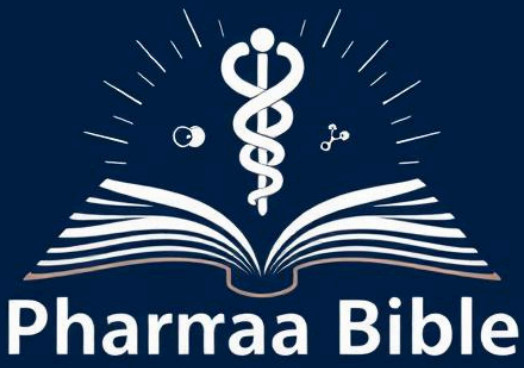
FIRST EDITION




THE COMPLETE REFERENCE

# PHARMAA BIBLE

PHARMACOLOGY FOUNDATIONS

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NAVIGATION

# Contents



Bonus Quiz with Answers  after chapter 15
Learn well!!

CHAPTER 1

# GENERAL PHARMACOLOGY

(Foundation)

PHARMACOKINETICS (PK)

# What the Body Does to the Drug

## A. ABSORPTION

DEFINITION
Movement of drug from site of administration to the bloodstream

### Factors Affecting Absorption

#### Route of Administration

- Oral (slow, first-pass metabolism)
- IV (100% bioavailability)
- IM / SC (moderate absorption)
- Inhalation (rapid onset)
- Topical (local or systemic)

#### Blood Flow

Increased blood flow leads to increased absorption rate

#### Surface Area

Intestine has greater surface area than stomach

#### Lipid Solubility

Lipophilic drugs absorb more readily through cell membranes

#### pH and Ionization

- Weak acids absorb in acidic environment
- Weak bases absorb in alkaline environment

*Based on Henderson-Hasselbalch equation*

## B. BIOAVAILABILITY (F)

KEY CONCEPT
Fraction of drug reaching systemic circulation unchanged

- IV Administration: F = 1 (100%)
- Non-IV Routes: F < 1 due to degradation, absorption issues, or first-pass effects

BIOAVAILABILITY FORMULA

$$F = (AUC_{oral} / AUC_{IV}) \times 100$$

AUC = Area Under the Curve

### Key Determinants

- Drug formulation affects dissolution rate
- GI motility influences absorption time
- Food interactions can enhance or reduce absorption
- First-pass metabolism in liver reduces F

CLINICAL NOTE
Drugs with low bioavailability may require higher oral doses or alternative routes. Monitor for variability between patients.

# C. DISTRIBUTION

## DEFINITION
Drug movement from blood to tissues

### Important Factors
#### Plasma Protein Binding

- Primarily binds to albumin
- Only free (unbound) drug is active
- Drug-drug interactions at binding sites

### Blood-Brain Barrier (BBB)

- Lipid-soluble drugs cross easily
- Tight junctions limit polar drugs
- P-glycoprotein efflux pumps

### Volume of Distribution (Vd)

Vd = Amount in Body / Plasma Conc.

- High Vd= drug distributed to tissues
- Low Vd = drug remains in plasma

CLINICAL EXAMPLES

- Warfarin: Low Vd (~0.14 L/kg) - plasma
- Digoxin: High Vd (~7 L/kg) - tissues
- Chloroquine: Very high Vd (~200 L/kg)

# D. METABOLISM

## LOCATION
Mainly in the liver (biotransformation)

### Phase I Reactions
*(Functionalization)*

- Oxidation, Reduction, Hydrolysis
- Mediated by CYP450 enzymes

KEY CYP ENZYMES

CYP3A4 (most important), CYP2D6, CYP2C9

### Phase II Reactions
*(Conjugation)*

- Glucuronidation, Sulfation, Acetylation
- Makes drugs water-soluble for excretion

INDUCERS

(Decrease drug effect)

- Rifampicin
- Phenytoin
- Carbamazepine
- Phenobarbital

INHIBITORS

(Increase toxicity risk)

- Erythromycin
- Ketoconazole
- Cimetidine
- Grapefruit juice

PHARMACODYNAMICS (PD)

# What the Drug Does to the Body

## A. RECEPTORS

RECEPTOR TYPES

- G-protein coupled receptors (GPCR)
- Ion channel receptors
- Enzyme-linked receptors
- Nuclear receptors (intracellular)

## B. AGONISTS vs ANTAGONISTS

AGONIST

Binds to receptor and ACTIVATES it to produce a response

*Examples: Morphine, Salbutamol*

ANTAGONIST

Binds to receptor and BLOCKS agonist action

*Examples: Naloxone, Propranolol*

### Types of Antagonism

Competitive -Reversible, surmountable

Non-competitive - Irreversible binding

Functional -Opposing physiological effects

## C. DOSE-RESPONSE CURVE

KEY CONCEPTS

Emax = Maximum effect achievable

EC50 = Concentration for 50% effect (potency)

