高等医药教育教材

药理学

Pharmacology

英文版　第2版

主　编　JIANG Zhiwen（蒋志文）

人民軍醫出版社
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内 容 提 要

本书在第 1 版的基础上修订而成，作者参考多部国外流行的新版药理学教材和专著，吸纳国内药理学教科书之风格，并结合作者从事十多年药理学双语教学之经验，编写了英文版药理学。全书共 44 章，包括药理学总论 4 章，传出神经系统用药 7 章，中枢神经系统用药 8 章，心血管系统用药 5 章，化疗用药 11 章，激素类药物 3 章，H-受体阻断药、利尿药和呼吸、消化、解热镇痛、缩宫保胎用药各 1 章。本书内容新颖、阐述准确，可作为医药卫生本、专科药理学双语教学之用，亦可作为药理学专业工作者自修用书。

Preface for the First Edition

We have expected to gain our own textbook of pharmacology in dual language for a long time. Because we have found there are lots of differences between oversea textbooks and ours'. Or in other words, oversea pharmacological textbooks are not quite suitable for us. Therefore we have decided to write teaching textbook by ourselves.

Since 2000, We have started to put English into our teaching step by step. In order to promote our teaching quality and let students accept this teaching manner, We have unrelentingly revised our teaching outline, plan and textbooks. Now the writing work has been complished finally.

We are sure there must have some shortcomings, even some errors included in this book. So, any suggestion or comment will be highly appreciated. We will share no efforts to improve our teaching work in the future.

Editor

Jan,10,2006

Preface for the Second Edition

This is the second edition of《Pharmacology》, also the new version we have made after pharmacology bilingual teaching practice for more than 10 years. Bilingual teaching practices of several years for pharmacology make us have discovered the miss-distance and shortage of the first version, It is this that stirs up our rewriting passion.

The second edition has been thoroughly revised and updated to comprehensively cover drug's action mechanism, pharmacokinetics, pharmacodynamics and rational usage. rewriting endows the new version pharmacology a function of more easy reading, more easy understanding and more competently to be used as textbook for pharmacology education.

The second edition has still been designed for bilingual education of pharmacology. However it will also be useful to other health care professionals such as nursing, pharmacy, and other students interested in pharmacology. We hope that the readers of this second edition enjoy reading this book as much as we have enjoying preparing it.

We acknowledge Xu Shuxiu, Tan Lei, Xu Jincheng, Gong Jiyong, Jiang Yumei, Li Jinzhi, Xu Xiaoyue, Jiang Yumin and Tiang Yanyan for their great contribution to this book.

Editor

Jan,10,2012

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Chapter 1

Introduction

The word "pharmacology" can be split into *pharmaco* and logy, *pharmaco* comes from "pharmakon", a ancient Greek word for drug, and logy is from another Greek word,-*logia* which means science, thus pharmacology is a science about drugs where a drug can be broadly defined as any man-made, natural, or endogenous (within the cell) molecule which exerts a biochemical and/or physiological effect on the cell, tissue, organ, or organism. More specifically, pharmacology is the study of the interactions that occur between a living organism and chemicals that affect normal or abnormal biochemical function.

Pharmacology is not synonymous with pharmacy. Pharmacology is the study of drugs, of the reactions of the body and drug on each other. In contrast, pharmacy is a health services profession that is concerned with the manufacture, preparation and dispensing of drugs.

The two main areas of pharmacology are pharmacodynamics and pharmacokinetics. The former studies the effects of the drugs on biological systems, while the latter studies the effects of biological systems on the drugs. In broad terms, pharmacodynamics discusses the interactions of drugs with biological receptors, the effects of drug and action mechanism by which the therapeutic effects are gained. Pharmacokinetics discusses the absorption, distribution, biotransformation, and excretion of drugs from the biological systems. By this research the relationship between drug effect and drug concentration in the body will be exposed, the therapeutic effect will be elevated and adverse reaction, even more toxicity will be avoided effectively.

Knowledge of pharmacology is essential in the practice of human medicine, where drugs are used to treat diseases of humans. The principle of pharmacology also apply to toxicology, where the toxic effects of drugs are studied, whether or not a drug is used for therapy, a knowledge of its pharmacology is essential if it is to be used selectively for a defined purpose.

Chapter 2

Pharmacokinetics

The pharmacokinetics is to deal with the fate of the drug in the body, to study the changes of the activity and sites of drug in the body. That is to say, the goal of the pharmacokinetics is to study the disposition process of drug in the body.

The pharmacokinetics includes two parts: transportation and transformation of the drugs.

Transportation of drug in the body includes absorption, distribution and excretion.

