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药理学

（第3版）

STEPHANIE T. WEISS

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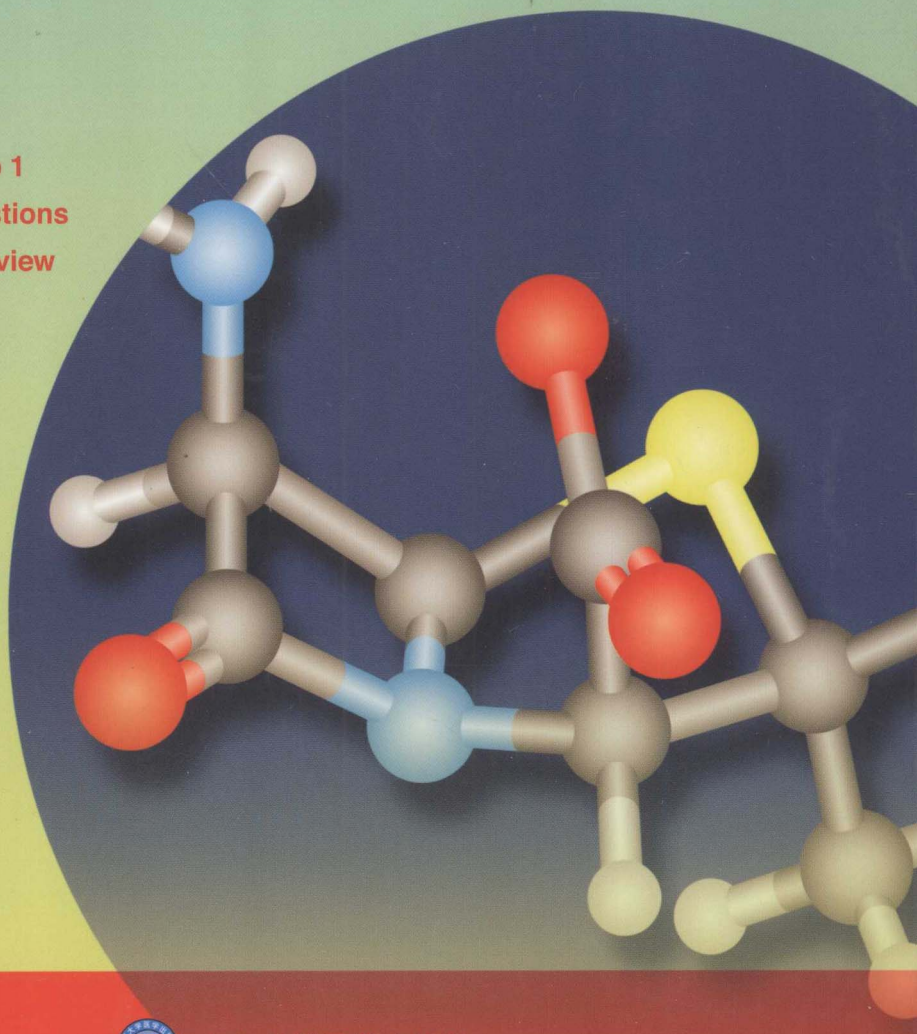

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High-Yield™ 药理学

Pharmacology

（第3版）

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出版说明

High-Yield™ 系列丛书是针对美国医师执照考试（United States Medical Licensing Examination, USMLE）的知名品牌图书，受到世界各地读者的欢迎。该系列丛书具有以下特色：

1. 内容高度概括，重点突出，有利于读者快速掌握学科的核心知识。
2. 编排新颖，既有基础知识要点的介绍，又有以疾病为核心的综合归纳，并体现了相关学科的横向联系。
3. 语言规范、地道，既有利于读者快速掌握专业词汇，又有利于医学英语思维的培养。

本系列丛书是参加美国医师执照考试的必备辅导用书，也可作为我国医学院校从事双语教学的教材和参考用书，对教师进行英语授课，学生学习、参加考试具有重要的参考价值。

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This book is dedicated to the spirit of the Cleveland Clinic Lerner College of Medicine.

