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MEETING ABSTRACT

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Dose optimization of antibacterials: plasma *vs*. tissue concentrations

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Background: The outcome of antibiotic treatment depends on several complex interactions between the infectious agent, the antimicrobial drug and host defence mechanisms, and treatment outcome shows high variability of the dose–response relationship.
Methods: A thorough search of available databases using the terms "antibacterials", "antibiotics", "PK/PD", "dose optimization".
Results: Dosing regimens for antibacterials should be designed using integrated pharmacokinetic/pharmacodynamic approaches especially in case of serious systemic infections and in certain groups of patients whose present condition may influence the usual activity of antibacterial drugs. Knowledge of antibiotic pharmacokinetic and pharmacodynamic properties can help clinicians in choosing antibiotic and dosing regimen that are linked to the highest likelihood of treatment success. Three measures of drug exposure are commonly used to link drug exposure with bacterial killing: the fraction of the dosing interval that the concentration of unbound (free) drug is greater than MIC, the ratio of the area under the unbound drug concentration–time curve to the MIC, and finally the ratio of the peak unbound-drug concentration during a dosing interval to the MIC. However, as the PK/PD indices are based on plasma concentration, for antibiotics that do not penetrate into site of the infection sufficiently, the pharmacokinetic/pharmacodynamic values may overestimate the expected efficacy. Microdialysis (μD) is an *in vivo* sampling technique that has been successfully applied to measure the distribution of antibiotics in the interstitial fluid of various tissue sites both in animal studies and clinical setting. μD enables continuous *in vivo* sampling and provides direct measurement of unbound concentration–time profile of antibacterials in the interstitial fluid.
Discussion: An antibacterial drug can exert its therapeutic action only with adequate penetration at the infection site. Multiple factors, such as rate of protein binding, drug liposolubility and organ blood flow all influence the ability of antibiotics to penetrate into target tissues. Clinical μD studies demonstrated that tissue concentrations for certain antibiotics and clinical conditions may be suboptimal despite adequate plasma levels. Standard tissue concentration measures based on tissue homogenates offer only values for total drug concertation (intracellular and extracellular) while for the majority of infections the interstitial free concentrations are relevant. Integration of μD-derived tissue pharmacokinetics with pharmacodynamic data offers crucial information for correlating exposure with antibacterial effect. Using μD-derived information for consecutive pharmacokinetic/pharmacodynamic models is increasingly becoming state-of-the-art for optimizing dosing regimens of antibiotics.
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