Drug absorption

Absorption of drug refers to the procedures through which the drug enters the circulation. Here the drug must cross membranes before its entrance to the circulation. So absorption of drug is affected by the factors below(Fig. 2-1):

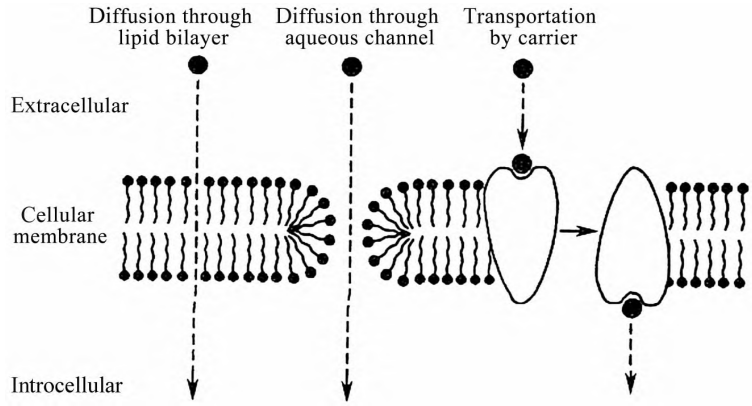

Figure 2-1 Cellular membrane structure and transmembrane diffusion of drug

1. Cell membranes Cell membrane is composed of lipid bilayer, aqueous channels and carriers located in the membrane. So the transmembrane transportation should be affected by many factors such as drug's liposoluble ability, polarity, size and so on.

2. Liposoluble properties of drugs The diffusion speed of drugs exhibit the direct relationship with the liposoluble properties of the drug.

3. Un-ionization degree Un-ionized molecules [B] are far more soluble than those are ionized [BH^+] and surrounded by a "shell" of water.

4. Size The smaller the drug molecule is, the more favorable the drug passes through the membrane. Most drugs are small molecules (molecular weight $<1,000$) that are able to diffuse across membranes in their original state.

5. pH of the environment Since most drugs are either weak bases, weak acids, or amphoteric, the pH of the environment in which they dissolve, as well as the pKa value of the drug, will be important in determining the fraction in the un-ionized form that is in solution and able to diffuse across cell membranes. The pKa of a drug is defined as the pH at which 50% of the molecules in solution are in the ionized form, and is characterized by the Henderson-Hasselbalch equation:

weak acids	weak bases
$HA=H^+ + A^-$	$HB^+ = H^+ + B$
$Ka=\frac{[H^+][A^-]}{[HA]}$	$Ka=\frac{[H^+][B]}{[BH^+]}$
$pKa=pH-\log\frac{[A^-]}{[HA]}$	$pKa=pH-\log\frac{[B]}{[BH^+]}$
$pKa-pH=\log\frac{[A^-]}{[HA]}$	$pKa-pH=\log\frac{[BH^+]}{[B]}$
$10^{pH-pKa}=\frac{[A^-]}{[HA]}$	$10^{pKa-pH}=\frac{[BH^+]}{[B]}$
when $pH=pKa$	
$[A^-]=[HA]$	$[BH^+]=[B]$

Drugs will tend to exist in the ionized form when exposed to an environment with a pH opposite to their own state. Therefore, acids become increasingly ionized with increasing pH (e.g., basic drug)

It is useful to consider three important body compartments which interfere with the transportation of drug.

Plasma (pH=7.4),

Stomach (pH=2.0)

Urine (pH=8.0)

Napoxen is a weak acid (pKa=5.0) and its absorption will therefore be favored in the stomach, where it is uncharged, and not in the plasma or the urine, where it is highly charged; aspirin in high doses may even damage the stomach.

Morphine is a weak base (pKa= 8.0) that is highly charged in the stomach, quite charged in the plasma, and half charged in the urine.

Morphine(pKa=8.0)

	Stomach pH 2.0	plasma pH 7.4	urine pH 8.0
BH^+ / B	1,000,000/1	3.98/1	1/1

So morphine is able to cross the blood-brain barrier but is poorly and erratically absorbed from the stomach and intestines, and metabolized by the liver, and must therefore be given by injection or delayed-release capsules.