Preface

The discipline of pharmacology encompasses both how drugs affect the body (pharmacodynamics), as well as how the body affects drugs (pharmacokinetics). Because it is such an interdisciplinary field, pharmacology necessarily is built upon a foundation consisting of nearly every other basic science discipline that is part of a medical school curriculum. You must have a good grasp of physiology, pathology, biochemistry, microbiology, and molecular biology in order to study pharmacology. Even many disciplines that people have not traditionally associated with pharmacology are turning out to be essential for understanding pharmacology, such as anatomy and genetics. In fact, one of the hottest areas in pharmacology right now is pharmacogenomics, where a patient's treatment is tailored based upon his or her unique genetic makeup.

This edition of *High-Yield Pharmacology* has been substantially updated and revised. Specifically, new sections on biologics have been added in the appropriate chapters, as well as several new figures and tables. In addition, the cardiovascular pharmacology chapter has been expanded and split in half, reflecting the rapid growth in the pharmacology of this area. Readers who desire a very brief review can read the bolded printed text, which highlights the most important concepts in each chapter. In addition, the index can be used to help you review the class of every drug in the book.

It is unfortunate that many medical students approach pharmacology as just a list of drug names and side effects that must be memorized for the United States Medical Licensing Examination. You may be using this book to review pharmacology for Step 1 of the USMLE, and I hope you will find it helpful as you prepare. But I also hope that it will give you at least an inkling of how interesting and dynamic the field of pharmacology is. Please feel free to contact me at weisss@ccf.org if you have any comments or suggestions about the book.

Stephanie T. Weiss

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Contents

Chapter 1

General Principles

I Pharmacokinetics: General Principles

A. PHARMACOKINETICS is the study of the movement of drugs into and out of the body, including **absorption (bioavailability), distribution, metabolism (biotransformation),** and **elimination (ADME).**

B. Clinical pharmacokinetics, which involves the **mathematical description** of the **processes of ADME,** is useful to predict the serum drug concentrations under various conditions.

C. PHARMACOKINETICS can be thought of as **what the body does to the drug.**

II Pharmacokinetics: Administration and Absorption of Drugs

A. Many routes of drug administration can be used.

1. The oral route (PO) is usually preferred.

a. **Advantages** include:

i. **Convenience**

ii. A **large surface area** for absorption

iii. Fewer **abrupt changes of serum drug concentrations** than with parenteral administration

b. **Disadvantages** include:

i. **First-pass metabolism** by the liver

(a) All the blood flow from the intestinal tract goes initially to the liver through the portal vein; therefore the **drug may be metabolized before being distributed** to the other tissues in the body

(b) First-pass metabolism of a drug can be **avoided by parenteral administration of the drug** and partially avoided by rectal administration.

ii. **Systemic exposure to the drug**

2. The parenteral routes of administration are technically more difficult and usually must be performed by a health care professional. Common methods are **inhalation, sublingual, intravenous (IV), intramuscular (IM), and subcutaneous (SQ) administration.**

a. **Advantages** include:

i. A **faster onset** (usually)

ii. **More reliable** absorption

iii. **No first-pass metabolism**

b. **Disadvantages** include:

i. **More difficult** administration

ii. **Pain or necrosis** at the site of infection
iii. Possibility of **infection**
iv. **Toxicity from a bolus intravenous (IV) injection**
v. **Necessity of dissolving the drug if given intravenously**

B. Some drugs are actively or passively transported by carrier proteins, but the movement of drugs across cell membranes usually occurs passively by **diffusion.**

C. THE RATE OF DIFFUSION IS HIGH IF:

1. The unionized form of a drug has a high lipid solubility.

a. Lipid solubility is related to the oil-water partition coefficient.
b. Cell membranes are basically lipoidal in nature, and only lipid soluble substances will diffuse through them.

