高等医药教育试用教材

·英文版·

药理学

Pharmacology

主　编　蒋志文

人民军医出版社
PEOPLE'S MILITARY MEDICAL PRESS

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ISBN 7-5091-0243-X
9 787509 102435 >

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◇封面设计　龙　岩

ISBN 7-5091-0243-X
定价：35.00元

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人民军医出版社
People's Military Medical Press

北　京

图书在版编目(CIP)数据

药理学(英文版)/蒋志文主编．—北京：人民军医出版社，2006.3
高等医药教育试用教材
ISBN 7-5091-0243-X

Ⅰ.药… Ⅱ.蒋… Ⅲ.药理学—医学院校—教材—英文 Ⅳ.R96

中国版本图书馆 CIP 数据核字(2006)第 011831 号

策划编辑：杨磊石　**文字编辑**：魏文青　**责任审读**：李　晨
出 版 人：齐学进
出版发行：人民军医出版社　　**经销**：新华书店
通信地址：北京市复兴路 22 号甲 3 号　**邮编**：100842
电话：(010)66882586(发行部)、51927290(总编室)
传真：(010)68222916(发行部)、66882583(办公室)
网址：www.pmmp.com.cn

印刷：北京国马印刷厂　**装订**：京兰装订有限公司
开本：787mm×1092mm　1/16
印张：16.75　**字数**：402 千字
版、印次：2006 年 3 月第 1 版第 1 次印刷
印数：0001～4500
定价：35.00 元

内 容 提 要

本书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，并揉进作者从事五年余药理学双语教学之体验，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、呼吸、消化、解热镇痛和缩宫保胎用药各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。

责任编辑　杨磊石　王丛妙

Preface

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

Contents

Chapter 1

Introduction——The nature and task of pharmacology

What's drug?

A drug is any natural or synthetic substance that alters the physiologic or biochemical state of a living organism. According the clinical usage, the drugs can be divided into two large groups:

Medical drugs are referred to be used for the treatment, prevention, and diagnosis of the disease.

Non-medical drugs or social drugs are referred to be used for recreational purposes. These drugs include illegal mood altering such as cannabis, heroin, and cocaine as well as everyday substances such as caffeine, nicotine and alcohol.

What is pharmacology?

The word 'pharmacology' is from the combination of Pharmakon (Greek), and English suffix, -ology. As the term suggests, Pharmacology is a kind of science to study both the mechanisms and the actions of drugs, to tell why and how to choose or use them reasonably.

The contents of pharmacology include pharmacodynamics and pharmacokinetics. The former is to study the action of the drug on the body, and the mechanism of the drugs. The later is to study the metabolistic procedure of the drugs in the body. That is to say, it aims at the study of absorption, distribution, biotransformation, and excretion of the drugs.

The task of the pharmacology is to describe the drug mechanism, to study how to promote the therapeutic effects of the drug, and to provide data for exploring the cellular physiologic and biochemical mechanism as well as pathological process of the disease.

Chapter 2

Pharmacokinetics

The pharmacokinetics is to deal with the fate of the drug in the body, to study the metabolism and action of drugs with particular emphasis on the time required for absorption, distribation, duration of action, metabolism and excretion 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 drugs in the body

Transportation of drugs 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):

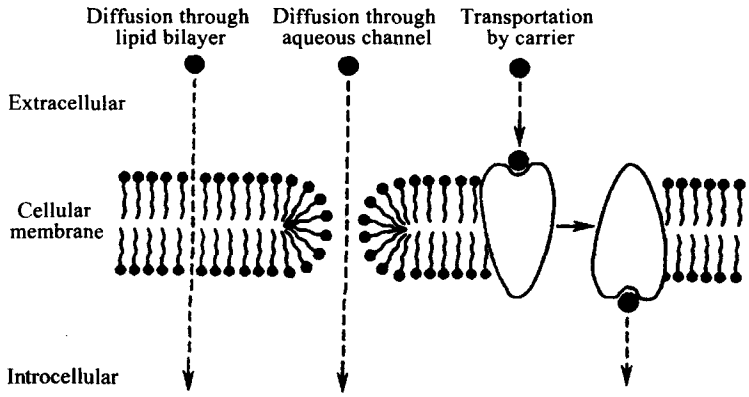

fig 2-1. Cellular membrane structure and transmembrane diffusion of drug

(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 rela-

tionship 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 favorably for 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
$HA=H^+ + A^-$	$HB^+ = H^+ + B$
$Ka=\frac{[H^+][A^-]}{[HA]}$	$Ka=\frac{[H^+][B]}{[BH^+]}$
$pKa=pH-\log\frac{[A^-]}{[HA]}$	$pKa=pH-\log\frac{[B]}{[BH^+]}$
$pKa=pH=\log\frac{[A^-]}{[HA]}$	$pKa-pH=\log\frac{[BH^+]}{[B]}$
$10^{pH-pKa-pH}=\frac{[A^-]}{[HA]}$	$10^{pKa-pH}=\frac{[BH^+]}{[B]}$
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 that interfere with the transportation of drug.

Plasma (pH=7. 4)

Stomach (pH=2. 0)

Urine (pH=8. 0)

Naproxen is a weak acid (pKa=5. 0) and its absorption will therefore be favored in the stomach, where it is uncharged, but 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 pH2. 0	plasma pH7. 4	urine pH8. 0
BH^+ / B	1,000,000/1	3. 98/1	1/1

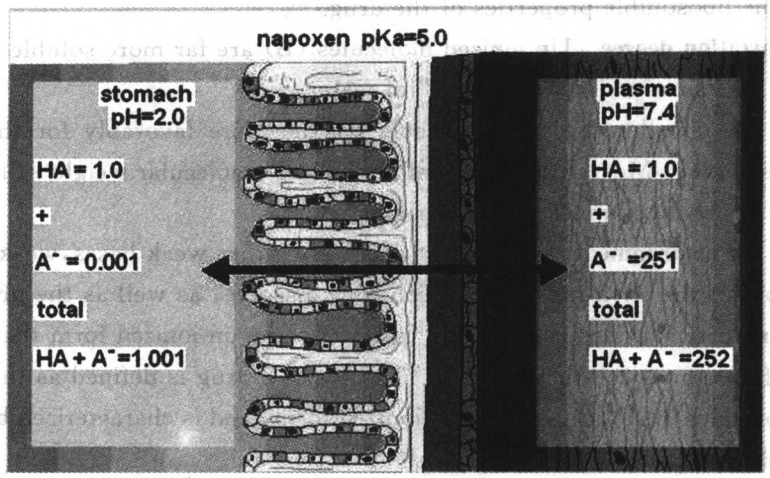

fig 2-2. The variations of ionization and unionization of napoxen in different pH environments

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.

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

(6) Routes 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 some components (e. g. , protein). 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 suppository, means that

there is less interference first-pass elimination 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 effects in the stomach and may be considered as being topical administration.

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 (Table 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 elimination may be significant
Rectal	30 to<100	Less first-pass elimination than oral
Inhalation	5 to<100	Often very rapid onset
Transdermal	80 to≤100	Usually very slow absorption; almost no first-pass elimination; 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 matebolized 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 the **first-pass loss** or **elimination.**

• **Extraction ratio(ER)**

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