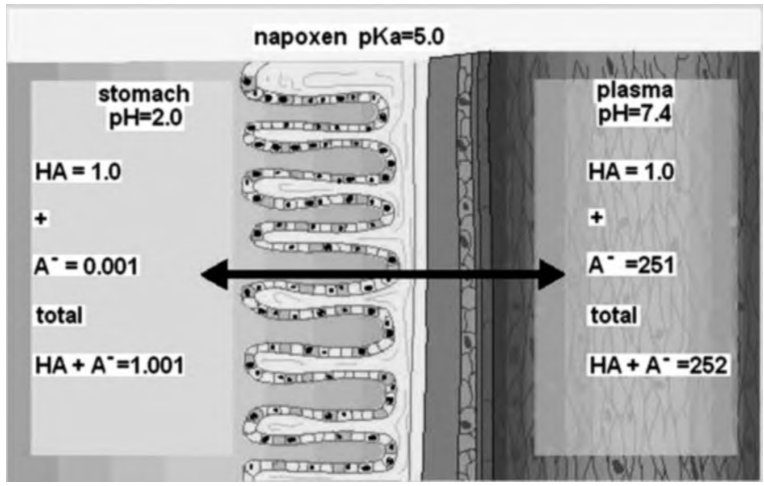

Figure 2-2 The variations of ionization and unionization of napoxen in different pH environments

Some drugs, such as quaternary ammonium compounds (e. g. , suxamethonium, tubocurarine) are always charged, and must therefore be injected.

6. Routs of administration

(1) Topical route Topical administration are placed when they are needed, giving them the advantage that do not have to cross any barriers or membranes, Examples include skin ointment; ear, nose, or eye drops; and aerosols inhaled in the treatment of asthma.

(2)Enteral route Enteral administration means that the drug reaches its target via the gut. It is the least predictable rout of administration, owing to metabolism by the liver, chemical breakdown, and the possible binding to food. Drugs must cross several barriers, which may or may not be a problem according to their physicochemical properties such as charge and size. However:

① Most drugs are administered orally unless the drug is unstable, or is rapidly inactivated in the gastrointestinal tract, or if its efficacy of absorption from the gastrointestinal tract is uncertain owing to metabolism by the liver or the intestines, vomiting, or a disease that may affect drug absorption.

② Absorption of drug via the buccal or sublingual rout avoids the portal circulation and is therefore valuable when administering drugs subject to a high degree of first-pass metabolism. It is also useful for potent drugs with a non-disagreeable taste, such as sublingual nitroglycerin given to relieve acute attacks of angina.

③ Administration of drugs rectally, such as in the form of suppositories, means that there is less first-pass metabolism by the liver because the venous return from the lower gastrointestinal tract is less than that from the upper gastrointestinal tract. It has the disadvantage, however, of being inconsistent.

④ Antacids have their effect in the stomach and may be considered as being topical.

⑤ Bioavailability and First-pass elimination, Extraction ratio.

· **Bioavailability(F)** is defined as the fraction of unchanged drug reaching the systemic circulation following administration by any route

$$F=\frac{dose\ absorbed\ into\ the\ systemic\ circulation}{dose\ administered}\times 100\%$$

So the route of administration will alter the bioavailability of drugs (Tab. 2-1).

Table 2-1 Influences of the different administrations on the availability of drugs

Routes	Bioavailability (%)	Characteristics
Intravenous	100	Most rapid onset
Intramuscular	75 to≤100	Large volumes often feasible; may be painful
Subcutaneous	75 to≤100	Smaller volumes than IM; may be painful
Oral	5 to<100	Most convenient; first-pass effect may be significant
Rectal	30 to<100	Less first-pass effect than oral
Inhalation	5 to<100	Often very rapid onset
Transdermal	80 to≤100	Usually very slow absorption; used for lack of first pass effect; prolonged duration of action

· **First-pass elimination** Following absorption across the gut wall, the portal blood delivers the drug to the liver, prior to entry into the systemic circulation. A drug can be metabolized in the gut wall (e. g., by the CYP3A4 enzyme system) or even in the portal blood, but most commonly it is the liver that is responsible for metabolism before the drug reaches the systemic circulation. In addition, the liver can excrete the drug into the bile. All of these can contribute to its reduction in bioavailability. And the overall process is known as **first-pass loss or elimination.**

· **Extraction ratio(ER)**

ER is hepatic extraction ratio,represents the effect of first-pass hepatic elimination.

Drugs with high extraction ratios will show marked variations in bioavailability between subjects because of their differences in hepatic function and blood flow. These differences can explain the marked variation in drug concentrations that occur among individuals given similar doses of highly extracted drugs. For drugs that are highly extracted by the liver, shunting of blood past hepatic sites of elimination will result in substantial increases in drug availability, whereas for drugs that are poor extracted by the liver(for which the difference between entering and exiting drug concentration is small), shunting of blood past the liver will cause little change in availability.

7. Extent of absorption after oral administration A drug may be incompletely absorbed, e. g., only 70% of a dose of digoxin reaches the systemic circulation. This is mainly due to: