Mechanism of Actions of Anti-bacterial Agents

Anti-bacterial drugs work by exploiting differences between mammalian and microbial physiologic processes. Since bacteria, unlike mammals, have cell walls, many anti-bacterial agents work by binding to components of the cell wall or inhibiting the synthesis of the cell wall. These agents include the beta-lactam and glycopeptide antibiotics. Other anti-bacterial agents function by exploiting differences in DNA replication (the quinolones inhibit DNA gyrase that are used in bacterial replication) or transcription (rifampicin). Still other agents exploit differences in the translational process, as bacteria use ribosomes that are different from mammalian ribosomes. The macrolides, tetracyclines, and aminoglycoside antibiotics exert their anti-bacterial effects by binding to different components of the bacterial ribosome. Still other anti-microbial agents such as the sulfonamides function by exploiting differences in the metabolic pathways between mammals and bacteria. Since bacteria are unable to use folic acid but must synthesize it from para-aminobenzoic acid, drugs that inhibit this pathway will selectively inhibit bacterial growth without toxicity to mammalian cells (see Fig. 2.1).

Role of Pharmacokinetics and Pharmacodynamics in the Management of Bacterial Infectious Diseases

The minimal inhibitory concentration (MIC) for anti-microbial agents is the concentration at which the drug inhibits growth of the organism in vitro. Historically, the doses of anti-bacterial agents for use in humans have been chosen based on the MIC of the drug for the specific pathogen being treated. Drug levels are typically measured in human serum. However, dosing based solely on MIC may not be appropriate since MICs of certain pathogens labeled as “susceptible” can be higher than peak serum concentrations of some of the anti-microbial agents. Factors such as
specific anti-microbial agent, pathogen, and individual patient play an important role in achieving the desired outcome. Most importantly, inadequate serum concentrations at the site of infections may lead to anti-microbial resistance (Fig. 2.2).

Pharmacokinetic (PK) and pharmacodynamic (PD) principles are the tools used to optimize anti-microbial therapy for individual patients. PK and PD studies help us to understand factors such as the onset, magnitude, and duration of drug response that allow for optimization of specific therapies. PK and PD determine how much

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**Fig. 2.1** Mechanism of action of anti-bacterial agents

**Fig. 2.2** Peak serum concentration over time
Role of Pharmacokinetics and Pharmacodynamics in the Management…

and how often a drug should be administered. One can think of PK as “what the body does to the drug” and PD as “what the drug does to the body.” The integration of PK/PD helps to assess the interactions between a pathogen, host, and anti-microbial agent.

The pharmacokinetic (PK) profile of a drug describes its absorption, distribution, metabolism, and elimination. The PK defines the time course of drug concentrations in the body, tissues, and fluid. In essence, PK tells us how drug concentrations in the body change over time after administration of a dose. The parameters involved include: bioavailability (proportion of drug absorbed into the systemic circulation after drug administration; intravenous drugs are 100% bioavailable and other forms are mostly less bioavailable); minimum serum concentration of drugs ($C_{\text{min}}$); peak serum concentration of a drug following administration of a dose ($C_{\text{max}}$); time to peak serum concentration ($T_{\text{max}}$); volume of distribution ($V_d$ – a relative measure of distribution of a drug throughout the body); area under serum concentration–time curve (AUC); elimination half-life ($T_{1/2}$ – time required for serum concentration reduced by 50%); and amount of time serum concentration above the minimum inhibitory concentration ($T > \text{MIC}$) (see Fig. 2.3).

