Pharmacokinetics, Pharmacodynamics, and Monte Carlo Simulation

Selecting the Best Antimicrobial Dose to Treat an Infection

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When faced with a neonate, infant, or child with a suspected infection, the clinician must select a specific antimicrobial at a specific dose for a specific duration to treat that infection. Many issues require careful consideration, and include knowledge of the suspected pathogens and their susceptibility to the antimicrobials under consideration, the pharmacokinetic (PK) characteristics of the antimicrobials, and the clinician’s assessment of the need to achieve a cure for that particular patient (Table 1). PK and pharmacodynamics (PD) principles together with Monte Carlo simulation can assist the clinician in selecting the appropriate antimicrobial and dosing regimen. Recent advances in our understanding of antimicrobial PK and PD have lead to important insights in the parameters associated with a successful outcome, and in ways to minimize both drug toxicity and the development of antimicrobial resistance.

VARIABILITY IN PLASMA AND TISSUE CONCENTRATIONS ACROSS POPULATIONS

Given the availability of sensitive assays to measure antibiotic concentrations in plasma and various tissue sites using smaller quantities of blood or tissue fluids, our ability to assess antibiotic exposures at the tissue level, the actual site of infection, has increased. As regulatory agencies request more sophisticated antimicrobial exposure data for investigational drugs, these data are frequently collected in clinical trials and thus, are becoming more readily available for analysis. As a result, our knowledge of the PK of antimicrobials (ie, concentrations in plasma and in different tissue sites over time) and the variability inherent between patients receiving the same antimicrobial agent is better understood. Both the distribution of antimicrobials within tissue compartments and drug elimination differs by pediatric age group “populations,” from the neonate to the adolescent. Fortunately, antimicrobial PK and variability in each pediatric “population” can also be described. Children with organ dysfunction may not eliminate antimicrobials as effectively as those with normal organ function. For example, the PK of vancomycin in children with some degree of renal failure will be different than in children with normal renal function. Data from populations with organ failure are becoming more widely available, increasing our knowledge of the variability of drug elimination among those populations. The description of the statistical characteristics of the variability of antimicrobial concentrations across carefully defined populations is known as “population pharmacokinetics.”

PHARMACODYNAMICS

Our understanding of how antimicrobial agents eradicate bacteria has also increased. The relationship between the antimicrobial concentrations required at the infection site over the dosing interval to eradicate a pathogen and hence, achieve a cure, is known as pharmacodynamics. These defined exposures, indexed to the minimum inhibitory concentration (MIC) of the antimicrobial to that pathogen, have been used to evaluate the PK-PD measure that best describes antimicrobial activity for that particular antimicrobial/pathogen pair. The 3 most common PK-PD measures associated with efficacy are (1) the percent of the dosing interval that a drug concentration remains above the MIC (%T > MIC); (2) the ratio of the maximal drug concentration to the MIC (Cmax:MIC); and (3) the ratio of the area under the drug concentration-versus-time curve (AUC) to the MIC (AUC:MIC).

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For aminoglycosides (eg, gentamicin) and fluoroquinolones (eg, ciprofloxacin), the PK-PD measure that is most predictive of efficacy is one for which bactericidal activity is concentration-dependent (Cmax:MIC for gentamicin, and AUC:MIC for ciprofloxacin). In contrast, amoxicillin and other beta-lactam agents demonstrate a time-dependent pattern of bactericidal activity (%T > MIC). Therefore, when fluoroquinolone concentrations increase, the rate and extent of bacterial eradication will increase. For amoxicillin, maximal bacterial eradication occurs when infection site concentrations exceed the MIC for approximately 40% of the dosing interval. Eradication rates do not further increase as the amoxicillin concentration at the infection site increases or as the percent of time that the amoxicillin concentration is present at the infection site above the MIC increases beyond 40%. For each antimicrobial/pathogen pair, the degree of exposure described by the PK-PD measure, that is associated with a positive outcome (eg, cure), is commonly referred to as the “PK-PD target.” This can most easily be evaluated in a nonclinical system (eg, in vitro or animal infection models), but is increasingly being assessed in human clinical trials. In other words, one can now demonstrate for a patient infected by a particular organism and treated with a particular antimicrobial, the magnitude, shape, and duration of antimicrobial exposure that is likely to result in a cure.

