Efficacy of generic meropenem products in combination with colistin in carbapenemase-producing Klebsiella pneumoniae experimental osteomyelitis


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Background: The therapeutic equivalence of antibiotic generics has been challenged. We evaluated the efficacy of colistin alone and combined with the meropenem princeps (Astra-Zeneca), or different generic products (Actavis, Kabi, Mylan, Panpharma), in vitro and in vivo in, a new experimental model of Carbapenemase-producing Klebsiella pneumoniae osteomyelitis.

Materials/methods: KPC-99YC is a clinical strain intermediate to meropenem (MIC 4 mg/L), and susceptible to colistin (MIC 1 mg/L). As meropenem alone was not bactericidal on KPC99YC, the comparison of innovator and generic products of meropenem by time-kill curves were performed in combination with colistin, both at 4 MICs. Plasma antibiotic concentrations were measured in uninfected rabbits, to select doses equivalent to those used in humans (H). An osteomyelitis was induced in rabbits by tibial injection of a sclerosing agent followed by 10⁹ CFU/mL (0.2 mL) of KPC-99YC. Treatment started 14 days after inoculation, for 7 days, in 7 groups of 12 rabbits: control group, colistin 150 000 IU/kg im tid (equivalent to 3 M IU tid in H), colistin + meropenem princeps or generics, 80 mg/kg sc tid (1 g tid in H). Three days after the end of treatment, bacterial density were measured on bone homogenates, and colistin-resistant strains were checked.

Results: In vitro, meropenem + colistin were bactericidal with no remaining viable bacteria after 6 h, and this effect was similar with all compounds of meropenem. Colistin alone were not different from controls with a median (IQR) bacterial count of 5.67 (4.96, 6.16) log₁₀ CFU/g of bone and no sterile bone at D24. All generics of meropenem associated with colistin decreased bone bacterial concentrations compared to controls. There was no significant difference between the different meropenem generics and the princeps when combined with colistin. Colistin-resistant strains were detected with colistin + meropenem princeps from Astra Zeneca (n=3), generic Mylan (n=2), and Actavis (n=2).

Conclusions: In this KPC-producing K. pneumoniae experimental osteomyelitis, the efficacy of four different generics of meropenem were not different to innovator.