2. A large proportion of the drug is present in the unionized form.

a. **Only the unionized form can cross cell membranes,** because the ionized form will have a very low solubility in lipids.
b. The equilibrium between the ionized (A^-) and unionized (HA) forms of a weak acid is:

$$\mathbf{HA \leftrightarrow H^+ + A^-}$$

c. The equilibrium constant (K_a) for the dissociation of an acid is defined as:

$$\mathbf{K_a = \frac{[A^-][H^+]}{[HA]}}$$

d. By taking the negative log (–log) of both sides of the K_a expression and rearranging, we can get the Henderson–Hasselbalch equation for a weak acid:

$$\mathbf{pH = pK_a + \log \frac{[A^-]}{[HA]}}$$

e. The proportion of unionized drug will depend on the pH and can be determined with the Henderson–Hasselbalch equation.
f. Weak bases also dissociate, and the equation for dissociation of the conjugate acid of a weak base is:

$$\mathbf{HB^+ \leftrightarrow H^+ + B}$$

g. The equilibrium constant (K_a) for the dissociation of the conjugate acid of a weak base is defined as:

$$\mathbf{K_a = \frac{[B][H^+]}{[HB^+]}}$$

h. By taking the negative log (–log) of both sides of the K_a expression and rearranging, we can get the Henderson–Hasselbalch equation for a weak base:

$$\mathbf{pH = pK_a + \log \frac{[B]}{[HB^+]}}$$

i. Note that the conjugate base should always go in the numerator, while the conjugate acid belongs in the denominator.
j. When the pH equals the pK_a, 50% of a drug will be ionized and 50% will be unionized.
k. The most dramatic changes in the amounts of ionized and unionized drug occur with pH changes near the pK_a.

3. **The membrane is thin.**
4. **The membrane is porous.** Porosity is especially important for water-soluble drugs.
5. **The surface area of the membrane is large.**
6. **The difference in concentrations on the two sides of the membrane is large.**
7. **The diffusion constant, based on molecular size, molecular shape, and temperature, is large.**

D. At the **basic pH** in the small intestine

1. **Weak bases are well absorbed** because most of the drug is unionized.
2. **Weak acids are poorly absorbed** because most of the drug is ionized.
3. The opposite scenario occurs in the acidic environment of the stomach; however, the stomach does not have a very large absorptive capability.

E. ION TRAPPING occurs with weak acids and weak bases if there is a difference in pH on the two sides of a membrane.

1. **The ionized form of the drug will be trapped on one side.**
   a. The ionized form of a **weak base** will be protonated and trapped on the side with the **lower pH.**
   b. The ionized form of a **weak acid** will be deprotonated and trapped on the side with the **higher pH.**
2. Figure 1-1 illustrates ion trapping for a weak acid with a pK_a of 6.4. At equilibrium, the unionized concentrations on either side of the membrane will be equal, but 91% of the drug will be in the compartment at pH 7.4.

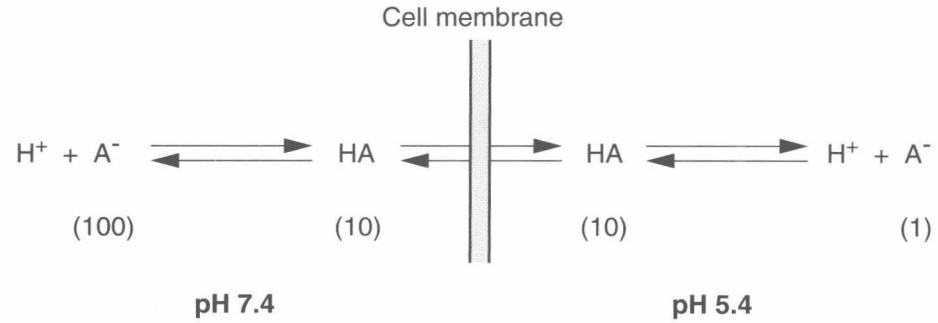
F. STRONG BASES AND STRONG ACIDS are **totally dissociated** or ionized in solution; thus, they are **poorly absorbed at any pH.** Quaternary ammonium compounds are completely ionized at physiological pHs and therefore are also poorly absorbed.

