EV0071

ePoster Viewing

Antimicrobials: antimicrobial PK/PD, pharmacogenomics, pharmacoeconomics and general pharmacology, drug interaction studies

Pharmacokinetic/pharmacodynamic modelling of the quickly occurring and reversible adaptive resistance of *Pseudomonas aeruginosa* to colistin using a bioluminescent strain *in vitro*

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Objectives: The pharmacodynamics of antimicrobial agents is usually studied by observing changes in viable counts of colony forming units (CFU) over time in the presence of a range of drug concentrations. Bioluminescence is a non-destructive, real-time reporter of bacterial metabolism that can be used to monitor the effect of antimicrobials much more easily than by counting CFU. The aim of this study was to use bioluminescence imaging to investigate the pharmacodynamics of colistin on an isolate of *P aeruginosa*.

Methods: A strain of *P. aeruginosa* rendered bioluminescent by the luxCDABE operon was used (CNRS GDR3171, Besançon, France). A first set of kill curves was conducted in triplicates with an initial bacterial suspension at $5x10^6$ CFU/mL in Muller-Hinton broth, and colistin concentrations at 0, 0.5, 2, 4, 16, 32 and 64 µg/mL. Bioluminescence was measured by a luminometer (IVIS, Caliper Life Sciences, Hopkinton, MA) at 0, 2, 5, 8, 24 and 30h. Bacteria in the regrowth phase after being exposed to 2 µg/mL of colistin over 30h, were washed and plated on drug-free agar for a washout period of 0, 18, 42 or 66h before a new series of kill curves was performed with colistin concentrations ranging from 0 to 512 µg/mL. Bioluminescence data were log-transformed and fitted using NONMEM7.

Results: Without prior exposure to colistin, an initial decay of bacterial load was followed by regrowth for colistin concentrations up to 16 µg/mL. After being pre-exposed to 2 µg/mL of colistin for 30h, bacteria were able to regrow in the presence of colistin concentrations up to 256 µg/mL, but this resistance acquired during initial exposure to colistin was reversed after washout periods. Colistin effect and resistance appearance were satisfactorily modelled with an Emax model and a “binding model” respectively (1).

Conclusion: A reversible adaptive resistance of *Pseudomonas aeruginosa* to colistin was properly described using bioluminescence imaging and mathematical PK-PD modelling.

1. Mohamed AF et al. Antimicrob Agents Chemother .2012; 56, 179-188.