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P1678 In vitro and in vivo activity of the manganese carbonyl complex [Mn(CO)3(bqpa-k3N)]Br alone and in combination with polymyxin B against multidrug-resistant clinical isolates of Acinetobacteri baumannii

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Background: *Acinetobacter baumannii* is an important nosocomial pathogen; frequently multidrug-resistant (MDR) and causes infections, often with high mortality rates, due to limited therapeutic options. With few anti-Gram-negative antibiotics under development, novel therapies are urgently required. Manganese carbonyl complexes show potential as antimicrobials and act synergistically with licensed antibiotics. The aim of this study was to determine *in vitro* and *in vivo* efficacy of the novel manganese carbonyl complex $[Mn(CO)_3(bqpa\text{-}\kappa^3N)]Br$ (bqpa = bis(2-quinolylmethyl)(2-pyridylmethyl)amine) alone and in combination with polymyxin B against MDR *A. baumannii* strains.

Materials/methods: Minimum inhibitory combinations and *in vitro* kill kinetics of $[Mn(CO)_3(bqpa\text{-}\kappa^3N)]Br$ alone and in combination with polymyxin B were performed over 24 h against MDR *A. baumannii* strains. The effect of $[Mn(CO)_3(bqpa\text{-}\kappa^3N)]Br$ – polymyxin B combinations on mortality and morbidity was assessed in the insect model *Galleria mellonella*. Larvae were injected via a proleg, with overnight cultures of *A. baumannii* diluted to 10^5 CFU/larvae, before administering phosphate buffered saline (PBS), $[Mn(CO)_3(bqpa\text{-}\kappa^3N)]Br$, polymyxin B or a combination of both compounds. Larvae were scored for melanisation (scale: 0-4) and for mortality over 96 hrs. All assays were performed in triplicate.

Results: Minimum inhibitory concentrations (MICs) of 128-256 µg/mL were observed for $[Mn(CO)_3(bqpa\text{-}\kappa^3N)]Br$. However, in the presence of polymyxin B this was dramatically reduced (1-8 µg/mL). Kill-kinetic assays revealed no difference in colony forming units/mL at 24 h after monotherapy with $[Mn(CO)_3(bqpa\text{-}\kappa^3N)]Br$ (0.5 MIC), polymyxin B (0.25 MIC) or no drug control. However, combination therapy with both agents was bactericidal, resulting in total bacterial killing at 2-6 h. *In vivo* survival rates after monotherapy with $[Mn(CO)_3(bqpa\text{-}\kappa^3N)]Br$ was 55% (0.5 MIC), 36% with polymyxin B (0.25 MIC) and 22% with PBS. However, combination therapy significantly increased (*t*-test; $p = <0.05$) larval survival at 96 h to 83%. Morbidity was also lower in combination treated larvae.

Conclusions: Combinations of $[Mn(CO)_3(bqpa\text{-}\kappa^3N)]Br$ and polymyxin B show potential for the treatment of infections caused by MDR *A. baumannii*. Significant increases in *Galleria* survival were observed after treatment with combination therapy over monotherapy. This is the first report detailing where this novel organometal-drug combination has shown to produce significant *in vitro* and *in vivo* antibacterial activity.