TITLE: MUTANT PREVENTION CONCENTRATION OF POLYMYXIN B PLUS MEROPENEM AGAINST CARBAPENEM-RESISTANT *Acinetobacter baumannii*

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ABSTRACT:

The increase in the prevalence of *Acinetobacter baumannii* resistant to Carbapenem has been a global concern. Determining the Mutant Prevention Concentration (MPC) is a parameter that aims to prevent the emergence of resistance during antimicrobial treatment. According our best knowledge, there are no studies evaluating the antimicrobial activity of Polymyxin B (PMB) plus Meropenem (MEM) by method for MPC testing. The objective of this work was to determine the Minimum Inhibitory Concentration (MIC) and MPC values of PMB and MEM alone and in combination against five clinical isolates of *A. baumannii* resistant to carbapenem (two sensitive and three resistant to PMB) and against *A. baumannii* ATCC 19606. The MIC of PMB was determined using the agar dilution technique according to the protocols for determining antimicrobial sensitivity proposed by the Clinical and Laboratory Standards Institute. The MPC was measured by the same agar dilution strategy for determinations of MIC, however, reaching a bacterial concentration of 10^{10} CFU/mL. MIC and MPC were determined in Mueller Hinton Agar plates containing different concentrations of antibiotics alone and in combination. There were calculated fractional inhibitory concentration index (FICI) and fractional mutant prevention concentration index (MPCI), where FICI=MICA+B/MIC + MICB+A/MICB and MPCI= MPCA+B/MPCA + MPCB+A/MPCB. The FICI and MPCI was interpreted as follows: index ≤ 0.5, synergistic; 0.5 < index ≤4, indifferent and index >4, antagonistic. For MEM the MPC values were 2 to 3-fold higher than MIC, revealing MICs between 4 and 64µg/ml and MPCs between 16 and >512 µg/ml. For PMB, MPC was 1 to 6-fold higher than MIC, showing MICs between 1 and 32 µg/ml and MPCs between 4 and >256 µg/ml. In the combination of PBM and MEM, about two-thirds of the isolates, presented FICI<0.5 with MIC reduction ranged from 1 to 2-fold for MEM and 2 to 7-fold to for PMB. All isolates exhibited MPCI <0.5 and MPC reduction ranged from 2 to 4-fold for MEM and 4 to 10-fold for PMB. Our results indicate a risk of growth of mutant colonies at concentrations higher than MIC when the inoculum is high, which might suggest the possibility of therapeutic failure in these cases. Although it is an in vitro study we believe that the present findings indicate a potential antimicrobial combination to treat infections caused by *A. baumannii* resistant to multiple antimicrobials, considering the values of MIC and MPC.

Keywords: *Acinetobacter baumannii*, Mutant Prevention Concentration, Polymyxin B, Meropenem

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