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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 require 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 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; few of them are as follows: 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; 4) Many infections cannot be modeled in a mouse or other animal. To address these shortcomings, the two-compartment *in vitro* pharmacokinetic model, the hollow fiber infection model (HFIM) utilizing hollow fiber bioreactors was developed. 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.

Biography

John James Stewart Cadwell received his Degree in Pharmacology from the University of Miami in 1981. He spent additional time studying at the University of Nottingham and the National Institute of Medical Research at Mill Hill, U.K. In 2000, he founded FiberCell Systems Inc., a company specializing in the research and supply of hollow fiber bioreactors. He has over 10 publications in the field and three patents relating to hollow fiber systems and is considered a World Expert in the field.

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