Practical PK/PD of Antimicrobials

Benjamin G. Co, MD, FPPS, FPSECP

Executive Director

Center for Excellence in Drug Research,
Evaluation & Studies, Inc.

at the Research Institute for Tropical Medicine

Disclosure on conflicts of interest

- Medical Director, Otsuka Philippines Pharmaceuticals, Inc.
- Honoraria received from MSD Vaccines, Natrapharm-Patriot, Abbott Pharmaceuticals in the past year for lectures
- No CME activities received
- No grants for clinical trials received
- Not advisory board positions for the industry

Treating infectious diseases

- 1. What is the RIGHT DRUG to treat the clinical condition?

- 2. What is the most suitable regimen for the administration of the drug?

Treating infectious diseases

- Unlike other drugs used to treat physiologic abnormalities, it is imperative to consider the microorganism with respect to the PK of antimicrobials
- *"There is no benefit to develop an antibiotic with good oral bioavailability, low host toxicity and long duration in the body if it is not capable of penetrating the bacterial cell wall or is destroyed by a bacterial enzyme"*

Treating infectious diseases

- What is the correct dosage?
  - *Alleviates the symptoms*
  - *Does not give rise to a toxic response*
  - *AVOIDANCE OF CREATING CONDITIONS FAVORABLE TO THE DEVELOPMENT OF DRUG RESISTANCE!*

OBJECTIVES DURING ANTIMICROBIAL THERAPY

- 1. To maximize blood concentration (preferably several-fold higher than the MIC for the particular agent)

- 2. But to minimize both the risk of toxicity to the patient and of promoting microbial resistance

Basic concepts of Clinical pharmacokinetics

- Pharmacokinetics
  - Time course of drug movement in the body
  - PK profile is important to design the optimal dose regimen
  - PK principles are relevant only when they are integrated with the PD property of a drug
- Pharmacodynamics
  - The effects of patient