G. ABSORPTION OF A DRUG IS USUALLY FAST, as compared to the elimination; thus, it is often ignored in kinetic calculations. The rate of gastric emptying can affect the absorption and bioavailability of a drug.

H. BIOAVAILABILITY is the **fraction of drug administered that reaches the systemic circulation without being metabolized.**

1. **Bioavailability *(F)* equation:**

$$F = \frac{\textbf{[drug] in the systemic circulation after oral administration}}{\textbf{[drug] in the systemic circulation after IV administration}}$$



● **Figure 1-1** Ion trapping of a weak acid (pK_a 6.4) on the side of the cell membrane with the higher pH. The numbers in parentheses represent the relative concentrations of each form of the weak acid under steady-state conditions.

a. The **bioavailability** after oral administration depends on
   i. The **disintegration** of a tablet
   ii. The **dissolution** of the drug in the intestinal contents
   iii. Gastrointestinal and **first-pass metabolism**

b. **A drug that is administered by IV will be 100% bioavailable.**

2. **Bioequivalence** occurs when drugs with equal *F* have the same drug concentration versus time relationship (i.e., similar rate and extent of drug absorption).
3. **Therapeutic equivalence** (TE) is commonly said to occur when two drugs have the same maximal response; it may be different than bioequivalence. (Note that the FDA defines TE as having the same ingredients, dosage form, route of administration, and concentration.)

III Pharmacokinetics: Distribution of Drugs

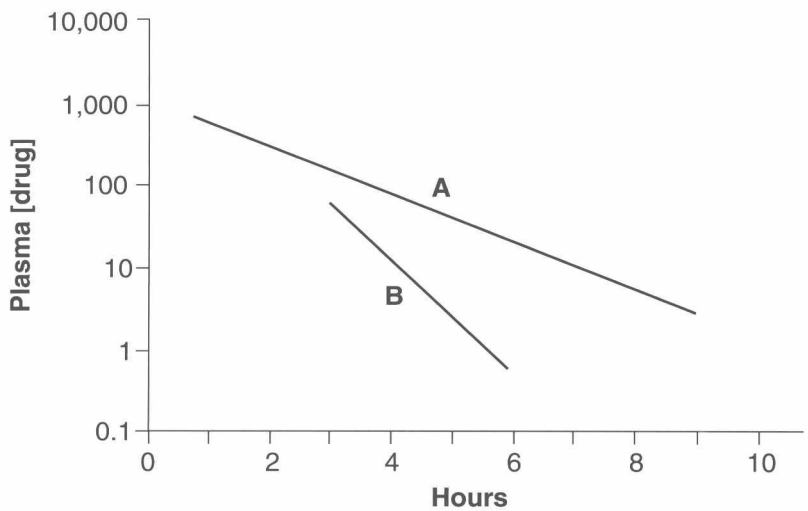
A. THE INITIAL DISTRIBUTION of a drug to the tissues is determined by the **relative blood flows** to the tissues. Sites with high blood flows will initially receive more of the drug.

B. THE VOLUME OF DISTRIBUTION V_d is an approximation of the hypothetical fluid volume that a drug appears to distribute in.

1. It can be very large, even larger than the total body volume, if a drug is highly bound to tissues. This makes the serum drug concentration very low and the V_d very large.
2. The V_d must be calculated at the time of administration.
   a. **Apparent volume of distribution equation:**

$$V_d = \frac{\textbf{amount of drug administered}}{\textbf{serum [drug]}}$$

   b. For the drugs illustrated in Figure 1-2, if the same amount of each was administered, the concentration of drug A at time 0 will be lower; thus, it will have the larger V_d (the numerator is constant, but the denominator is smaller for A than for B). This occurs because more of drug A than drug B is distributed in extravascular tissue.



● **Figure 1-2** Relationship of plasma drug concentration versus time for two drugs. Drug A has the larger apparent volume of distribution.

