

Principles of Antibiotic Formulary Selection for P&T Committees

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Part 2: Pharmacokinetics and Pharmacodynamics

PHARMACOKINETICS

General Concepts

Antibiotic pharmacokinetics (PK) is concerned with the disposition of drugs in the body. Antimicrobial pharmacokinetics is concerned with absorption when the drug has an oral form and with the drug's bioavailability. When antimicrobial agents are given intravenously, the rate of the antibiotic infusion determines peak serum concentrations. Peak serum concentrations fall briefly and rapidly during the *alpha phase* of elimination. Shortly thereafter, the *beta terminal phase* of elimination is a constant decrease in antimicrobial serum concentrations over time as the drug is excreted. It is the beta phase of elimination of an antimicrobial that determines its serum half-life ($t_{1/2}$). The half-life is the amount of time that halves the concentration of a drug in the serum.

After an antimicrobial agent is absorbed into the bloodstream by any route, it is reversibly bound to serum albumin, the predominant protein in the blood. *Protein binding* is expressed as a percent, and it represents the percentage of the antibiotic that is reversibly bound to serum albumin. Antibiotics also bind to tissue sites, but protein binding varies according to the type of tissue; this facet has not been well studied.

The serum compartment, which contains the antibiotic reversibly bound to serum albumin, is transported via the circulation to all body sites. Moving along a concentration gradient, the antibiotic dissociates itself reversibly from albumin and penetrates a series of membrane barriers to reach the site of infection. After traversing a variable number of membranes, depending on the tissue being penetrated, the antibiotic becomes reversibly bound to tissue proteins. It is the *free* or *unbound* portion of an antibiotic in the serum or at the tissue level that is effective in microbial eradication.

As the concentration in the tissue decreases, more of the antibiotic, if it is available from the serum compartment, moves along a concentration gradient into the tissues. When the tissue concentration falls, the concentration gradient is reversed and the antibiotic can move back into the serum compartment until it is eliminated if it is not metabolized at the tissue level.

The dose and dosing interval recommendations are based largely on peak serum concentrations and the beta elimination half-life to determine an appropriate dosing interval. Putting these three factors together, appropriate dosing provides for the interplay of these factors, which results in a concentration for a sufficient duration at the intended target site of infection.¹⁻³

Absorption

Some antibiotics are given via the intravenous (IV) or the intramuscular (IM) route because they are not well absorbed

via the oral (PO) route. IV antibiotics achieve peak serum concentrations rapidly; IM antibiotics achieve somewhat lower serum concentrations but have more prolonged serum levels.

The absorption of orally administered antibiotics is variable. The relative absorption is termed *bioavailability* and is expressed as the percentage absorbed. High-bioavailability antibiotics (greater than 90%) are ideal for IV-to-PO switch programs, because serum/tissue levels are comparable. Antibiotics with low bioavailability (below 50%) are incompletely absorbed and are often associated with gastrointestinal side effects.^{1,2}

Route of Elimination

Most antibiotics are eliminated by hepatic or renal mechanisms. Some antibiotics are metabolized, although their precise mode of excretion is not entirely clear. Excessive amounts of drug in the serum compartment (or the amount of drug remaining after reaching tissue sites and returning to the serum compartment) are eliminated. Most antibiotics are eliminated via the kidney and are excreted into the urine as active or inactive drug, plus or minus active or inactive metabolites. Most antibiotics eliminated via hepatic mechanisms are excreted into the bile and into the feces as active or inactive drug, plus or minus active or inactive metabolites.