Basic pharmacokinetic principles

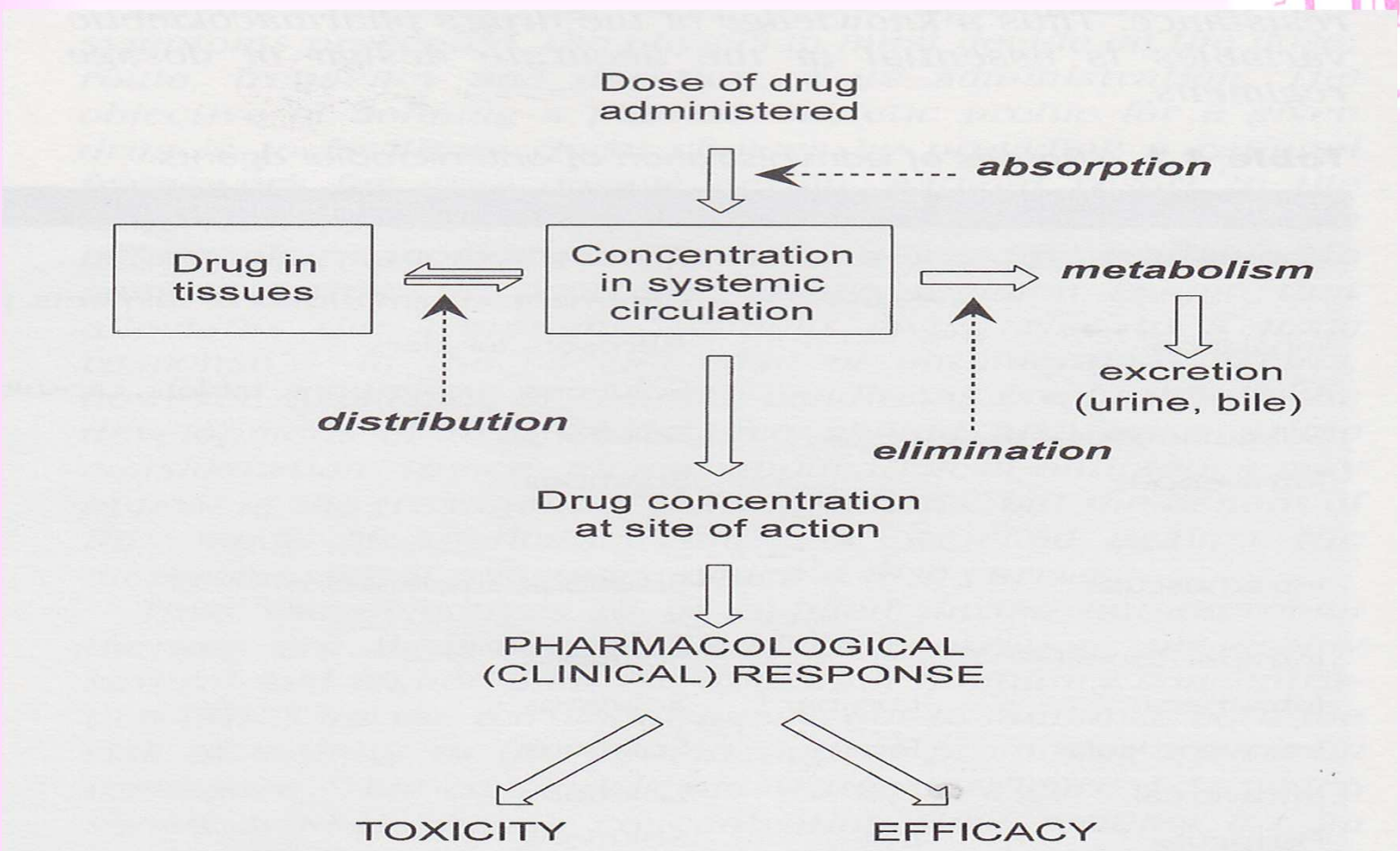


Fig. 4.2 *The influence of pharmacokinetic factors (absorption, distribution, metabolism and elimination) on the pharmaco-dynamics and toxicity of drugs.*

PK/PD basis of optimal antibiotic therapy

(adapted from Michael N. Neely and Michael D. Reed in Principles & Practice of Pediatric Infectious Diseases, 2012)

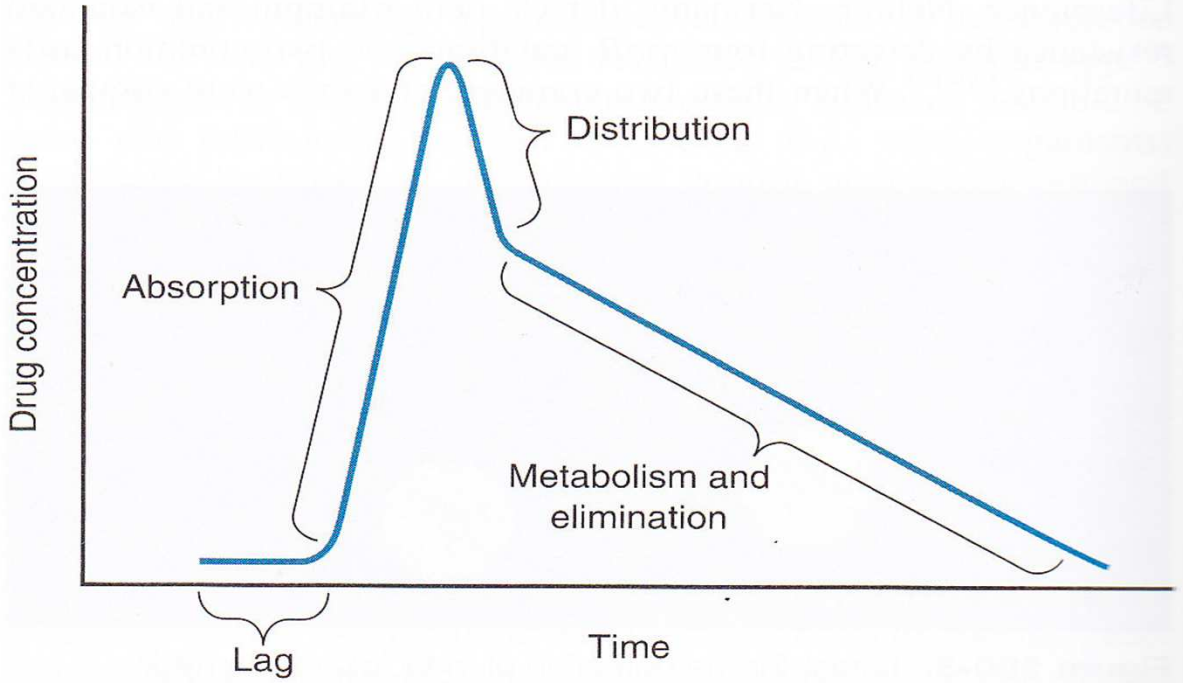


Figure 291-1. Overall biologic fluid (e.g., serum) drug concentration–time curve after extravascular drug administration. Each important process of drug disposition is indicated. Although these processes are compartmentalized graphically in the figure, in reality they occur simultaneously (see text for details).