3. **The loading dose** for a drug is based on the $\mathbf{V_d}$.

$$\textbf{Oral loading dose} = \frac{\mathbf{V_d} \times \mathbf{C}}{\boldsymbol{F}}$$

where C is the desired or target serum drug concentration and F is the bioavailability (fraction of administered drug in the blood).

C. The final **apparent volume of distribution (V_d)** will be affected by
   1. **The lipid solubility** of a drug, which, if high, will result in good penetration into cells and a high V_d
   2. **Plasma protein binding and tissue binding**
      a. **Plasma protein binding, especially to albumin,** will reduce the V_d.
      b. **Tissue binding** will increase the V_d.
      c. Both types of binding act as **reservoirs** for the drug, as only the unbound drug can activate pharmacological receptors. Thus binding will
         i. **Slow the onset** of drug action
         ii. **Prolong the duration** of drug action, if the drug is eliminated by glomerular filtration in the kidney
   3. **Competition** for binding sites on albumin between two drugs A and B **can raise free levels** of A in the blood if
      a. The concentration of B exceeds the number of albumin binding sites
      b. B is able to displace A from the albumin binding sites

IV Pharmacokinetics: Metabolism of Drugs

A. The **liver** is the **primary site of drug metabolism.**

B. Metabolism can change a drug in several ways.
   1. The **polarity is usually increased,** enhancing the water solubility and renal excretion of the drug metabolite.
   2. The **activity of the drug is reduced. Exceptions** are the **prodrugs,** which are drugs that are inactive in the form administered but are metabolized to their active forms.
   3. A drug metabolite usually has a **smaller V_d** due to its increased water solubility.

C. **PHASE 1** metabolic reactions usually lead to the **alteration or inactivation** of the drug's activity. Often, new functional groups are introduced that make further metabolism possible.
   1. **Oxidation by cytochrome P450 (CYP)** enzymes (also known as **mixed function oxidases [MFO],** microsomal enzymes, mono-oxygenases) **occurs** in the **smooth endoplasmic reticulum (ER).**
      a. Nicotinamide adenine dinucleotide phosphate **(NADPH), cytochrome P450 reductase,** and elemental oxygen **(O_2)** are required.
      b. Many reactions can be produced, including:
         i. **Hydroxylation**
         ii. **Dealkylation**
         iii. **Deamination**
         iv. **Sulfoxidation**
         v. **Oxidation**
      c. Highly lipid soluble drugs are more readily metabolized by CYPs.
   2. **Reductive reactions** can occur in the ER or the cytosol.
   3. **Hydrolytic reactions** do not occur in the ER.

D. **PHASE 2** metabolic reactions are **conjugative,** adding highly polar groups to the drug to increase renal elimination.

1. **Glucuronidation** occurs in the **ER.** Glucose is used to form uridine diphosphate glucuronic acid (UDPGA), which then transfers a glucuronide to the drug in the presence of glucuronyl transferase.
2. Other substances can be conjugated (by transferases primarily in the cytosol) to drugs. These conjugates generally reduce the drug's activity and increase its polarity, including:
   a. Sulfate
   b. Acetyl
   c. Methyl
   d. Glutathione
   e. Amino acids, especially glycine

E. Many drug **interactions** are due to changes in CYP activity in the liver.

1. **Induction** of CYPs results from increased levels of CYPs in the ER.
   a. The onset of induction is **slow** (days) and the duration is **long** (taking a week or more for recovery after the drug is withdrawn).
   b. Many drugs that are metabolized by the CYPs also induce the CYPs, including:
      i. **Barbiturates, phenytoin, rifampin**
      ii. **Alcohol**
      iii. **Cigarette smoke**
   c. This induction hastens the metabolism of the inducing drug along with other drugs metabolized by the same CYPs.
2. **Inhibition** of drug metabolism occurs if there is **competition** between drugs at the CYP, or if a drug tightly binds to the CYP.
   a. Potent CYP inhibitors include **cimetidine, ritonavir,** and **azole antifungals.**
   b. Grapefruit juice has a similar inhibitory effect.

F. Liver enzymes are polymorphic in the population, such that individuals with different enzyme forms may metabolize a drug at different rates.