Efficacy = Maximum response produced

Potency = Amount needed to produce effect

KEY INSIGHT

Potency is NOT the same as Efficacy

## D. THERAPEUTIC INDEX (TI)

FORMULA

TI = TD50 / ED50

TD50 = Dose causing toxicity in 50%

ED50 = Dose producing effect in 50%

HIGH TI

Safer drug with wide margin between effective and toxic doses

LOW TI

Narrow therapeutic window (e.g., Digoxin, Warfarin)

PHARMACOKINETICS (PK)

# Elimination Pathways

## E. EXCRETION

**DEFINITION**

Removal of drugs and metabolites from the body, primarily through kidneys (urine) and liver (bile)

### Renal Excretion

Primary route for most water-soluble drugs

#### Glomerular Filtration

- Free (unbound) drug filtered
- Protein-bound drug NOT filtered

#### Tubular Secretion

- Active transport into tubule
- Can lead to drug interactions

#### Tubular Reabsorption

- Lipid-soluble drugs reabsorbed
- Ionized drugs remain in urine
- pH manipulation affects excretion

**RENAL CLEARANCE FORMULA**

$$CL_r = (C_u \times V) / C_p$$

Cu = urine conc. | V = urine flow | Cp = plasma conc.

### Biliary Excretion

- Large molecular weight drugs
- Conjugated metabolites
- Enterohepatic circulation can prolong drug action

**ENTEROHEPATIC CIRCULATION**

Drug excreted in bile → intestine → reabsorbed → back to liver. Prolongs half-life (e.g., oral contraceptives, digoxin)

### Other Excretion Routes

#### Lungs

- Volatile anesthetics
- Alcohol (breathalyzer basis)

#### Sweat and Saliva

Minor route, used for drug testing

#### Breast Milk

- Lipid-soluble drugs pass readily
- Important for nursing mothers

**CLINICAL CONSIDERATIONS**

**Renal Impairment:**
- Reduce dose or extend interval
- Monitor creatinine clearance (CrCl)

**Hepatic Impairment:**
- Affects biliary excretion
- Monitor liver function tests

**URINE pH MANIPULATION**

**Alkalinize urine** ($NaHCO_3$):Increases excretion of weak acids(aspirin, barbiturates)
**Acidify urine** ($NH_4Cl$):Increases excretion of weak bases(amphetamines)

**KEY EXCRETION FACTORS**

- **GFR** affects filtration rate
- **Protein binding** limits filtration
- **Lipophilicity** promotes reabsorption
- **Ionization** prevents reabsorption
- **Transporters** mediate secretion

PHARMACOKINETICS (PK)

# Half-life and Dosing

## F. HALF-LIFE (t½)

**DEFINITION**

Time required for plasma drug concentration to decrease by 50%

**HALF-LIFE FORMULA**

$$t_{\frac{1}{2}} = 0.693 \times Vd / CL$$

Vd = Volume of Distribution | CL = Clearance

### Clinical Significance

- Determines **dosing interval**
- Predicts **time to steady state**
- Guides **drug accumulation**
- Affects **time to elimination**

**DRUG ELIMINATION OVER TIME**

**1 half-life:** 50% eliminated
**2 half-lives:** 75% eliminated
**3 half-lives:** 87.5% eliminated
**4 half-lives:** 93.75% eliminated
**5 half-lives:** ~97% eliminated (practical)

## G. STEADY STATE (Css)

**KEY CONCEPT**

Rate of drug input = Rate of elimination. Achieved after approximately 4–5 half-lives of continuous dosing.

**STEADY STATE CONCENTRATION**

$$Css = (F \times Dose) / (CL \times \tau)$$

*τ (tau) = dosing interval*

## H. LOADING DOSE

**PURPOSE**

Achieve therapeutic concentration rapidly without waiting for 4–5 half-lives

**LOADING DOSE FORMULA**

$$LD = (Cp \times Vd) / F$$

Cp = target plasma concentration
F = bioavailability

## I. MAINTENANCE DOSE

**PURPOSE**

Maintain steady-state concentration

**MAINTENANCE DOSE FORMULA**

$$MD = (Css \times CL \times \tau) / F$$

**CLINICAL EXAMPLES**

**Digoxin** (t½ ~36 hrs)Loading dose needed, once daily dosing
**Warfarin** (t½ ~40 hrs)Takes 5–7 days to reach steady state
**Phenytoin** (t½ ~22 hrs)Loading dose common in seizures
**Aspirin** (t½ ~15–20 min)Short t½, frequent dosing or sustained release

**CLINICAL WARNING**

Loading doses bypass the safety margin of gradual accumulation. Use with caution in drugs with narrow therapeutic index.