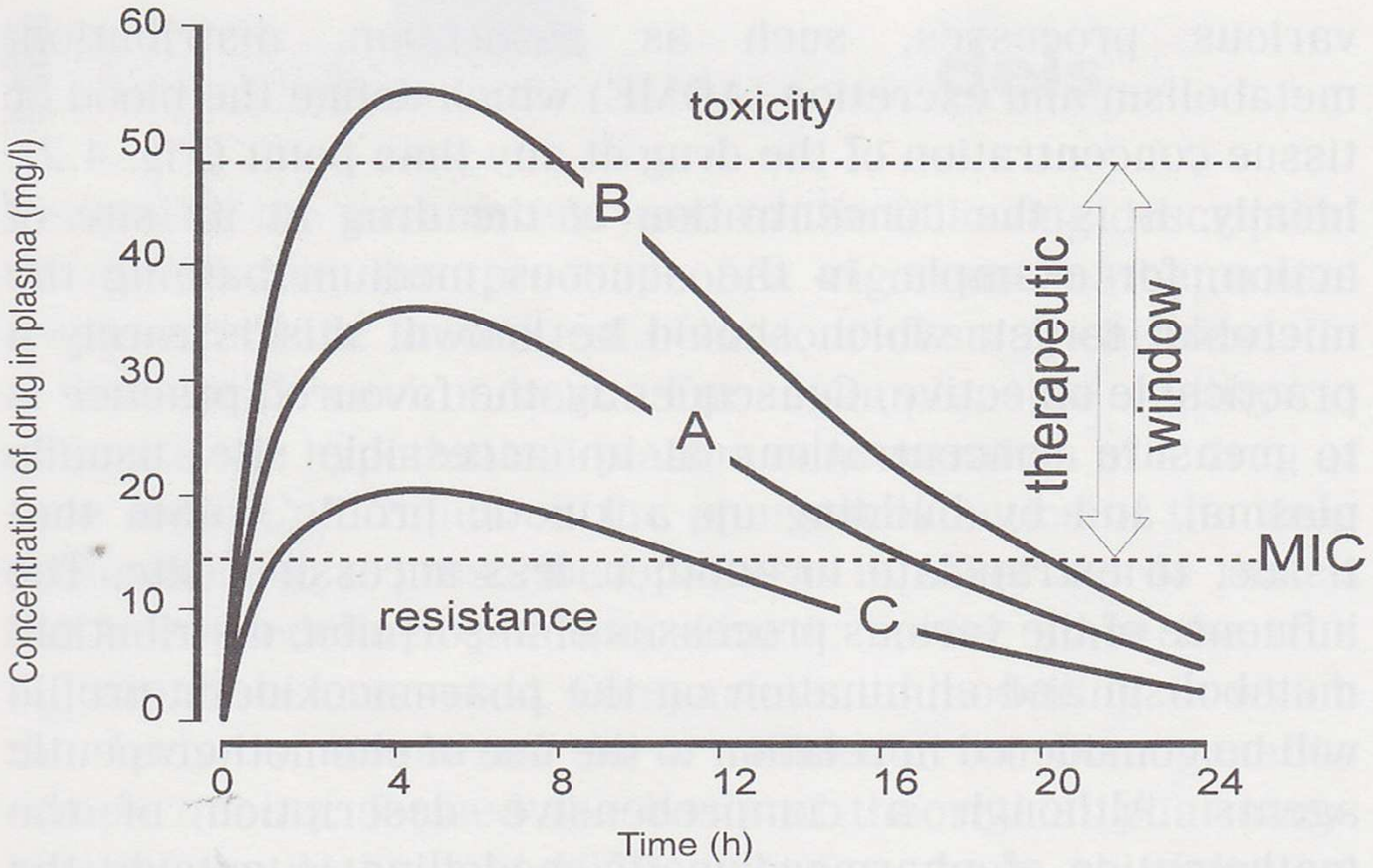


Fig. 4.1 *Plasma concentration–time curves for a hypothetical antibiotic given orally at three different doses (A–C) (see text).*

Routes of administration

- Topical
- Oral
- Intravenous
- Intramuscular
- Intraperitoneal
- Intravitreal, Periocular
- Rectal
- Vaginal
- Intrathecal

Drug disposition in specific patient populations – the practical perspective

- 1. Neonates
- 2. Patients with organ failure and principles of dialyzable drugs
- 3. ECMO
- 4. Dialysis
- 5. Septic shock or burns

Drug disposition in neonates

TABLE 291-1. Physiologic Changes in Children That Affect the Pharmacokinetic Characteristics of Drugs[2,3]

Parameter	Neonates	Approximate Age Approaching Adult Level
ABSORPTION		
Gastric pH	↑	3 months
Gastric emptying	↓	6–8 months
Pancreatic function	↓	9 months
DISTRIBUTION		
Body water	↑[a]	Adolescence
Protein binding	↓	12 months
METABOLISM		
Hepatic drug-metabolizing	↓	Adolescence
ELIMINATION		
Renal function	↓	Glomerular filtration: 3–5 months
		Tubular secretion: 8–9 months

[a]The distribution of body water depends on age: the total body water (TBW) of neonates is about 75% of body weight, with about 50% intracellular (IC) and 50% extracellular (EC). A gradual decrease in TBW and a shift to IC distribution occur until adult values of 50% to 60% TBW, 33% EC, and 66% IC are reached at puberty.

