**TITLE:** POST-ANTIBIOTIC EFFECT AND KILLING ACTIVITY OF CU-PHENDIONE AND AG-PHENDIONE AT DIFFERENT *IN VITRO* CONDITIONS AGAINST *ACINETOBACTER BAUMANNII* MDR CLINICAL STRAINS

**AUTHORS**: PEREGRINO, I. V.; AMORIM, L. F. V. S.; VENTURA, R. F.; SANTOS, A. L. S.; NUNES, A. P. F.

**INSTITUTIONS:**
[1]UNIVERSIDADE FEDERAL DO ESPÍRITO SANTO – UFES (AV. MARECHAL CAMPOS, 1468, CEP 29.040-090, VITÓRIA – ES), [2]PROGRAMA DE PÓS-GRADUAÇÃO EM DOENÇAS INFECCIOSAS – PPGDI, UFES (AV. MARECHAL CAMPOS, 1355 - SANTA CECÍLIA. 29043-260 VITÓRIA-ES), [3]UNIVERSIDADE FEDERAL DO RIO DE JANEIRO – UFRJ (AV. CARLOS CHAGAS FILHO, 373, RIO DE JANEIRO - RJ, 21941-590), [4]INSTITUTO DE MICROBIOLOGIA PAULO DE GÓES – IMPG, UFRJ (CIDADE UNIVERSITÁRIA DA UNIVERSIDADE FEDERAL DO RIO DE JANEIRO, RIO DE JANEIRO - RJ, 21941-902).

**ABSTRACT:**
Over the past years, our research group has demonstrated that phendione-based compounds are potential new therapeutics to treat multidrug-resistant gram-negative infections. In the process of evaluating the activity of these compounds, the simple determination of MIC and MBC values proved to be incomplete. The clinical relevance of more complex *in vitro* tests of antimicrobial activity is increasingly recognized, since they describe more precisely the course of antimicrobial activity. So, the pharmacodynamics of Cu-phendione and Ag-phendione on six *A. baumannii* MDR (MDR-Ab) clinical strains and the reference strain ATCC 19606 were investigated. We determined the effect of CFU concentration on MIC, applying inocula ranging from $10^4$ to $10^8$ CFU/ml. Bacterial time-kill assays (TKA) were performed at different conditions, revealing the rates of bacterial killing, the effects of sub-MIC, increasing concentrations and fractionated dosing. And finally, we investigated the postantibiotic effect (PAE). Our results demonstrated that increasing concentrations of CFU do not directly affect the MIC values of the compounds, since 100-fold increments in the inoculum did not modify the MIC in all six clinical strains. Both compounds, at a concentration of 3.12 µg/ml, were able to eradicate more than 97% of the tested inocula. TKA showed bactericidal effects at low concentrations and more time-dependent than dose-dependent killing. These findings suggest that the study compounds: 1) have a mechanism of action related to a stable interaction with their target sites, leading to saturation of these; or 2) need to enter the bacterial cell, being conditioned to a permeability limit. It was also demonstrated that application of ½× MIC, followed by reapplication after 6h, exert a bactericidal effect after 9-12h of testing and eradicate all strains within 24h. These findings suggest the efficacy of treatments with sub-inhibitory concentrations, administered continuously. The results of PAE assay, performed with Cu-phendione in three clinical strains, showed recovery growth rate similar to the maximum growth rate of these strains under compound-free condition, meaning that Cu-phendione has only a short PAE against MDR-Ab. The data obtained demonstrate the potential of Ag-phendione and Cu-phendione as drug candidates, as they exhibit convenient pharmacological properties and exert potent antimicrobial effects against MDR-Ab clinical strains. Financial support: CAPES, FAPES and CNPq.

**Keywords:** *Acinetobacter baumannii* MDR; metal-compounds; pharmacodynamics; postantibiotic effect.

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