* and *K. pneumoniae* strains (>3log₁₀).

PAE induced by colistin ranged between 2.5 and 3.5 h, but the addition of either meropenem or vancomycin did not significantly prolong the duration of PAE induced by colistin (20-30 minutes).

Conclusions:

From the clinical point of view, the improved bactericidal activity of colistin combinations with either meropenem or vancomycin could provide a rationale for the optimization of the treatment regimen and minimize the drug-induced side effects.