Organ failure & principles of dialyzable drugs

- Most drugs are eliminated by the kidneys into urine and liver into bile
- Alterations in drug disposition from failure of these organs or failure of the cardiovascular system which perfuse these organs with oxygenated blood essential for proper function alter the drug concentrations
- Drugs with small Vd are more affected because they tend to be distributed extracellularly
- Route of metabolism and elimination determine impact of hepatic or renal function

Extracorporeal membrane oxygenation

- ECMO circuitry add up to 500 mL of volume to the patient (↑Vd); children < 20kg likely to have a corresponding lower peak concentration and longer $t_{1/2}$
- Drugs can bind to the oxygenation membrane → ↑Vd and ↑CL
- ↑binding with more lipophilic drugs; ↓CL due to altered perfusion of liver and kidneys

Septic shock or burns

- Dramatic physiologic changes
- Any child with hemodynamic changes requiring significant fluid resuscitation and/or pharmacologic pressure support will be neither physiologically nor pharmacokinetically normal
- Phases of the disease state (early, resuscitated, or late) affect the PK and PD of a drug

Dosing strategies in patients with septic shock or extensive burns

Antibiotic	Pharmacokinetic change	Suggested dose adjustment
Aminoglycosides	Generally ↑CL and ↑Vd	1. Administer twice the standard multiple-daily dose 2. Measure drug concentration at the end of infusion and 4 h after end of infusion 3. If 4-hr concentration is <2 µg/mL (gentamicin, tobramycin) or < 5µg/mL (amikacin), administer another dose; otherwise estimate Vd and t1/2 and administer a second dose when trough concentration expected to be at target 4. Continue dose and schedule from step 3.

Dosing strategies in patients with septic shock or extensive burns

Antibiotic	Pharmacokinetic change	Suggested dose adjustment
Aminoglycosides (Gentamicin, Amikacin, Tobramycin, Netilmicin)	Generally ↑CL and ↑Vd	Once-daily dosing of aminoglycosides has been shown to result in extended periods of sub-therapeutic plasma concentrations in excess of those seen in non-burned patients, potentially compromising efficacy and standard multiple-daily dosing carries a significant risk of sub-therapeutic peaks. Therefore, HIGHER DOSE MULTIPLE DAILY DOSING IS PREFERRED INITIALLY.

Dosing strategies in patients with septic shock or extensive burns

Antibiotic	Pharmacokinetic change	Suggested dose adjustment
Glycopeptides (Vancomycin, Teicoplanin)	Generally ↑CL; fair correlation with CLCr. Vd is not affected.	1. Measure ClCr as soon as possible (after initial 48 hrs postburn) 2. Administer highest end of standard dose based on shortest dosing interval 3. Measure peak concentration at end of infusion 4. Time the measurement of trough level on ClCr, if available; if unavailable, measure trough before next dose is due after standard short interval 5. Adjust dose/interval based on serum trough

Dosing strategies in patients with septic shock or extensive burns

Antibiotic	Pharmacokinetic change	Suggested dose adjustment
Glycopeptides (Vancomycin, Teicoplanin)	Generally ↑CL; fair correlation with CLCr. Vd is not affected.	The standard dose of vancomycin in children with the shortest interval is 15 mg/kg q6h Based on the PK/PD characteristics of vancomycin, continuous infusion may be an alternative for patients with rapid clearance to avoid excessively large or frequent doses. Best targeted serum concentration is unclear.

Dosing strategies in patients with septic shock or extensive burns

Antibiotic	Pharmacokinetic change	Suggested dose adjustment
β-lactams (Cefepime, ceftazidime, ticarcillin-clavulanate, piperacillin-tazobactam)	Vd is substantially ↑ Total CL generally is correlated with CLCr T1/2 is variably ↑ but initial serum concentrations are less than normal	1. Measure CLCr as soon as possible (after initial 48 hrs postburn) 2. Consider 50% increase over highest usual dose 3. Dosing interval depends on CLCr. If above normal, choose moderate interval; if below normal, choose long interval

Dosing strategies in patients with septic shock or extensive burns

Antibiotic	Pharmacokinetic change	Suggested dose adjustment
Carbapenems/Monopenems (Imipenem, Meropenem, Aztreonam)	CL correlates well with CLCr No change in Vd	1. Measure CLCr as soon as possible (after initial 48 hrs postburn) 2. Use high end of standard dose 3. Dosing interval depends on CLCr. If above normal, choose short interval; if below normal, choose long interval.

Basis for drug-drug interactions

PK/PD basis of optimal antibiotic therapy

(adapted from Michael N. Neely and Michael D. Reed in Principles & Practice of Pediatric Infectious Diseases, 2012)