G. The rate of metabolism is first order for most drugs

1. **First-order** metabolism is **proportional** to the **concentration** of **free drug.**
2. A constant fraction of drug is metabolized per unit of time (i.e., the metabolism of the drug has a half-life.)

V Pharmacokinetics: Elimination of Drugs and Drug Metabolites

A. The **kidney** is the primary organ that excretes drugs and drug metabolites.

1. If the drug is excreted in the unmetabolized form, the kidney also decreases that drug's pharmacological activity.
2. **Polar drugs and drug metabolites** are readily eliminated by the kidney.

B. **GLOMERULAR FILTRATION** of the unbound molecule accounts for the excretion of most drugs.

1. **Drug molecules bound by plasma proteins will not be filtered** by the glomerulus.
2. **Hydrophilic** substances are most **efficiently eliminated** by the kidney, because they are not readily reabsorbed across the nephron tubule after they are filtered.
3. If a drug is a **weak base,** administration of ammonium chloride will **acidify the urine** and increase the amount of the base that is in the ionized form.

   a. The **excretion of the weak base will be increased.**
   b. This will be most effective if the pK_a of the drug is near the physiological pH.
4. The **excretion of a weak acid can be increased by alkalinizing the urine** with sodium bicarbonate.

C. ACTIVE TRANSPORT of a few drugs occurs in the **proximal tubule.**

1. It usually involves **secretion of strong acids or strong bases.**
2. **P-glycoprotein** is an important **transporter** in renal and other cells.
3. **Characteristics** of active transport are
   a. **Competition** between substrates for the carrier
   b. **Saturability** of the carrier
   c. **Being unaffected by plasma protein binding**
4. **Active reabsorption** can also occur.
5. A few substances are both actively secreted and actively reabsorbed (e.g., uric acid, aspirin).

D. BILIARY EXCRETION occurs in the liver.

1. **Large polar compounds,** often conjugated metabolites, are actively excreted into the bile.
2. **Enterohepatic cycling** occurs with a few drugs that are eliminated in the bile, reabsorbed from the intestine, returned to the liver and again eliminated in the bile.
   a. **Glucuronidase** in the intestine can cleave off the glucuronide, so the free drug can be reabsorbed (Figure 1-3).
   b. **Digitoxin,** a cardiac glycoside, undergoes enterohepatic cycling.
   c. This **may increase the half-life** of the drug.

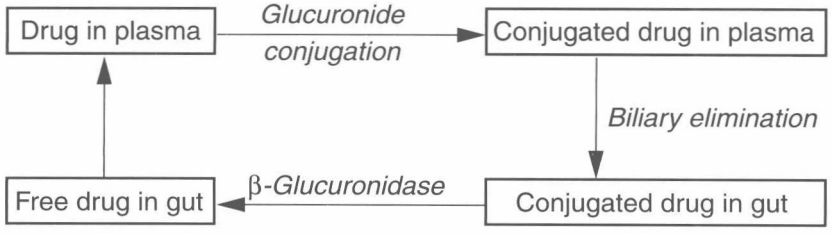
E. ELIMINATION usually follows the principles of **first-order kinetics,** which means that a constant fraction of the drug is eliminated per unit of time (k_e).

1. **Clearance (Cl) equals $V_d \times k_e$**
   a. Clearance is measured as a volume per unit of time.
   b. The rate of drug elimination equals Cl × C_{ss}, where C_{ss} is the drug concentration at steady state.
   c. The **oral maintenance dose** simply involves the replacement of the amount of drug that has been eliminated in the dosage time interval (T).

$$\textbf{Oral maintenance dose} = \frac{Cl \times C_{ss} \times T}{F}$$

2. **The half-life** ($t_{1/2}$) of a drug is the time required for the serum drug concentration to be reduced by 50%.

   a. $$t_{1/2} = \frac{0.69}{k_e} = \frac{0.69 \times V_d}{Cl}$$



● **Figure 1-3** Enterohepatic cycling of a conjugated drug.