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CASE FILES[®]

Pharmacology

药理学案例56例

Eugene C. Toy, MD

Vice Chair of Academic Affairs and
Residency Program Director
Department of Obstetrics and Gynecology
The Methodist Hospital, Houston
John S. Dunn, Senior Academic Chair of
Obstetrics and Gynecology
St. Joseph Medical Center
Clinical Professor and Clerkship Director
Department of Obstetrics and Gynecology
University of Texas Medical School
at Houston
Houston, Texas

David S. Loose, PhD

Associate Professor
Department of Integrative Biology and
Pharmacology & Graduate School of
Biomedical Sciences
University of Texas Medical School
at Houston
Houston, Texas

Shelley A. Tischkau, PhD

Associate Professor
Department of Pharmacology
Southern Illinois University School
of Medicine
Springfield, Illinois

Anush S. Pillai, DO, FAAFP

Attending/Faculty Physician
Methodist Family Medicine Residency
Program
Deputy Vice Chair – The Methodist
Hospital
Clinical Associate Professor
Weill Medical College, Cornell University
Vecino Health Centers – Denver Harbor
Clinic
Houston, Texas



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出版说明

Case Files 是美国麦格劳 - 希尔教育出版公司医学图书中的著名品牌系列图书, 被世界多所著名医学院校选定为教学用书。北京大学医学出版社与麦格劳 - 希尔教育出版公司合作, 全套影印出版了该丛书。包括:

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- 妇产科学案例 60 例
- 神经病学案例 54 例
- 心脏病学案例 50 例
- 生物化学案例 60 例
- 病理学案例 50 例
- 微生物学案例 60 例
- 外科学案例 56 例
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该丛书具有以下特点:

一、形式上, 原版图书影印, 忠实展现原版图书的原汁原味, 使国内读者直接体会医学原版英文图书的叙述方式和叙述风格。

二、内容上, 每个分册包含几十个经典案例。基础学科强调与临床的结合, 临床学科强调临床思维的培养。

三、以案例和问题导入, 互动式学习, 尤其适合 PBL (问题为中心的学习) 和 CBL (案例为中心的学习)。

本系列书可作为医学院校双语教学或留学生教学的教材或教学辅导用书, 也是医学生学习医学英语的优秀读物。在世界范围内, 该系列书还是参加美国医师执照考试的必备用书。

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DEDICATION

To Dr. Larry C. Gilstrap III, whose encouragement is largely responsible for my writing this series of books. He has been a personal inspiration, mentor, and role model of an outstanding physician, teacher, and leader; and to Dr. Edward Yeomans, who has been a dear friend and gleaming light of brilliance in obstetrics.

—ECT

To the medical and graduate students of the UT Health Medical School in Houston who continually challenge and make both teaching and research far more interesting; and to my son William and innumerable colleagues for their patience and encouragement during the writing and editing of the manuscript.

—DSL

To my patients, who humble me with their trust and respect; to my residents, students, and colleagues who challenge, teach, and inspire me; and of course to my family who support and encourage my passion.

—ASP

To my students, who continue to provide inspiration.

—SAT

CONTRIBUTOR

Kathleen Bottum, MD, PhD

Assistant Professor

Department of Internal Medicine

Division of Medicine and Psychiatry

Southern Illinois University School of Medicine

Springfield, Illinois

The inspiration for this basic science series occurred at an educational retreat led by Dr. L. Maximilian Buja, who at the time was the dean of the medical school. It has been such a joy to work together with Dr. David Loose, who is an accomplished scientist and teacher. It has been rewarding to collaborate with Dr. Anush Pillai, a scholar and an excellent teacher. It has been a pleasure to work with our new author Dr. Shelley Tischkau, who is both a content expert and an excellent educator. I would like to thank McGraw-Hill for believing in the concept of teaching by clinical cases. I owe a great debt to Catherine Johnson, who has been a fantastically encouraging and enthusiastic editor.

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Eugene C. Toy, MD

Often, the medical student will cringe at the “drudgery” of the basic science courses and see little connection between a field such as pharmacology and clinical problems. Clinicians, however, often wish they knew more about the basic sciences, because it is through the science that we can begin to understand the complexities of the human body and thus have rational methods of diagnosis and treatment.