The pharmacodynamic profile (PD) describes the impact of anti-microbial plasma concentration and response. It describes the effects of an agent on human cells and the pathogen. Interestingly, the body of knowledge in PD is limited
relative to the PK studies, which can easily be determined. Drug concentrations in plasma are monitored at different times which can be used to determine the primary PK parameters such as clearance and volume of distribution. On the other hand, the study of PD is difficult since it is hard to determine objective, precise ways to quantify drug response. PD parameters include the time that a drug’s serum concentration remains above the MIC for a dosing period (T > MIC), ratio of the maximum serum antibiotic concentration to MIC (C_{max}/MIC) and the area of the concentration time curve during a 24-h time period (AUC) divided by the MIC (AUC/MIC). Some agents continue to exhibit bactericidal effects even after clearance of the agent from the infected site. These post-antibiotic effects (PAE) have been observed with inhibitors of nucleic acid and protein synthesis (including aminoglycosides – see Chap. 9, and quinolones – see Chap. 12) and with beta-lactams against *Staphylococcus aureus*. Nucleic acid and protein synthesis inhibitor agents with significant PAE prevent pathogen growth even after serum concentrations fall below MIC.

Combined use of PK and PD helps us to optimize effective use of an antimicrobial agent. Integrated use of PK and PD data provides a rational basis to understand the impact of various dosage regimens on the time course of pharmacologic responses. It provides information on the effective dose and duration of therapy of a specific agent against a specific pathogen (Fig. 2.4).
PK/PD Profiles of Anti-microbial Agents

Time-Dependent Agents (Duration of Exposure to a Specific MIC)

For this class of agents, anti-microbial activity occurs after reaching the maximum threshold and then stops after the serum concentrations fall below the MIC. Bacterial killing is achieved once a threshold is reached. T>MIC results in anti-bacterial activity and is expressed as a percentage of dosing interval. The time above MIC can be extended by frequent dosing.

Beta-lactams (penicillins, cephalosporins and carbapenems) reach peak efficacy at concentrations approximately 4–5 times above the MIC and further higher concentrations do not result in increased bactericidal activity. The magnitude of pathogen killing is determined by the duration of exposure of the bacterium to the drug (T>MIC) rather than the degree of exposure above the MIC. T>MIC between 40 and 70% of the dosing interval is considered effective for the beta-lactams. An effective T>MIC can be achieved by administering high doses at short intervals or with continuous infusions. Continuous infusions can maximize the time course of treatment and minimize fluctuations in serum concentrations. Continuous infusion regimens maintain trough levels and eliminate high peak serum concentrations which do not contribute to any additional benefit. Several studies report comparable outcomes with savings in the amount of drug administered.

Numerous animal studies indicate that varying drug concentrations and longer exposure time at or above MIC achieves maximum bacterial killing.

Macrolides, clindamycin, tetracyclines, and oxazolidinones achieve time-dependent bacterial killing with significant PAE. The AUC/MIC ratio predicts the efficacy. An AUC/MIC ratio of 25–35 for macrolides has been reported to achieve therapeutic efficacy against *Streptococcus pneumoniae*.

Concentration-Dependent Killing

$C_{\text{max}}$/MIC and AUC/MIC are predictors that correlate well with bactericidal efficacy.

Fluoroquinolones exhibit rapid concentration-dependent killing. The efficacy depends upon AUC/MIC or $C_{\text{max}}$/MIC ratio values. Few studies have documented the impact of PK/PD studies on clinical outcome in humans. Animal studies have demonstrated that AUC/MIC ratios of 25–30 for gram-positive organisms and 100–125 for gram-negative organisms are necessary to achieve successful clinical outcomes. Recent studies have suggested that the variability of pharmacodynamic parameters depends on specific pathogens.

Similar to the quinolones, aminoglycosides (e.g., gentamicin, tobramycin, and amikacin) exhibit rapid concentration-dependent killing. Experimentally, a high peak serum concentration of an aminoglycoside agent relative to MIC leads to faster killing of the bacteria. Achieving a $C_{\text{max}}$/MIC ratio of 8:1 against gram-negative
organisms has been reported as a measure of success. Traditionally, PK monitoring was done to avoid serum levels associated with nephrotoxicity and dosage regimens were adjusted based on target serum concentrations. However, elevated $C_{\text{min}}$ (trough) concentrations have been associated with toxicity. Administration of high doses for extended intervals (e.g., 5–7 mg/kg every 24 h for patients with normal renal function) is currently utilized by many practitioners to achieve enhanced bacterial killing and avoid the toxicity associated with higher $C_{\text{min}}$. With the extended dosing, serum concentrations fall below MIC for a period of time. All aminoglycosides demonstrate PAE which refer to suppression of bacterial growth despite zero serum concentration of the agent. PAE is more prevalent for aminoglycosides than any other class of anti-microbial agents against gram-negative bacilli. However, the role of PAE in achieving successful clinical outcomes is not established.