### STATISTICAL DESCRIPTION OF ANTIMICROBIAL RESISTANCE

Antimicrobial resistance is an increasing problem. Certain bacterial species contain intrinsic resistance mechanisms that are induced as we apply antimicrobial pressure; other species have the ability to mutate quickly to develop resistance while others have the ability to acquire mechanisms of resistance from other bacteria. For a population of children who are all treated for the same infection, otitis media for example, a range of susceptibilities of otitis pathogens to each antimicrobial can be described. Published data are available on the susceptibility of *Streptococcus pneumoniae* causing ear infections in children from Kentucky to Costa Rica, to Israel. These data assist us in predicting how likely an infecting pathogen will be susceptible to each of several different antimicrobials we are considering for therapy. This variability in bacterial susceptibility to specific agents can be described and tracked as it changes over time, providing the clinician with an accurate and ongoing assessment of the likelihood of drug resistance. The distribution of MIC values for specified pathogens, considered together with the distribution of antimicrobial exposure in the population of children all given the same antimicrobial dose, is used in the Monte Carlo simulation to evaluate the probability of achieving a cure at that dose.

#### COMPUTER MODELING AND MONTE CARLO SIMULATION

Monte Carlo simulation provides a computer-based mathematical construct that can simultaneously integrate different variables such as tissue concentrations of an antibiotic and antimicrobial susceptibility, each with its own probability distribution, together with information about the PK-PD measure associated with efficacy, to estimate the likelihood of achieving the PK-PD target (and thus, the likelihood of achieving cure). With these data inputs, antimicrobial exposures associated with a particular dosing regimen for a virtual population of children (often 5000, but any number can be selected) can be simulated, determining the proportion of infected children expected to achieve the PK-PD target. The clinician compares the proportion of simulated children predicted to be cured with the proportion desired to be cured (eg, 95% of children treated for pneumococcal pneumonia should be cured when treated). Such an analysis allows the clinician to understand, given the variability in the inputs, the statistical likelihood of achieving a cure for a particular child using a particular dosing regimen.

To illustrate this concept, one can examine amoxicillin treatment of pneumococcal pneumonia. A cure is expected if amoxicillin concentrations are present in lung tissue (epithelial lining fluid) at concentrations above the MIC of the infecting pneumococcus for approximately 40% of the dosing interval. Assuming a child is infected by *Streptococcus pneumoniae* at a MIC of 2.0 mcg/mL, if the child is treated with 90 mg/kg/d divided into 2 doses, then only 65% of children will achieve the PK-PD target associated with cure; if 90 mg/kg/d is given, but divided into 3 doses (increasing the duration that amoxicillin is present in lung tissue), the chance of achieving the PK-PD target increases to about 90%. To achieve a 95% likelihood of cure in this child, a dose of about 100 mg/kg/d divided into 3 doses will be required. If pneumococcal resistance to amoxicillin increases to 4.0 mcg/mL, the percent of children who achieve the desired target will decrease, and the dose of amoxicillin will need to be increased further to achieve the goal of 95% cure. On the other hand, if resistance decreases to 0.5 mcg/mL, then an overwhelming 99.6% of children given 90 mg/kg/d in 2 doses will achieve the PK-PD target associated with cure. The Figure 1 illustrates a Monte Carlo simulation using one of many different software programs (Oracle Crystal Ball, version 11.1.1.30, Oracle Corporation). In this illustration, a 30 mg/kg dose of am-

### TABLE 1. Considerations in Antimicrobial Management of the Infected Child

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site(s) of infection</td>
<td>Consideration for how important it is to cure the infection (eg what risk is the clinician willing to accept for treatment failure)</td>
</tr>
<tr>
<td>Patient-specific plasma antimicrobial concentrations over time</td>
<td>Patient-specific plasma antimicrobial concentrations over time</td>
</tr>
<tr>
<td>Patient-specific tissue site antimicrobial concentrations over time</td>
<td>Patient-specific tissue site antimicrobial concentrations over time</td>
</tr>
<tr>
<td>Susceptibility of pathogen(s) (if cultures are positive)</td>
<td>Susceptibility of pathogen(s) (if cultures are positive)</td>
</tr>
<tr>
<td>Variability of the susceptibilities of pathogen(s) in specimens collected in the population of children being treated, if therapy is empirical</td>
<td>Variability of the susceptibilities of pathogen(s) in specimens collected in the population of children being treated, if therapy is empirical</td>
</tr>
<tr>
<td>Antibacterial spectrum of activity</td>
<td>Antibacterial spectrum of activity</td>
</tr>
<tr>
<td>Antibiotic tissue penetration characteristics</td>
<td>Antibiotic tissue penetration characteristics</td>
</tr>
<tr>
<td>Variability of antimicrobial plasma and tissue concentrations over time among children in the population being treated</td>
<td>Variability of antimicrobial plasma and tissue concentrations over time among children in the population being treated</td>
</tr>
<tr>
<td>Size of dose (mg/kg)</td>
<td>Size of dose (mg/kg)</td>
</tr>
<tr>
<td>Frequency of dosing</td>
<td>Frequency of dosing</td>
</tr>
<tr>
<td>Duration of dosing</td>
<td>Duration of dosing</td>
</tr>
</tbody>
</table>

