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IMPORTANCE OF PHARMACOKINETICS IN ANTIBIOTIC THERAPY

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Antibiyotik tedavisinde farmakokinetiğin önemi.

In patients with severe defects in host defenses, such as those with mucosal defects, neutropenia, AIDS and multiple organ system failure in the ICU, optimal dosing of antimicrobial agents assumes major importance in determining the outcome of therapy.

For beta-lactam antibiotics, there are multiple lines of evidence indicating that the time drug concentrations remain above the MIC of the pathogen involved is important in determining outcome. The laboratory of Craig et al at the University of Wisconsin has demonstrated that in mice made neutropenic with cyclophosphamide and infected with a variety of pathogens (e.g, *Streptococcus pneumoniae, E.coli* and *Pseudomonas aeruginosa)* that the time concentrations of various beta-lactams exceeded the MIC of these pathogens was directly related to the change in the numbers of organisms at the primary infection site.

This finding was confirmed in clinical patients at the University of Maryland, where the outcome for ten patients with a single organism Gram negative rod bacteremia was correctly predicted in nine instances by examining the time drug concentrations exceeded the MIC. Likewise, Schentag and colleagues were able to demonstrate a linear relationship between increasing time above the MIC and the rapidity of clearance of Gram negative pathogens from the lower respiratory tract of ICU patients treated with a beta-lactam drug. Consequently, optimal beta-lactam therapy can be obtained by employing doses and schedules of drug which provide concentrations always in excess of the MIC of the infecting pathogen.

For aminoglycosides, the animal model data of Craig et al demonstrates that Area Under the Plasma Concentration-time Curve (AUC) is most closely linked to changes in the number of organisms at the primary infection site. In-vitro data developed by Blaser et al, however, indicate that peak concentration/MIC ratio was most closely linked to organism kill. This is understandable, as there is a high degree of co-variance between peak contration and AUC (i.e. for any particular half life, a higher peak must result in a higher AUC). These data were validated clinically by Moore, Smith and Lietman who demonstrated that either peak concentration or its ratio to the MIC of the infecting pathogen was closely linked to outcome. Consequently, optimal therapy is obtained by employing doses and schedules which obtain high peak/MIC ratios.

For fluoroquinolones, similar data are available. Blaser et al as well as Dudley et al demonstrated that peak/MIC ratio was also important in determining organism kill in their in-vitro model. Animal model data developed at the University of Maryland by Drusano, Johnson and Standiford indicated that peak/MIC ratio was important if a ratio greater than 8-10/1 could be obtained, but that AUC/MIC ratio was important if ratios were less than this critical point. They speculated that emergence of resistant GyrA mutants could be prevented by obtaining the higher ratios. Forrest et al were able to varify this in patients by demonstrating patients with Gram negatives in their lower respiratory tract had a relationship between AUC/MIC ratio and the time to eradication.

Clearly, different drug classes require different schedules of administration to insure optimal therapy.

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