Dose Optimization of Anti-infective Agents - On Earth and in Space

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Scope of the lecture:

The presentation will feature a number of recent examples from our group where we contributed to dose optimization and development of anti-infective agents. The examples will include some recent work in collaboration with NASA to explore if doses of antibiotics will need to be modified on the planned mars missions.

Learning objectives:

1. Microdialysis is an excellent technique for experimental target site measurement
2. MICs or PK/PD-indices based on MIC are inadequate
3. Integrated modeling of unbound target site concentrations and kill curve data allows for dose optimization

Extended abstract:

The cost of anti-infective drug development can be dramatically lowered by applying pharmacometric concepts and selection of some key experiments based on pharmacokinetic/pharmacodynamic (PK/PD) concepts to identify the dose most likely to be successful in Phase 3 clinical trials. In the vast majority of pharmacokinetic studies, plasma or serum concentrations are measured under the assumption that they represent good surrogates for drug concentrations at the target site. Furthermore, they are easy to obtain. However, these concentrations may not be the most appropriate parameters to characterize drug exposure at the target site. First, the use of serum concentrations does not consider protein binding when total drug concentrations are used. Furthermore, for most drugs, the site of action is not in the blood but somewhere in the tissue. 'Total tissue concentrations' which are derived from tissue biopsies are sometime used to address this issue. However, these concentrations are hybrid numbers which do not reflect the pharmacologically active free drug concentrations at the infection site. Also, the commonly used approach of tissue partition coefficients to quantify tissue concentrations is not acceptable since it implies homogenous distribution of drug in the tissues. Microdialysis allows measurement of unbound drug concentrations in the extravascular space without damaging the surrounding tissue. In this way, differences between total plasma and free extracellular fluid concentrations can be monitored. A number of recent examples will be presented where these unbound concentrations in extracellular fluids in the tissues produce more appropriate pharmacokinetic input parameters for PK/PD models than serum concentrations. This is particularly true if the target site is the extracellular fluid as it is the case for the vast majority of anti-infective agents. Further examples include the use of microdialysis for large molecules with specialized probes, fluid-neutral drug level monitoring in neonates, lung microdialysis in patients with multi-resistant tuberculosis, use of microdialysis in preclinical drug development of drugs to treat leishmaniasis and impetigo as well as methodological issues related to the assessment of topical bioequivalence and unbound intracellular concentrations. Combined with target-site concentrations,

pharmacodynamic activities can be much better captured by analyzing time-kill curves rather than simple minimum inhibitory concentrations (MICs). The use of the MIC has been a major obstacle for fully using all available data in anti-infective pharmacology. MIC is imprecise as it is measured in twofold increments. It is monodimensional and only assessed at one time-point. MIC does not disclose any information about the maximum kill rate since it is defined by reaching visible growth, independent of maximum kill rate. This is a fundamental difference to EC50 which is defined as the concentration that produces half-maximum effects. There are many situations where the use of MIC is grossly inadequate but the field has been creative in inventing 'patches' (post-antibiotic effect, sub-MIC effect) that are widely accepted without rationale. Kill curve measurement can be shown to provide much more detailed information about the quantitative concentration-effect relationships. Examples from various classes of antibiotic drugs will be presented where these concepts are applied and illustrated. Application of these concepts will help to develop new anti-infective treatments at low cost to combat resistance development with optimum efficacy and safety. MIC is seen as a threshold value that results from the inability of our brains to integrate multiple simultaneous quantitative relationships. In the old days these situations were often resolved by gut-level decisions. If it gets too complicated we like to draw a line to visualize 'how much we need'. Fortunately, we do now have computers that can aide us in making better and explicit decisions. Appropriate computer software and apps are currently being developed that will make the applications of these PK-PD concepts user friendly and easy to implement [1-14].

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