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ticillin is given intravenously to a child in a population of otherwise healthy children. The serum concentrations over time after a single dose are evaluated against a collection of pneumococci isolated during an era of relative resistance, with approximately 20% of strains having an MIC of 2.0 mcg/mL or greater, but most being susceptible at 0.06 mcg/mL. The blue-shaded areas denote the proportion of children who will achieve serum concentrations that are above the MICs noted in the population of pneumococci, for 40% or more of an 8 hour dosing interval (3.2 hours). In this simulation of 5000 virtual children, 88% given this dose will achieve this PK-PD target and be expected experience a cure. One can also calculate the dose that would be required to achieve a cure in 95% of children, by either increasing the mg/kg dose, or by dividing the total daily dose into more frequent intervals.

Similarly, in treating a child with streptococcal pharyngitis, given the high degree of susceptibility of *Streptococcus pyogenes* to penicillins, once daily dose of amoxicillin at 50 mg/kg predicted a tonsillar antimicrobial exposure that would result in an approximately 95% of children achieving the targeted exposure for cure. In addition to predicting targets for antimicrobial/pathogen pairs for bacterial infections, population PK and PK-PD relationships have been explored for antimicrobial agents for tuberculosis, as well as for anti-infective agents for fungal and viral infections, thus permitting similar evaluations of dosing regimens using Monte Carlo simulation, as described above.

**ANTIMICROBIAL STEWARDSHIP**

Minimizing antimicrobial resistance by using the most appropriate dosing regimen for the most appropriate duration is a priority. While lowering the dose of an antimicrobial may save a healthcare system funds and decrease dose-dependent toxicity, it may ultimately lead to increased resistance, and thus, more difficult-to-treat infections that require more costly and toxic antimicrobials. Prospective data on the duration of therapy required to achieve cure without relapse is an area of great importance for future research. Some orally administered beta-lactam antimicrobials are Food and Drug Administration-approved for a 5-day treatment course of streptococcal pharyngitis. It seems logical that most beta-lactams that display similar PK-PD measures and tissue penetration characteristics should also be prescribed for no more than 5 days. However, prospectively collected data on the efficacy of a 5-day treatment course for streptococcal pharyngitis for each and every penicillin and cephalosporin antimicrobial are not available, and for generic antibiotics, such studies are not likely to be performed.

**FUTURE DIRECTIONS**

Human validation of these concepts has lagged far behind their creation. Data from in vitro systems and animal models validate the concepts, and limited retrospective data in adults with invasive infections such as pneumonia have demonstrated that, below a certain drug exposure, patients are more likely to fail treatment, whereas those whose exposures are above a certain PK-PD target, are more likely to be cured. While limited data exist for children treated for otitis media, no data yet exist for invasive infections such as pneumonia, meningitis, or osteomyelitis. As one might expect, prospective studies would require appropriate plasma and tissue site antimicrobial concentration profiling for the population studied, together with confirmation of bacterial etiology and antimicrobial susceptibility testing. Furthermore, a study design using ascending doses, in which doses and resulting exposures straddle the drug exposure “breakpoint” associated with efficacy (eg, exposures below which patients fail and above which, they are cured), is inherently unethical to perform in children. Pediatric investigators and human research committees would not knowingly administer a dose of antimicrobial to a child that is likely to fail. For the moment, animal studies remain the most widely available in vivo support to validate the outcomes of Monte Carlo simulation.

Additional PK data that provide relevant tissue concentration values are needed for a wide variety of infections. For some infections such as staphylococcal pneumonia, multiple tissue sites of infection require step-wise modeling, with each subsequent step integrating PK data from each of the different potential intrathoracic infection sites (eg, pneumonia, empyema, lung abscess, and necrotic pulmonary tissue) to account for all the sites of antimicrobial exposure. Another complexity that is difficult to
account for in Monte Carlo simulation is the polymicrobial nature of certain infections, such as complicated appendicitis, in which multiple pathogens are involved, as well as multiple tissue sites.

**CONCLUSIONS**

The use of PK-PD concepts and tools such as Monte Carlo simulation provide the best opportunity to gain insight about the most appropriate dose required to treat an infection and prevent antimicrobial resistance, while minimizing drug toxicity. As new antimicrobial agents are developed, PK-PD concepts represent a critical component for appropriate dose selection for clinical trials in different patient populations, and for pathogens of differing susceptibilities. Ongoing evaluation of the “correct dose” should be conducted in the context of changing susceptibilities of bacterial pathogens of interest.

**REFERENCES**