Mastering the knowledge in a discipline such as pharmacology is a formidable task. It is even more difficult to retain this information and to recall it when the clinical setting is encountered. To accomplish this synthesis, pharmacology is optimally taught in the context of medical situations, and this is reinforced later during the clinical rotations. The gulf between the basic sciences and the patient arena is wide. Perhaps one way to bridge this gulf is with carefully constructed clinical cases that ask basic science-oriented questions. In an attempt to achieve this goal, we have designed a collection of patient cases to teach pharmacology-related points. More importantly, the explanations for these cases emphasize the underlying mechanisms and relate the clinical setting to the basic science data. The principles are explored rather than overemphasizing rote memorization.

This book is organized for versatility: to allow the student “in a rush” to go quickly through the scenarios and check the corresponding answers and to provide more detailed information for the student who wants thought-provoking explanations. The answers are arranged from simple to complex: a summary of the pertinent points, the bare answers, a clinical correlation, an approach to the pharmacology topic, a comprehension test at the end for reinforcement or emphasis, and a list of references for further reading. The clinical cases are arranged by system to better reflect the organization within the basic science. Finally, to encourage thinking about mechanisms and relationships, we used open-ended questions in the clinical cases. Nevertheless, several multiple-choice questions are included at the end of each scenario to reinforce concepts or introduce related topics.

HOW TO GET THE MOST OUT OF THIS BOOK

Each case is designed to introduce a clinically related issue and includes open-ended questions usually asking a basic science question, but at times, to break up the monotony, there will be a clinical question. The answers are organized into four different parts:

Part I

1. **Summary**
2. **A straightforward answer** is given for each open-ended question.
3. **Clinical Correlation**—A discussion of the relevant points relating the basic science to the clinical manifestations, and perhaps introducing the student to issues such as diagnosis and treatment.

Part II

An approach to the basic science concept consisting of three parts:

1. **Objectives**—A listing of the two to four main knowledge objectives that are critical for understanding the underlying pharmacology to answer the question and relate to the clinical situation.
2. **Definitions of basic terminology.**
3. **Discussion of the specific class of agents.**

Part III

Comprehension Questions—Each case includes several multiple-choice questions that reinforce the material or introduces new and related concepts. Questions about the material not found in the text are explained in the answers.

Part IV

Pharmacology Pearls—A listing of several important points, many clinically relevant, reiterated as a summation of the text and to allow for easy review, such as before an examination.

Contributor / vi

Acknowledgments / vii

Introduction / ix

Section I

Applying the Basic Sciences to Clinical Medicine 1

Part 1. Approach to Learning Pharmacology..... 2

Part 2. Approach to Disease..... 3

Part 3. Approach to Reading 3

Section II

Clinical Cases 9

Fifty-Six Case Scenarios 11

Section III

Listing of Cases..... 421

Listing by Case Number 423

Listing by Case Topic (Alphabetical) 424

Index / 427

Applying the Basic Sciences to Clinical Medicine

- Part 1 Approach to Learning Pharmacology
- Part 2 Approach to Disease
- Part 3 Approach to Reading

Part 1. Approach to Learning Pharmacology

Pharmacology is best learned by a systematic approach, understanding the physiology of the body, recognizing that every medication has desirable and undesirable effects, and being aware that the biochemical and pharmacologic properties of a drug affects its characteristics such as duration of action, volume of distribution, passage through the blood-brain barrier, mechanism of elimination, and route of administration. Rather than memorizing the characteristics of a medication, the student should strive to learn the underlying rationale such as, "Second-generation antihistamine agents are less lipid soluble than first-generation antihistamines and therefore do not cross the blood-brain barrier as readily; thus, second-generation antihistamines are not as sedating. Because they both bind the histamine H₁ receptor, the efficacy is the same."

KEY TERMS

Pharmacology: The study of substances that interact with living systems through biochemical processes.

Drug: A substance used in the prevention, diagnosis, or treatment of disease.

Toxicology: A branch of pharmacology that studies the undesirable effects of chemicals on living organisms.

Food and Drug Administration (FDA): The federal agency responsible for the safety and efficacy of all drugs in the United States, as well as food and cosmetics.

