J Drug Metab Toxicol 2018, Volume 9
DOI: 10.4172/2157-7609-C1-012

The hollow fiber infection model: Principles and practice

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Emerging antibiotic resistance presents a serious global health threat. Two million people in the United States were infected with antibiotic resistant bacteria in 2014 and more than 20,000 died as a direct result of these infections, many more from complications. Antimicrobial resistance has been identifed as one of the three greatest threats to human health. Antibiotic discovery and development requires static susceptibility testing to screen compounds, *in vitro* pharmacodynamics/pharmacokinetic (PK/PD) studies to model drug dynamics and efficacy, and testing in animal models to provide critical information prior to the clinical evaluation of new antibiotics. The one compartment PK/PD model typically consists of an open central reservoir containing the organism of interest, a source of diluent and a waste reservoir. 1) open system, not bio safe 2) bacteria numbers change over time 3) large volume requires large amount of drug and diluent and; 4) rapid changes in drug concentration not possible, cannot model short half-lives. Animal models have many shortcomings though they have served as a primary development tool for many years: 1) PK/PD may not match human values 2) cannot sample same animal over time 3) difficult to study large numbers of bacteria to reveal resistance and; 4) many infections cannot be modeled in a mouse or other animal. To address these shortcomings the two-compartment *in vitro* pharmacokinetic model utilizing hollow ber bioreactors was developed, the Hollow ber infection model (HFIM). The advantages of the HFIM are as follows: 1) closed, bio-safe system 2) large number of organism can be tested, revealing resistance 3) precisely simulates human PK/PD 4) repetitive sampling over time, both drug and organism 5) total kill can be determined 6) single use, disposable, reproducible 7) two drug models can be tested 8) can model both dosing curve and elimination curve and; 9) can look at bacteria in different growth phases and in combination with cells. The clinical utility of the HFIM has been demonstrated and is now endorsed by the EMA. An overview of historic pk/pd models is presented and the utility of the system as it relates to antibiotics and other drugs are discussed.

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