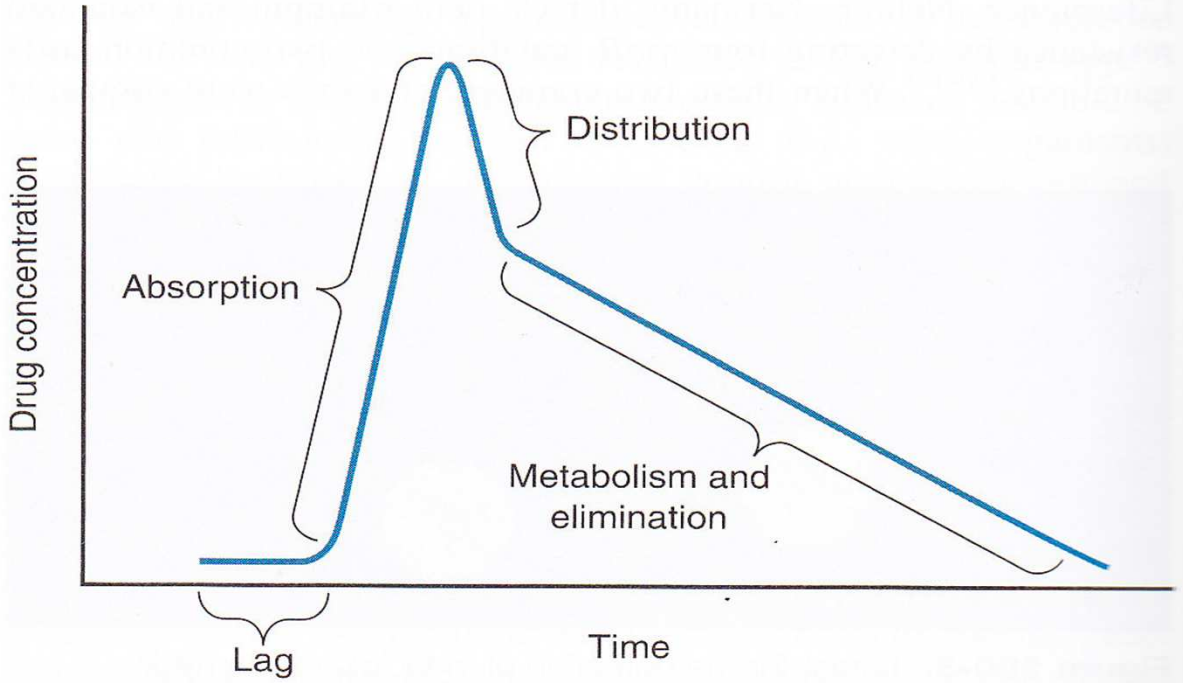


Figure 291-1. Overall biologic fluid (e.g., serum) drug concentration–time curve after extravascular drug administration. Each important process of drug disposition is indicated. Although these processes are compartmentalized graphically in the figure, in reality they occur simultaneously (see text for details).

PK – what the body does to the drug

- Absorption
- Distribution
- Metabolism
- Elimination

Absorption

- Used loosely to describe the process whereby a drug gains entry to the circulation
- Applicable only in situations where the drug must cross a plasma membrane
- The choice of route of administration will determine whether or not an absorption phase occurs

Bioavailability

- F, defined as the fraction of the administered dose that is absorbed intact.

Bioavailability concerns

- Situation that presents more of a problem to the clinician is inconsistent and unpredictable absorption, since ineffective plasma levels may result.

Absorption

- 1. Alterations in GI motility by pharmacologic or nonpharmacologic means
- 2. Presence of food in the GI tract (e.g., itraconazole tablets better with fatty food while itraconazole solution is best on an empty stomach)
- 3. Alterations in gastric pH; since most drug absorption occurs in the small intestine, gastric pH generally plays a minor role in overall bioavailability of orally administered drugs
- 4. Binding substances (e.g., Fluoroquinolones and tetracyclines are poorly absorbed when cationic ions such as those found in vitamin supplements & antacids are given concomitantly).

Other factors affecting bioavailability

- Size of the molecule
  - Neomycin (MW>700kDa) is slowly absorbed
  - Normal 2-4 hr passage time through the small intestine is insufficient for complete absorption

Distribution

$V_d = Dose/C_{(0)}$

where V_d = volume of distribution

$C_{(0)}$ = concentration in plasma at time 0

When does a drug interaction become problematic?

1. The antibiotic is highly protein bound (> 80%)
2. Drug has a small Vd (< 1 L/kg). A large Vd means that the bulk of the drug is extravascular and is not affected by changes in serum protein binding
3. Drug must have a long T1/2
4. The antibiotic must have a low therapeutic index (i.e., toxicity occurs at serum concentration slightly above the therapeutic concentrations)

Antibiotics classified according to possible ability to displace bilirubin from albumin in cord blood serum in vitro

High	Intermediate	Low	No data
Cefoperazone Ceftriaxone Dicloxacillin Sulfamethoxazole Sulfisoxazole	Ampicillin Cefonicid Cefoxitin Cephalexin Erythromycin Imipenem Nafcillin Vancomycin	Aminoglycosides Amoxicillin Aztreonam Cefamandole Cefazolin Cefotaxime Ceftazidime Cefuroxime Ciprofloxacin Penicillin G Piperacillin Ticarcillin	Acyclovir Amantadine Amphotericin B Cidofovir Clindamycin Fluconazole Ganciclovir Meropenem Metronidazole Neuraminidase inhibitors Protease inhibitors Reverse transcriptase inhibitors

