

Role of pharmacokinetics in early stages of antimicrobial development

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The importance of diligent pharmacokinetic (PK) profiling in the early drug research and development stages to reduce late attrition rate has been increasingly recognized over the last decade and major advances have been made. Based on the results of ADME screening (absorption, distribution, metabolism, and excretion) during the lead optimization phase, relevant predictive information on the pharmacokinetic behavior of a preclinical candidate is typically obtained in two or three animal species before administration to humans. The preclinical PK assessment provides the input for in vitro and in vivo PK/PD (pharmacodynamic) models that evaluate exposure-effect relationships. Such PK/PD models are powerful tools for dose selection for the clinical phases of drug development. If phase 1 PK data are available, population based PK/PD models support effectively dose selection for late stage clinical trials. Moreover, a PK/PD guided approach can provide decision support for susceptibility breakpoints as well as strategies to mitigate resistance development. Recent late stage clinical failures illustrate the importance of understanding the impact of PKs such as protein binding and concentrations at infection sites and incorporating them early into adequate PK/PD evaluations.

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