432d Modeling of Microbial Population Response to Antimicrobial Agents: a High-Throughput Drug Development Tool

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Before clinical investigations in humans, various in-vitro (e.g. hollow-fiber) and animal infection models are often used to demonstrate antimicrobial activity of new compounds. However, initial choice of dosing regimens to be tested in these pre-clinical studies is poorly guided and often empirical (mostly trial-and-error). Pharmacodynamic modeling can be used as a decision support tool to facilitate rational dosage design. It emphasizes the fact that effective antimicrobial treatment is attributed to neither antimicrobial agent exposure nor pathogen susceptibility alone, but rather a complex interplay of both factors. Mathematical modeling and computer simulation of microbial response to antimicrobial agents hold great promise in accelerating / improving the development of antimicrobial agents. They have the capability to perform comprehensive screening of a large number of agent candidates to guide highly targeted testing. Only promising agents and dosing regimens with high probability of success would be subsequently investigated in (pre-) clinical studies. Investigations of agents predicted to have limited clinical utility will be abandoned, avoiding unnecessary use of resources. Consequently, the efficiency and cost-effectiveness of drug development will be enhanced. A prototype model has been developed and experimentally validated with an in-vitro infection model. We have further developed our model to enhance its ability to predict microbial response to fluctuating pharmacokinetic (PK) profiles, which are more realistic than the constant-concentration profiles used in standard time-kill studies. Tests were performed on Pseudomonas aeruginosa (PA) using meropenem (a carbapenem antibiotic). Standard time-kill data of PA exposure to meropenem concentrations of 0.25, 1, 4, 16, 64 times the minimum inhibitory concentration (MIC) over 24 hours were used to fit model parameters. The model was subsequently used to predict microbial response to fluctuating meropenem profiles over 5 days. Various meropenem pharmacokinetic profiles were investigated, corresponding to periodic meropenem injection, with the maximum concentration and injection period varying, while keeping the total amount administered constant. The experimental system used to implement the pharmacokinetic profiles was an in-vitro hollow fiber infection model (HFIM). The model was fairly accurate in qualitatively predicting bacterial response to various pharmacokinetic profiles over 5 days. Such predictions hold great promise as a high-throughput screening tool to guide targeted investigation of dosing regimens in (pre-) clinical studies. Research is in progress to further validate the mathematical model predictions in an animal infection model. It is anticipated that further research is necessary to further refine the model before it can be adopted for routine use in antimicrobial agent development.