Adverse effect: Also known as side effect; all unintended actions of a drug that result from the lack of specificity of drug action. All drugs are capable of producing adverse effects.

Pharmacodynamics: The actions of a drug on a living organism, including mechanisms of action and receptor interaction.

Pharmacokinetics: The actions of the living organism on the drug, including absorption, distribution, and elimination.

Volume of distribution (V_d): The size of the "compartment" into which a drug is distributed following absorption and is determined by the equation:

$$V_d = \text{Dose (mg) drug administered} / \text{Initial plasma concentration (mg/L)}$$

Potency of drug: Relative amount of drug needed to produce a given response, determined largely by the amount of drug that reaches the site of action and by the affinity of the drug for the receptor.

Efficacy: Drug effect as the maximum response it is able to produce and is determined by the number of drug-receptor complexes and the ability of the receptor to be activated once bound. EC-50 refers to the drug concentration that produces 50 percent of the maximal response, whereas ED-50 refers to the drug dose that is pharmacologically effective in 50 percent of the population.

Absorption: The movement of a drug from the administration site into the blood stream usually requiring the crossing of one or more biologic membranes. Important parameters include lipid solubility, ionization, size of the molecule, and presence of

Elimination: Process by which a drug is removed from the body, generally by either metabolism or excretion. Elimination follows various kinetic models. For example, **first-order kinetics** describes most circumstances, and means that the rate of drug elimination depends on the concentration of the drug in the plasma as described by the equation:

$$\text{Rate of elimination from body} = \text{Constant} \times \text{Drug concentration}$$

Zero-order kinetics: It is less common and means that the rate of elimination is constant and does not depend on the plasma drug concentration. This may be a consequence of a circumstance such as saturation of liver enzymes or saturation of the kidney transport mechanisms.

Bioavailability: The percentage of an ingested drug that is actually absorbed into the bloodstream.

Route of administration: Drug may be delivered **intravenously** (IV or iv) for delivery directly into the bloodstream, **intramuscularly** (IM), and **subcutaneously** (SC). The medication may be depot and slow release, **inhalant** for rapid absorption and delivery to the bronchi and lungs, **sublingual** to bypass the first-pass effect, **intrathecal** for agents that penetrate the blood-brain barrier poorly, **rectal** to avoid hepatic first-pass effect and for nausea, and **topical** administration when local effect is desired such as dermatologic or ophthalmic agents.

Part 2. Approach to Disease

Physicians usually tackle clinical situations by taking a history (asking questions), performing a physical examination, obtaining selective laboratory and imaging tests, and then formulating a diagnosis. The synthesis of the history, physical examination, and imaging or laboratory tests is called the **clinical database**. After reaching a diagnosis, a treatment plan is usually initiated, and the patient is followed for a clinical response. Rational understanding of disease and plans for treatment are best acquired by learning about the normal human processes on a basic science level; likewise, being aware of how disease alters the normal physiologic processes is also best understood on a basic science level. Pharmacology and therapeutics require also the ability to tailor the correct medication to the patient's situation and awareness of the medication's adverse effect profile. Sometimes, the patient has an adverse reaction to a medication as the chief complaint, and the physician must be able to identify the medication as the culprit. An understanding of the underlying basic science allows for more rational analysis and medication choices.

Part 3. Approach to Reading

There are seven key questions that help to stimulate the application of basic science information to the clinical setting. These are:

1. Which of the available medications is most likely to achieve the desired therapeutic effect and/or is responsible for the described symptoms or signs?

2. What is the likely mechanism for the clinical effect(s) and adverse effect(s) of the medication?
3. What is the basic pharmacologic profile (e.g., absorption, elimination) for medications in a certain class, and what are the differences among the agents within the class?
4. Given basic pharmacologic definitions such as therapeutic index (TI) or certain safety factor (TD_1/ED_{99}), or median lethal dose (LD_{50}), how do medications compare in their safety profile?
5. Given a particular clinical situation with described unique patient characteristics, which medication is most appropriate?
6. What is the best treatment for the toxic effect of a medication?
7. What are the drug-drug interactions to be cautious about regarding a particular medication?
1. Which of the following medications is most likely to be responsible for the described symptoms or signs?

