

TITLE: COMBINATION OF CARBAPENEMS AND [CU(PHENDIONE)₃](2+) AGAINST KPC-PRODUCING *KLEBSIELLA PNEUMONIAE*

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ABSTRACT

Klebsiella pneumoniae is one of the most important causes of health care associated infections that are related with a high mortality. Of special concern is the resistance to carbapenems, which has increased radically worldwide. Considering this situation, the World Health Organization released a priority pathogens list aiming to ensure research and development of new antibiotics. The most critical group of all includes *Enterobacteriaceae* carbapenem-resistant, evidencing the urgent need for new therapeutic approaches. Synergistic combination of new substances and classic antimicrobials seems to be a useful path to rapid development of new efficient formulations. Among the many options, phendione and its copper and silver complexes are a promising group due to their proven antibacterial, antifungal and antitumor properties. Studies on the toxicity of these compounds showed *in vivo* well-tolerance by the insect larvae of *Galleria mellonella* and also by Swiss mice. The aim of this study was to evaluate the effect of combination of carbapenems and [Cu(phendione)₃](ClO₄)₂·4H₂O (Cu-phendio) in 5 KPC-producing *Klebsiella pneumoniae* strains presenting distinct genotypes by PFGE. Previous tests verified that these strains presented MIC values for Cu-phendio of 6,25 µg/mL and for carbapenems ranging from 0,5 to 8 µg/mL. Checkerboard test was performed in a 96-well plate where meropenem (MRM) or imipenem (IMP) was serially diluted along the ordinate, while Cu-phendio was diluted along the abscissa. Synergistic activity was observed in 3 (60%) strains tested with MRM and additive effect in the other 2 strains. For IMP, additive effect was obtained for all 5 strains. The synergistic activity was obtained with combined concentrations of 2 µg/mL of MRM and 1.56 µg/mL of Cu-phendio for the 3 strains, which had alone MRM MIC of 8 µg/mL, showing a four-fold reduction. The combination of metal compounds with carbapenems showed promising results due to the presence of synergistic and/or additive activity in all tested strains, requiring concentrations of compounds substantially lower than those considered toxic to mammals. These results encourage further studies on this combination, which involves an antibiotic already used therapeutically, offering relative safety about possible toxic effects and enabling the faster development of clinical trials. Financial support: FAPES - Fundação de Amparo à Pesquisa e Inovação do Espírito Santo e CAPES.

Keywords: *Klebsiella pneumoniae*, carbapenems, KPC, Cu-phendio, checkerboard

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