The mode of elimination is also important in the treatment of urinary tract infections. Most antibiotics that are renally metabolized or inactivated are excreted into the urine at high concentrations. Antibiotics that are eliminated through the kidney, for the most part, are concentrated to supraserum levels in the bladder urine. This is therapeutically useful because some organisms that may appear to be resistant to antimicrobials at the usual serum concentrations may, in fact, be susceptible in the bladder to urinary concentrations of renally eliminated antibiotics. The converse is also true: antibiotics that are eliminated hepatically (e.g., moxifloxacin HCl [Avelox®, Bayer]) usually do not achieve adequate urinary concentrations. Therefore, if a quinolone is selected to treat cystitis, then ciprofloxacin (Cipro®, Bayer), ofloxacin (Floxin®, Ortho-McNeil), levofloxacin (Levaquin™, Ortho-McNeil), or gatifloxacin (Tequin®, Bristol-Myers Squibb) should be used instead of moxifloxacin.^{1,3}

Tissue Penetration

Infectious diseases occur either in the bloodstream, as with bacteremia, or, as in most cases, in a particular organ site (e.g., the lungs) or in a target tissue (e.g., middle-ear fluid in patients with otitis media). When planning for effective antimicrobial therapy after the appropriate spectrum of coverage has been selected, we would next consider the agent's pharmacokinetic properties. Antimicrobial agents with a proper spectrum are ineffective if they cannot reach the site of infection. Hence the phrase "tissue is the issue" summarizes the importance of pharmacokinetics in antibiotic selection.

With the appropriate dosing interval used to ensure concentration at the target tissue, the chosen antibiotic must be

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administered by a route and dose that are in excess of the minimal inhibitory concentration (MIC), or M_{90} , for most of the dosing interval in order to eliminate the causative infectious microorganisms. There is a dynamic balance between the following factors:^{2,3}

- the tissue compartment, with its high concentrations
- the reversible binding to serum albumin
- the loss of antibiotic concentration across various capillary and cellular membranes
- entrance of the antibiotic into the tissue where the infection is occurring

Microbiologic Activity versus Antibiotic Concentration

Pharmacokinetic and activity relationships are also important in other clinical situations. For example, aminoglycosides have suboptimal antimicrobial activity in areas of local hypoxemia, increased cellular debris, and local acidosis. This is the case within the lungs with pneumonia and in other situations such as osteomyelitis. With respect to pneumonia, gentamicin (Elkins-Sinn) achieves high concentration in pulmonary tissue; however, it is probably not the best choice as monotherapy in pneumonia even when the infection is caused by susceptible organisms, because the activity of gentamicin and other aminoglycosides is greatly diminished in the presence of the factors explained earlier.

Vancomycin (Vancocin®, Eli Lilly) and the macrolides are large molecules that do not penetrate well into synovial fluid in patients with septic arthritis, simply because of their considerable molecular size. Other agents with an appropriate spectrum should be used in place of these agents if the infection involves the synovial fluid.²

Protein Binding

High serum protein binding (over 90%) was initially thought to be a disadvantage in an antibiotic. Conceptually, high protein binding means that the antibiotic is bound to serum proteins and is not available in the unbound (free) state to attack the infecting microorganisms. Intuitively, it would seem that antibiotics with a low protein binding (10%) have an advantage of being nearly all free and available for microbial killing. It has also been noted for many years that an increase in protein binding increases the MIC against certain organisms (e.g., *Staphylococcus aureus*) with certain antimicrobials. All of this suggests that low protein binding is preferable. Actually, however, the answer to the question depends on the achievable serum concentrations. For example, when cefazolin (e.g., Ancef®, Glaxo-SmithKline), which is 86% protein-bound, is compared with cephadrine (Velosef®, Apothecon), which is 10% protein-bound, cefazolin on a gram-for-gram basis achieves higher blood serum concentrations than does cephadrine. The serum concentrations after administration of 1 g of cefazolin (approximately 200 mg/ml) are sufficient to saturate the albumin-binding sites in the serum compartment and to still have an excess of free drug available in the serum for penetration into tissue sites. If we measure the amount of free antibiotic of cephadrine versus cefazolin in tissue using a 2-g (IV) dose for each as a comparison, the free levels with cefazolin are still higher than with cephadrine.

Therefore, protein binding of antibiotics is not a clinically relevant issue as long as the serum concentrations are high. This is also true with ceftriaxone, which has high protein binding, and yet, among third-generation cephalosporins, achieves very high serum levels of approximately 250 mcg/ml after a 1-g (IV) dose. Furthermore, high-protein antibiotics such as cefoperazone (Cefobid®, Pfizer) and ceftriaxone might have an additional advantage. The high-protein binding to serum albumin acts as an “antibiotic reservoir” and reversibly releases antibiotics from the binding sites as serum and tissue concentrations decrease. This represents the equivalent of a depot formulation of an antibiotic that slowly releases antibiotic back into circulation after serum concentrations have fallen from serum-binding and tissue-binding sites.

In general, then, protein binding for most infectious diseases is not an issue, provided that serum concentrations are sufficiently high to provide adequate amounts of antibiotic to be effective and to eradicate the infection in the blood.^{2,3}

Volume of Distribution

The volume of distribution (V_d) represents the “apparent” volume into which an antibiotic is distributed. This value is derived by the amount of antibiotic in the body divided by the serum concentration (L/kg). The V_d is related to total body water distribution ($V_d \text{ H}_2\text{O} = 0.7 \text{ L/kg}$). Water-soluble (*hydrophilic*) antibiotics are limited to extracellular fluid and have a V_d of 0.7 L/kg or less. Highly soluble (*hydrophobic*) antibiotics penetrate most body tissues well because of their large V_d . Most tissues are rich in lipids and are well penetrated by drugs with a high V_d .

The V_d can be affected by organ perfusion, lipid solubility, protein binding, and membrane diffusion or permeability. It can be increased in certain patient subsets with hydrophilic drugs, such as patients receiving dialysis, those with cirrhosis, those undergoing mechanical ventilation, patients with burns, or patients with heart failure. Decreases in the V_d for hydrophilic drugs can occur with pancreatitis, early loss of gastrointestinal fluid, trauma, or hemorrhage. Increases in the V_d may require increased daily antibiotic dosing to maintain drug effectiveness, and decreases in the V_d resulting from various pathological states may require a decrease in drug dosing.^{1,3}

Concentration-Dependent Susceptibility

Susceptibility is concentration-dependent; the usually recommended dose is not only optimal for achieving therapeutic serum and tissue concentrations but is also necessary to achieve the full therapeutic effect. The killing of organisms can be represented as a sigmoid curve of concentration versus the percentage of susceptible organisms.

As an example, the usual dose of cefoxitin is 2 g (IV) every six hours. Some prescribers have tried to decrease the cost of antimicrobial therapy by decreasing the dose. Unfortunately, this measure also decreases the activity of the drug against the organism in its usual spectrum. Thus, given the 2-g (IV) dose of cefoxitin, approximately 85% of *Bacteroides fragilis* organisms would be inhibited. If the dose were cut to 1 g, however, only 15% of *B. fragilis* isolates would be inhibited. This is an inadequate amount if cefoxitin (Mefoxin®, Merck) is being used to treat an intra-abdominal or pelvic infection.²

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Clinical Application of Pharmacokinetics

The pharmacokinetic parameters are essential for the optimal dosing of antibiotics. The usual recommended dose takes into account pharmacokinetic factors and represents the best dose for most pathogens at most body sites in normal adult patients. Some patients and infections in certain body sites, however, may warrant dosing modifications. For example, penetration into the central nervous system requires drugs with different physicochemical characteristics or dosing modifications to achieve therapeutic concentrations in the cerebrospinal fluid. Drugs that can be used in the usual dose to treat central nervous system infections include chloramphenicol, because of its high lipid solubility, and doxycycline (Vibramycin® Calcium, Pfizer), minocycline (Dynacin®, Medicis), linezolid (Zyvox™, Pharmacia & Upjohn), and TMP-SMX (trimethoprim-sulfamethoxazole [Bactrim®, Roche; Septra®, Monarch]).