**Pharmacokinetic Variability**

Appropriate consideration of inter-patient variability is critical for designing an individual patient’s anti-microbial therapy. Factors such as differences in absorption, distribution, metabolism, and elimination play a key role in the design. In addition, various disease states have a profound impact on PK parameters. For example, individualized weight based dosing for certain drugs such as beta-lactams, vancomycin, and fluoroquinolones would be appropriate for obese patients because of increased adipose tissue and volume results in an increased volume of distribution of the agent. Increased dosage of aminoglycosides is appropriate for burn patients because of increased renal perfusion and clearance.

**Renal Impairment**

The majority of the commonly used anti-microbial agents are renally excreted and it is critical to adjust the dosing in patients with renal impairment. The elderly population should be carefully monitored because of the approximate 5–10% reduction in glomerular filtration per decade beyond age of 30. Insufficient dosage adjustments play a key role in adverse events seen in the elderly. See Table 2.1 for a list of adverse events secondary to commonly used anti-microbials in the elderly.

**Hepatic Impairment**

Recommendations and methods for anti-microbial dosage adjustment in patients with renal dysfunction are well established. In contrast, this has not been established in drugs that are metabolized by the liver since the degree of impairment
Critically Ill Patients cannot be quantified by a single parameter. Adjustment in dosing schedules should be considered for agents significantly cleared by the hepatobiliary system. Patients with both hepatic and renal dysfunction are at greatest risk for potential adverse events since the elimination half-life of many agents is prolonged. Most importantly, PK trends are highly variable in this group rendering the evaluation of specific recommendations particularly difficult.

**Critically Ill Patients**

The PK parameters are altered and special consideration needs to be given for specific agent classes. For example, the inflammatory response associated with sepsis involves release of cytokines, endothelial damage, and changes in capillary permeability. These responses may in turn result in fluid shifts, third space losses, and decreased serum albumin levels. In addition, hepatic or renal impairment can result in prolonged half-life, decreased clearance, and drug accumulation.

For example, the volume of distribution of aminoglycosides can be significantly increased in critically ill (ICU) patients compared to non-critically ill patients with comparable renal function. As such, higher doses will be required to achieve therapeutic serum concentrations. For the same reason, aminoglycoside dosing nomograms cannot be used in this patient population. Adjustment of dosage will be required as patients recover from critical illness. Decreased serum albumin levels can result in adverse events for highly protein bound drugs, such as beta-lactams. Increased oral doses or use of intravenous antibiotics may be necessary for patients with decreased gastrointestinal perfusion and altered gastric emptying. Dosage regimens for beta-lactams or quinolones may require adjustment for patients with impaired renal perfusion and hepatic metabolism. On a similar note, a fluid load with an increase in drug volume of distribution may require a higher dosage regimen to address lower serum concentrations.

Continuous infusion of beta-lactam agents has been shown to produce more consistent serum levels than intermittent boluses. Oral fluoroquinolones have excellent bioavailability providing a great therapeutic management option in non-critically ill

<table>
<thead>
<tr>
<th>Class/agent</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Nephrotoxicity and ototoxicity</td>
</tr>
<tr>
<td>Beta-lactams</td>
<td>Fever, rash, thrombocytopenia, anemia, diarrhea, neutropenia</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Seizure</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Diarrhea, <em>Clostridium difficile</em>-associated colitis</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>CNS effects, decreased seizure threshold, nausea, vomiting</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Thrombocytopenia, neutropenia</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Photosensitivity</td>
</tr>
<tr>
<td>Trimethoprim–sulfamethoxazole</td>
<td>Drug fever, rash, blood dyscrasias</td>
</tr>
</tbody>
</table>
patients. However, administration in patients on enteral feeding may significantly impact absorption of the drug.