CLINICAL PHARMACOLOGY

# Drug Interactions

## TYPES OF INTERACTIONS

### 1. PHARMACOKINETIC INTERACTIONS

Affect **ADME** (Absorption, Distribution, Metabolism, Excretion)
**Absorption:**
Antacids reduce tetracycline absorption
**Distribution:**
Warfarin displaced by aspirin from albumin
**Metabolism:**
CYP450 inducers/inhibitors alter drug levels
**Excretion:**
Probenecid reduces penicillin excretion

### 2. PHARMACODYNAMIC INTERACTIONS

Affect drug action at receptor/target level
**Additive (1+1=2):**
Two similar drugs produce combined effect
**Synergistic (1+1 greater than 2):**
Penicillin + Aminoglycoside = enhanced killing
**Antagonistic (1+1 less than 1):**
Beta-blocker + Beta-agonist = opposing effects

### High-Yield Examples

#### DANGEROUS INTERACTIONS

**Warfarin + Antibiotics**
Increased bleeding risk (altered gut flora)
**ACE inhibitors + K-sparing diuretics**
Hyperkalemia risk
**MAOIs + Tyramine-rich foods**
Hypertensive crisis
**Methotrexate + NSAIDs**
Increased MTX toxicity
**Digoxin + Amiodarone**
Digoxin toxicity (reduced clearance)

## INTERACTION MECHANISMS

### CYP450 Enzyme System

The cytochrome P450 system is the most common site of drug-drug interactions. CYP3A4 metabolizes approximately 50% of all drugs.

#### INDUCERS

(Decrease Drug Effect)

- Rifampicin
- Phenytoin
- Carbamazepine
- Phenobarbital
- St. Johns Wort

#### INHIBITORS

(Increase Toxicity Risk)

- Erythromycin
- Ketoconazole
- Cimetidine
- Ritonavir
- Grapefruit juice

#### TIME COURSE

**Inhibition:** Rapid onset (hours to days)
**Induction:** Slow onset (days to weeks) - requires gene upregulation

#### CLINICAL PEARL

Always check for interactions when starting new medications, especially with narrow therapeutic index drugs (warfarin, digoxin, lithium, phenytoin).

### Managing Interactions

**Prevention Strategies:**

- Thorough medication history
- Use drug interaction databases
- Monitor therapeutic drug levels
- Adjust doses when combining drugs
- Choose alternative agents when possible
- Educate patients about OTC interactions

CLINICAL PHARMACOLOGY

# Adverse Drug Reactions (ADR)

## ADR CLASSIFICATION

### TYPE A – AUGMENTED

**Predictable, dose-dependent**
Extension of pharmacological effectCommon, rarely fatal
*Example:* Hypoglycemia from insulin
*Example:* Bleeding from warfarin

### TYPE B – BIZARRE

**Unpredictable, dose-independent**
Immunological or genetic basisUncommon but potentially fatal
*Example:* Penicillin anaphylaxis
*Example:* Malignant hyperthermia

### TYPE C – CHRONIC

**Long-term use effects**
Cumulative dose-related
*Example:* Corticosteroid osteoporosis
*Example:* Analgesic nephropathy

### TYPE D – DELAYED

**Appears after prolonged latency**
Carcinogenicity, teratogenicity
*Example:* Diethylstilbestrol (DES) – vaginal cancer
*Example:* Thalidomide – phocomelia

### TYPE E – END OF USE

**Withdrawal reactions**
Occurs when drug is stopped abruptly
*Example:* Opioid withdrawal syndrome
*Example:* Beta-blocker rebound hypertension

## SEVERITY GRADING

### WHO CLASSIFICATION

**Mild:** No treatment needed, no prolonged stay
**Moderate:** Requires treatment modification, may prolong hospitalization
**Severe:** Life-threatening, causes permanent damage
**Lethal:** Directly or indirectly contributes to death

## Risk Factors

**Patient factors:**

- Extremes of age (pediatric, geriatric)
- Renal or hepatic impairment
- Genetic polymorphisms
- Multiple comorbidities

**Drug factors:**

- Narrow therapeutic index
- Multiple drug regimens

## Reporting ADRs

### PHARMACOVIGILANCE

Report to national agencies (FDA MedWatch, Yellow Card UK).
Especially report:
– Serious or fatal reactions
– Reactions to new drugs
– Unexpected reactions
– Increased frequency of known ADRs

## Prevention Strategies

- Take thorough drug/allergy history
- Start low, go slow (especially elderly)
- Monitor narrow TI drugs
- Educate patients on warning signs
- Simplify regimens when possible
- Review medications regularly