Metabolism

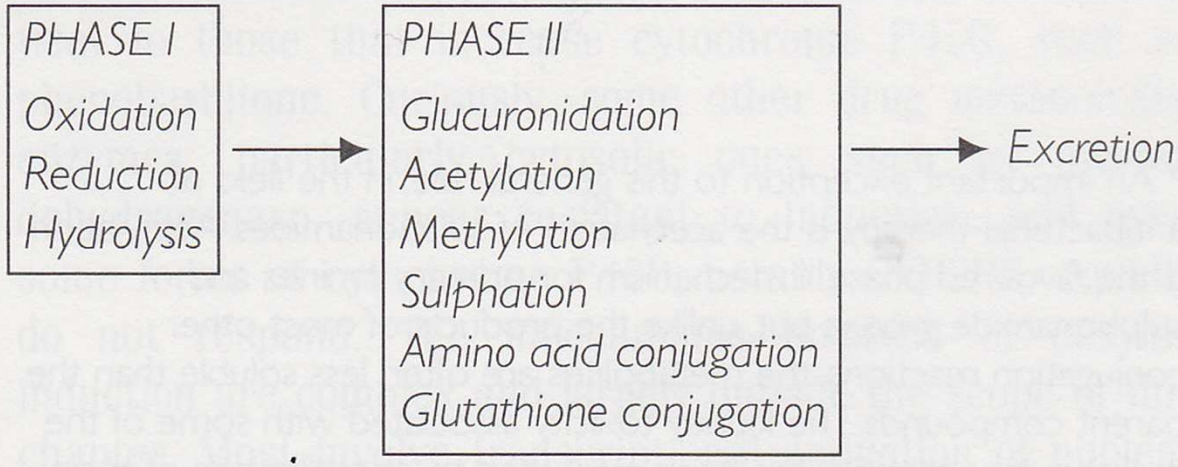
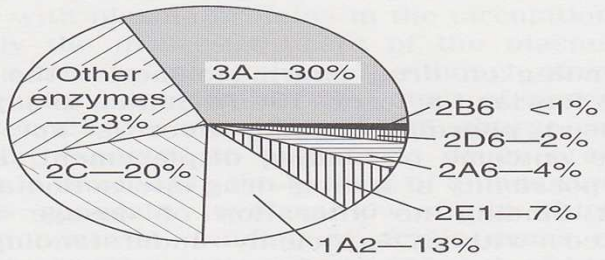


Fig. 4.12 *Classification of human drug metabolism.*

Table 4.4 *The family structure of human cytochromes P450. Each of the major drug metabolizing families (CYP1 to CYP3) are listed with their subfamilies, denoted by a capital letter, and individual isozymes, signified by a final arabic numeral. Families are defined as being < 40% similar with respect to their amino acid primary sequence, subfamilies <70% similar and individual isozymes must have an identical structure within the bounds of normal random mutation. The relative proportions of each of the major isoforms in human liver is shown in this pie chart:*



Enzyme	Substrates	Characteristics
CYP1A1	Caffeine	*Inducers:* cigarette smoke, omeprazole *Inhibitor:* enoxacin
CYP1A2	PAH, aromatic amines	
CYP2A6	Coumarin	
CYP2C8-10	Tolbutamide, (S)-warfarin, phenytoin	*Inducers:* phenobarbitone, rifampicin *Inhibitor:* sulphaphenazole
CYP2D6	Debrisoquine	*Inducers:* not inducible; genetic polymorphism *Inhibitor:* quinidine
CYP2E1	Ethanol, benzene, nitrosamines	
CYP3A3-6	Cyclosporin, oestrogens, nifedipine, cortisol, carbamazepine	*Inducers:* phenobarbitone, rifampicin, carbamazepine, phenytoin *Inhibitors:* ketoconazole, cimetidine

Factors that affect drug metabolism

- Enzyme induction
  - Enhanced biotransformation of compounds that are substrates for the enzymes and is due to an increase in the de novo synthesis of the enzyme apoprotein
- Enzyme inhibition
  - Results in more issues on drug toxicity through competitive inhibition or complexation phenomenon

Antibiotic-Cytochrome P450 interactions examples

Isoenzyme	Substrate	Inhibitor	Inducer
1A2	Efavirenz	Fluoroquinolones, INH	Nafcillin
2B6	Artemisinin		Rifampicin, Artemisinin
2C8	Chloroquine	Trimethoprim	Rifampicin
2C9	Etravirine	Chloramphenicol, Fluconazole, Isoniazid, SMX, TMP, Voriconazole	Rifampicin
2C19	Proguanil	Chloramphenicol, Ketoconazole, Probenecid	Artemisinin, Rifampicin
2D6		Ritonavir	Rifampicin
2E1		Isoniazid	Isoniazid
3A4,5,7	Azoles, chloroquine, rifampicin, TMP, macrolides	Azoles, ciprofloxacin, Macrolides, norfloxacin, HIV protease inhibitors	Rifampicin, Nafcillin, HIV protease inhibitors

Excretion

- Major routes:
  - Urine
  - Feces
- Other routes: (have little impact on antimicrobials)
  - Expired air
  - Sweat

Renal excretion

- Extent to which a drug is excreted in the urine is dictated by three processes:
  - 1. extent to which it is filtered in the glomerulus
  - 2. extent to which it is actively secreted into the kidney tubules
  - 3. degree to which it is reabsorbed from the tubules

Renal excretion

- The 3 processes are in turn influenced by:
  - 1. the physicochemical properties of the drug
  - 2. the degree to which the drug is protein bound in the circulation
  - 3. internal or external factors that can alter renal processes (such as disease, urine pH and other drugs that compete for transport mechanisms)

Pharmacodynamic interactions

Efficacy	Toxicity
INCREASED 1. Synergistic activity of βlactam plus aminoglycoside vs. enterococci 2. βlactam plus βlactamase inhibitor for extended G(-) and anaerobic coverage 3. TMP + SMX; quinopristin + dalfopristin	**INCREASED** Two potentially nephrotoxic antibiotics such as vancomycin plus aminoglycoside increases the likelihood of renal injury
DECREASED ARV (Zidovudine + Stavudine are antagonistic when co-administered)	**DECREASED** Probenecid mitigates nephrotoxicity of cidofovir

PK/PD properties of drugs

- Critical information to guide the selection of both drug and drug dosage in antimicrobial therapy:
  - 1. route of administration
  - 2. absorption
  - 3. tissue distribution of antibiotic at site of infection
  - 4. drug elimination characteristics

Schematogram of sites of action for various antibiotics

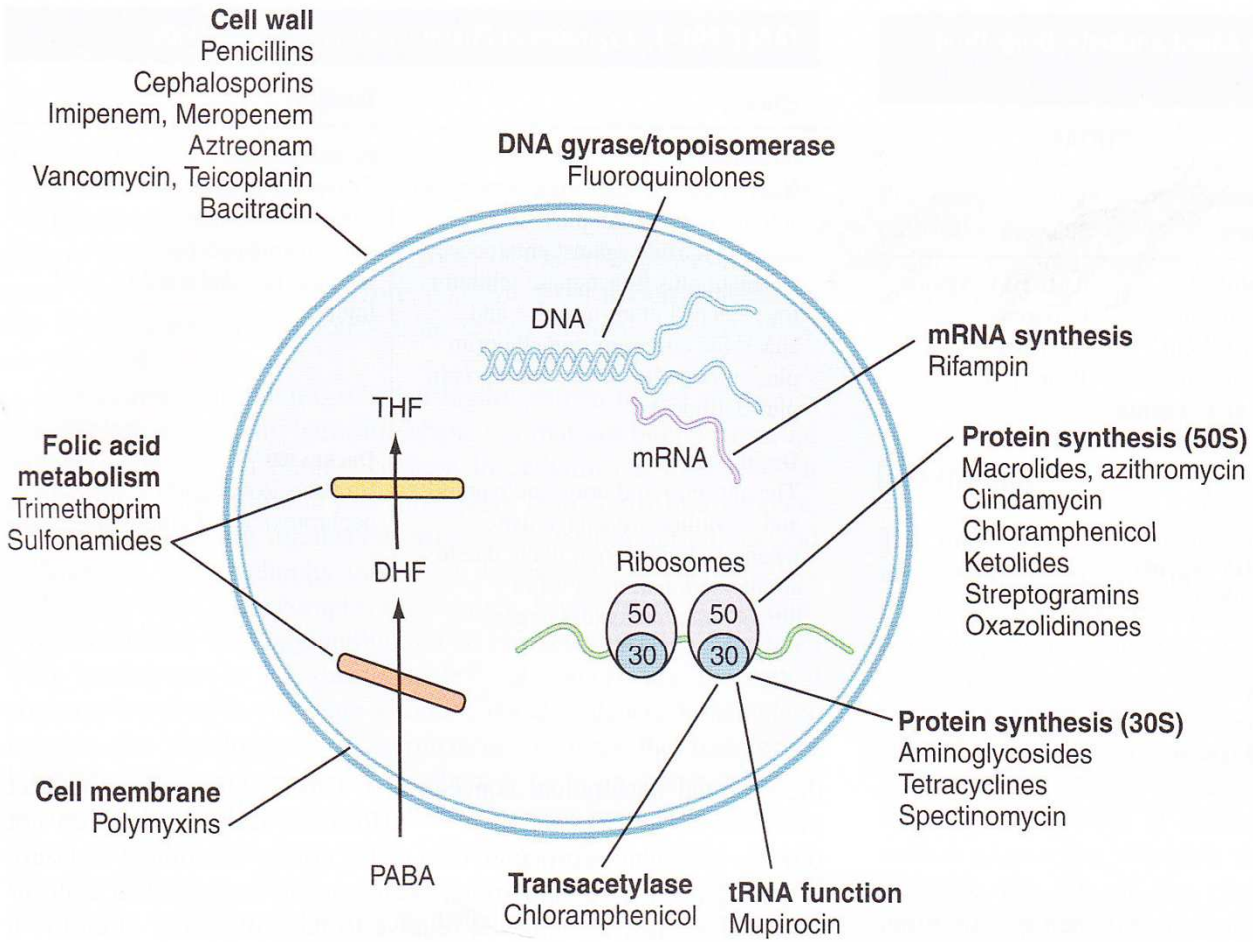


Figure 291-2. Sites of action for major antibacterial drugs. DHF, dihydrofolate; PABA, *para*-aminobenzoic acid; THF, tetrahydrofolate. (Adapted from Neu HC. The crisis in antibiotic resistance. Science 1992;257:1064–1073.)