Another example is ceftriaxone sodium (Rocephin®, Roche), an antibiotic with high serum levels that, even when given in the usual dose, penetrates the cerebrospinal fluid in adequate concentration. Other drugs require a higher than usual dose to achieve adequate concentration in the cerebrospinal fluid, for example:

- cefepime (Maxipime®, Elan): usual dose, 2 g IV every 12 hours; meningeal dose, 2 g IV every eight hours
- meropenem (Merrem®, AstraZeneca): usual dose, 1 g IV every eight hours; meningeal dose, 2 g IV every eight hours

Most other antibiotics do not penetrate the cerebrospinal fluid regardless of the dose given (e.g., cefazolin).¹⁻³

PHARMACODYNAMICS

Pharmacodynamics (PD) takes off where pharmacokinetics leaves off. Whereas pharmacokinetics concerns the disposition, metabolism, and elimination of antibiotics in the body, pharmacodynamics involves the effects of antibiotics when drug concentrations are subtherapeutic or nonexistent.

The after-effect of an antibiotic after it is no longer present in adequate serum or tissue concentrations has been called the *post-antibiotic effect*. This effect was first noted decades ago by Eagle.⁴ He described the inhibitory effects of penicillin long after it was no longer pharmacologically available to account for an effect on the susceptible bacteria. The *Eagle effect* (now renamed the post-antibiotic effect) differs for gram-positive and gram-negative organisms and varies with the antibiotic being used. Both pharmacokinetic and pharmacodynamic properties should be considered for optimal therapeutic effect.⁴⁻⁶

Concentration-Dependent and Time-Dependent Killing

Over the years, it has been established that antibiotics exert their optimal effect on susceptible microorganisms either as a function of concentration over the MIC or as a function of time over the MIC. Antibiotics that kill optimally at high concentrations have what are called *concentration-dependent* killing kinetics (i.e., the higher the concentration, the more effective

the microbial eradication). Other antibiotics kill by *time-dependent* (non-concentration-dependent) killing kinetics. With these antibiotics, as long as the concentration is maintained slightly above the MIC over time, killing is maximal.

With time-dependent killing antibiotics, there is no advantage to high serum concentrations, as killing is not increased. For concentration-dependent antibiotics, the pharmacokinetic parameter that best describes this relationship is a ratio of the peak serum/tissue concentration over the MIC₉₀ of the organism in question. This has been termed a *kill ratio* or *inhibitory index*; the higher the ratio, the more optimal killing with an antibiotic that utilizes concentration-dependent killing kinetics.

Conversely, an antibiotic that demonstrates time-dependent killing, the time above the MIC, is the key pharmacokinetic parameter. Alternatively, the serum concentration under the blood time curve has been called the *area under the curve* (AUC). AUC-to-MIC ratios are applied to time-dependent killing antibiotics. Their clinical significance has yet to be demonstrated *in vivo*.

Another factor, the *subinhibitory* concentration of antibiotics, is difficult to measure *in vivo* but has been well studied *in vitro*. Subinhibitory concentrations of an antibiotic impair either cell membrane or cell wall synthesis, or they affect the intracellular metabolic mechanisms to inhibit bacteria for various periods of time. The effect of subinhibitory concentrations of antimicrobials may make affected microorganisms more susceptible to host defense mechanisms (e.g., serum complement and phagocytosis).

Optimal ratios for concentration-dependent antibiotics vary according to the antibiotic and the susceptible organisms, but a ratio of 10:1 is a useful general guideline for optimal activity with concentration-dependent drugs (e.g., vancomycin and the aminoglycosides). The AUC/MIC ratios have applied to beta-lactams, macrolides, and fluoroquinolones, particularly against respiratory pathogens, such as *Streptococcus pneumoniae*.^{5,6}

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COMING NEXT MONTH:
Principles of Antibiotic Formulary Selection
Part 3: Antibiotic Resistance