**Tissue Concentrations**

Many bacterial infections are extracellular. However, it is hard to determine the extent of antibiotic penetration in the interstitial area. Tissue penetration also depends upon the lipid solubility and plasma protein binding of the agent. For example, beta-lactams and aminoglycosides are hydrophilic and only the unbound free portion of the drug can penetrate outside the plasma. Protein binding can result in increased serum concentrations. Serum concentrations provide a better estimation of the tissue concentration for agents with low protein binding (aminoglycosides, fluoroquinolones) than those agents with higher tissue and protein binding. Localized infections, such as meningitis and osteomyelitis, pose a special challenge since many agents are unable to penetrate the area of infection.

**Bacteriostatic Versus Bactericidal Drugs**

The MIC or minimal inhibitory concentration is the level of drug that inhibits growth of an organism. This effect is traditionally measured by assessing turbidity of a culture. The MBC or minimal bactericidal concentration of a drug is the level at which the drug kills the bacterium (this is conventionally determined by plating a culture of bacteria on a plate without any anti-microbial agent at the MIC level when the culture is not turbid). As a general rule, cell wall active agents such as the beta-lactam antibiotics are bactericidal and agents that inhibit protein synthesis, like the tetracyclines or the macrolides are bacteriostatic and do not kill the organism in vitro. However, it is not always possible to determine whether an antibiotic will be bactericidal or bacteriostatic for a given organism. Agents that are predominantly bacteriostatic, like trimethoprim/sulfamethoxazole, may be bactericidal for certain organisms. A given agent may be bactericidal for one strain and bacteriostatic for another strain of the same bacterium. In most cases this has little relevance to patients, as bacteriostatic anti-microbials have an excellent track record of helping the host eliminate infections. There are some exceptions, the most prominent being the treatment of bacterial endocarditis. In this situation, clinical experience has indicated that bactericidal antibiotics are necessary to successfully treat the infection. This is thought to be related to the inability of polymorphonuclear leukocytes or other host cells to enter the fibrin clot that forms on the valve which is itself not vascularized. Other situations in which the use of a bactericidal antibiotic could be important are CNS infections and in the treatment of immunocompromised patients.
Conclusion

Our knowledge on PK/PD has evolved over the past two decades. Optimization of dose and duration of therapy via PK/PD tools provides patient specific therapy. It is essential to develop a process to successfully utilize PK/PD parameters which include collection of blood or sputum samples before initial therapy, isolation of pathogens, determination of MICs, and adjustment of initial therapy to match PK/PD parameters.

However, PK/PD studies are difficult to perform because of the challenges associated with obtaining culture samples, differentiating between individual patient defense mechanisms, time and cost. For the same reason, most of the PK/PD data are available from animal and in vitro studies. Another challenge is associated with our current process of obtaining unbound serum concentrations to monitor efficacy of an anti-microbial agent. Penetration of an agent into various sites of infection is variable and serum levels cannot accurately predict efficacy at the intracellular level. It makes sense to obtain individual PK and MIC data to optimize dosing.

Successful management of an infectious disease depends on various factors, including comorbidities, immune status, organ function, anti-bacterial activity, efficacy, tissue penetration, protein binding, and metabolism and elimination properties. Application of PK/PD data to establish optimal dosing regimens should lead to better patient outcomes and avoid escalation of anti-microbial resistance.

Further Reading


Clinical Use of Anti-infective Agents
A Guide on How to Prescribe Drugs Used to Treat Infections
Finberg, R.W.; Guharoy, R.
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