CLINICAL PHARMACOLOGY

# Drug Toxicity and Routes

## DRUG TOXICITY

### TERATOGENIC DRUGS

Cause fetal malformations – AVOID in pregnancy

**Thalidomide** – Phocomelia (limb defects)
**Isotretinoin** – CNS, cardiac, craniofacial defects
**Warfarin** – Nasal hypoplasia, CNS abnormalities
**ACE inhibitors** – Renal dysgenesis (2nd/3rd trimester)
**Phenytoin** – Fetal hydantoin syndrome
**Methotrexate** – Multiple malformations

### NARROW THERAPEUTIC INDEX DRUGS

Require careful monitoring – small dose changes cause toxicity

**Digoxin** – Monitor levels, watch for arrhythmias
**Lithium** – Therapeutic range 0.6–1.2 mEq/L
**Warfarin** – Monitor INR regularly
**Phenytoin** – Non-linear kinetics
**Theophylline** – Narrow window
**Aminoglycosides** – Nephro/ototoxicity

### Common Toxicity Patterns

**Hepatotoxicity:** Acetaminophen, statins, isoniazid
**Nephrotoxicity:** NSAIDs, aminoglycosides, contrast
**Ototoxicity:** Aminoglycosides, loop diuretics
**Cardiotoxicity:** Doxorubicin, fluoroquinolones
**Pulmonary toxicity:** Amiodarone, bleomycin, MTX
**Bone marrow suppression:** Chemotherapy agents

### KEY ANTIDOTES

**N-acetylcysteine** – Acetaminophen OD
**Naloxone** – Opioid overdose
**Flumazenil** – Benzodiazepine OD
**Vitamin K / FFP** – Warfarin toxicity
**Digoxin Fab** – Digoxin toxicity

## ROUTES OF ADMINISTRATION

### 1. ENTERAL (GI TRACT)

**Oral (PO):** Most common, convenient, first-pass metabolism
**Sublingual/Buccal:** Rapid, bypasses first-pass (nitroglycerin)
**Rectal:** Partial first-pass bypass, useful if vomiting

### 2. PARENTERAL (INJECTION)

**Intravenous (IV):** 100% bioavailability, immediate effect, precise control
**Intramuscular (IM):** Depot injections, moderate absorption
**Subcutaneous (SC):** Slow sustained release (insulin, heparin)
**Intrathecal:** Direct CNS delivery, bypasses BBB

### 3. OTHER ROUTES

**Topical:** Local effect on skin/mucosa
**Transdermal:** Systemic via skin patches (fentanyl, nicotine)
**Inhalation:** Rapid lung absorption (anesthetics, bronchodilators)
**Intranasal:** Direct or systemic (decongestants, calcitonin)
**Ocular/Otic:** Local eye/ear effects

### BIOAVAILABILITY BY ROUTE

IV = 100% > IM > SC > Oral (variable, first-pass)

DOSING AND SPECIAL POPULATIONS

# Dosing Principles

## DOSING PRINCIPLES

Dosing regimens are designed to achieve and maintain therapeutic drug concentrations while minimizing toxicity.

### KEY DOSING CONCEPTS

**Loading Dose:** Rapidly achieve therapeutic levelLD = (Cp x Vd) / F
**Maintenance Dose:** Sustain therapeutic levelMD = (Css x CL x tau) / F
**Dosing Interval (tau):** Based on half-lifeUsually every 1-2 half-lives

## SPECIAL POPULATIONS

### PEDIATRICS

**Immature hepatic/renal function**

- Decreased drug metabolism
- Prolonged half-lives
- Higher body water percentage
- Weight-based dosing required
- Avoid certain drugs (tetracyclines, quinolones)

### ELDERLY

**Age-related physiological changes**

- Decreased renal function (GFR)
- Reduced hepatic blood flow
- Increased body fat, decreased water
- Polypharmacy risk
- Start low, go slow approach

### PREGNANCY

- Avoid teratogenic drugs
- Consider placental transfer
- Risk-benefit analysis essential
- Most critical: 1st trimester (organogenesis)

## DRUG DEVELOPMENT

The drug development process ensures safety and efficacy before reaching patients.

### PRECLINICAL

Laboratory and animal testing. Assess safety, toxicity, and basic pharmacology (ADME).

### PHASE I – SAFETY

20-100 healthy volunteers. Determine safe dosage range, identify side effects.

### PHASE II – EFFICACY

100-300 patients with target condition. Assess effectiveness and optimal dosing.

### PHASE III – LARGE TRIALS

300-3000+ patients, multicenter trials. Confirm efficacy, monitor side effects, compare to standard treatments. Supports NDA.

### PHASE IV – POST-MARKETING

General population after approval. Long-term safety monitoring, detect rare adverse effects, real-world performance.

### DEVELOPMENT TIMELINE

Average: 10-15 years from discovery to market
Cost: $1-2 billion per approved drug
Success rate: Less than 10% of candidates