Time vs concentration-dependent antibiotics

- PD of antibiotics are based on:
  - 1. kinetics of bacterial killing
  - 2. post-antibiotic effect (PAE)
  - 3. post-antibiotic leukocyte enhancing effect (PALE)
  - 4. inoculum effect

Time vs concentration-dependent antibiotics

- Concentration-dependent antibiotics
  - Exhibit a concentration-dependent killing:
    - The higher the concentration of the drug, the greater the bactericidal effect
  - PAE: the time period after an exposure to and removal of an antimicrobial agents during which inhibition of bacterial growth persists
  - In vivo PALE: enhanced leukocyte phagocytosis and intracellular killing of bacterial during the drug-free period

Time vs concentration-dependent antibiotics

- <u>Concentration-dependent antibiotics</u>
  - Aminoglycosides: goal is to attain maximum serum concentrations exceeding the MIC of the organism tenfold (10)
  - Fluoroquinolones: ratio of the area under the cure/MIC (AUIC) should be greater than 125
  - GIVE TOTAL DAILY DOSE LESS FREQUENTLY

Time vs concentration-dependent antibiotics

- <u>Time-dependent antibiotics</u>
  - Bactericidal effect is dependent upon the length of time that the bacteria are exposed to serum concentrations which exceed the MIC of the bacteria by at least 4x.
  - All drugs exert PAE vs *S. aureus* but not all drugs exert PAE against G(-) bacilli.
  - Goal is to attain serum concentrations of at least 4x MIC of the infecting agent for at least 60% of the dosing time interval.

Time vs concentration-dependent antibiotics

- <u>Time-dependent antibiotics</u>
  - Most cost-effective means of attaining this is:
    - 1. administering the drug by constant infusion following an initial bolus or loading dose
    - 2. OR, choosing the drug with the longest half-life

PD antibacterial effect of antimicrobial agents by primary bacterial target and by antibiotic class

Primary target	Antibacterial class	Pharmacodynamics	Intracellular activity
Cell wall	B-lactams - penicillins - cephalosporins - monobactams - carbapenems Glycopeptides - vancomycin - teicoplanin	Bactericidal Time-dependent PAE only against G(+) organisms Carbapenems PAE against G(+) & G(-) organisms	Not generally effective
Cell membrane	Lipopetides - Daptomycin Polymyxins - Polymyxin B - Colistin	Bactericidal Concentration-dependent Long PAE (Daptomycin) PAE (polymyxins)	Not known

PD antibacterial effect of antimicrobial agents by primary bacterial target and by antibiotic class

Primary target	Antibacterial class	Pharmacodynamics	Intracellular activity
Ribosome	Macrolides, azalides, ketolides	Bacteriostatic or –cidal (ketolides) Time- and concentration-dependent Long PAE	Yes
	Tetracyclines, glycylcyclines	Bacteriostatic Time-dependent Long PAE	Yes
	Lincosamides (Clindamycin)	Bactericidal or –static Time-dependent PAE	Yes

PD antibacterial effect of antimicrobial agents by primary bacterial target and by antibiotic class

Primary target	Antibacterial class	Pharmacodynamics	Intracellular activity
Ribosome	Aminoglycosides	Bactericidal Concentration-dependent PAE	Not effective partially
	Oxazolidinones	Bacteriostatic (except against S. pneumoniae) Concentration-dependent PAE	Not effective partially
	Rifamycins	Bactericidal Long PAE	Yes

PD antibacterial effect of antimicrobial agents by primary bacterial target and by antibiotic class

Primary target	Antibacterial class	Pharmacodynamics	Intracellular activity
Ribosome	Quinolones	Bactericidal Concentration-dependent Long PAE	Yes
	Streptogramins	Bactericidal (except against Enterococcus faecium) Concentration-dependent PAE	Yes

PD antibacterial effect of antimicrobial agents by primary bacterial target and by antibiotic class

Primary target	Antibacterial class	Pharmacodynamics	Intracellular activity
Nucleic Acid	Metronidazole	Bactericidal Concentration-dependent PAE	Yes
	Sulfamethoxazole-trimethoprim	Bactericidal Concentration-dependent	Yes
	PAE – postantibiotic effect OR the observation of delay in regrowth of organisms following removal of antibiotic from the media		

Classification of selected antibacterial agents based on their patterns of antimicrobial activity (updated 2012)

Pattern	Drug
PEAK/MIC Concentration-dependent killing, prolonged PAE	Aminoglycosides Daptomycin Fluoroquinolones Metronidazole
TIME>MIC Time-dependent killing, minimal PAE	Carbapenems, Aztreonam Cephalosporins Penillins
AUC/MIC Time-dependent killing, moderate to persistent antibiotic effects	Azithromycin Clindamycin Telithromycin Linezolid Macrolides Quinupristin/Dalfopristin Telavancin Tetracyclines Tigecycline Vancomycin

Summary

- As our knowledge of PK-PD relationships expands, drug dosing increasingly will be based on achieving PK-PD targets in individual patients rather than the traditional population-based recommendations of dosing ranges
- The ongoing challenge in pediatrics is to assure that the determination of these important surrogate markets/endpoints incorporate the important changes that occur with increasing age.

Not every patient is the same…

Thank you for your kind attention