The student must be aware of the various effects, both desirable and undesirable, produced by particular medications. Knowledge of desirable therapeutic effects is essential in selecting the appropriate drug for the particular clinical application; likewise, an awareness of its adverse effects is necessary, because patients may come into the physician's office with a complaint caused by a drug effect unaware that their symptoms are because of a prescribed medication. It is only by being aware of the common and dangerous effects that the clinician can arrive at the correct diagnosis. The student is encouraged not to merely memorize the comparative adverse effect profiles of the drugs, but rather to understand the underlying mechanisms.

2. What is the likely mechanism for the clinical effect(s) and adverse effect(s) of the medication?

As noted above, the student should strive to learn the underlying physiologic, biochemical, or cellular explanation for the described drug effect. This understanding allows for the rational choice of an alternative agent or the reasonable choice of an agent to alleviate the symptoms or explanatory advice to the patient regarding behavioral changes to diminish any adverse effects. For example, if a 60-year-old woman who takes medications for osteoporosis complains of severe "heartburn," one may be suspicious, knowing that the bisphosphonate medication alendronate can cause esophagitis. Instruction to the patient to take the medication while sitting upright and remaining upright for at least 30 minutes would be the proper course of action, because gravity will assist in keeping the alendronate in the stomach rather than allowing regurgitation into the distal esophagus.

3. What is the basic pharmacologic profile (absorption, elimination, volume of distribution) for medications in a certain class, and what are differences among the agents within the class?

Understanding the pharmacologic profile of medications allows for rational therapeutics. However, instead of memorizing the separate profiles for every medication, grouping the drugs together into classes allows for more efficient learning and better comprehension. An excellent starting point for the student of pharmacology would be to study how a **prototype drug** within a drug class organized by structure or mechanism of action may be used to treat a condition (such as hypertension). Then within each category of agents, the student should try to identify important subclasses or drug differences. For example, hypertensive agents can be categorized as diuretic agents, β -adrenergic-blocking agents, calcium-channel-blocking agents, and renin-angiotensin system inhibitors. Within the subclassification of renin-angiotensin system inhibitors, the angiotensin-converting enzyme inhibitors can cause the side effect of a dry cough caused by the increase in bradykinin brought about by the enzyme blockade; instead, the angiotensin-1 receptor blockers do not affect the bradykinin levels and so do not cause the cough as often.

4. Given basic pharmacologic definitions such as therapeutic index (TI) or certain safety factor (TD_1/ED_{99}), or median lethal dose (LD_{50}), how do medications compare in their safety profile?

Therapeutic index (TI): Defined as the TD_{50}/ED_{50} (the ratio of the dose that produces a toxic effect in half the population to the dose that produces the desired effect in half the population).

Certain safety factor (TD_1/ED_{99}): Defined as the ratio of the dose that produces the toxic effect in 1 percent of the population to the dose that produces the desired effect in 99 percent of the population; also known as **standard safety measure**.

Median lethal dose (LD_{50}): Defined as the median lethal dose, the dose that will kill half the population.

Based on these definitions, a desirable medication would have a high therapeutic index (toxic dose is many times that of the efficacious dose), high certain safety factor, and high median lethal dose (much higher than therapeutic dose). Likewise, medications such as digoxin that have a low therapeutic index require careful monitoring of levels and vigilance for side effects.

5. Given a particular clinical situation with described unique patient characteristics, which medication is most appropriate?

The student must weigh various advantages and disadvantages, as well as different patient attributes. Some of those may include compliance with medications, allergies to medications, liver or renal insufficiency, age, coexisting medical disorders, and other medications. The student must be able to sift through the medication profile and identify the most dangerous adverse effects. For example, if a patient is already taking a monoamine-oxidase-inhibiting agent for depression, then adding a serotonin reuptake inhibitor would be potentially fatal, because serotonin syndrome may ensue (hyperthermia, muscle rigidity, death).

6. What is the best treatment for the toxic effect of a medication?

If complications of drug therapy are present, the student should know the proper treatment. This is best learned by understanding the drug mechanism of action. For example, a patient who has taken excessive opioids may develop respiratory depression, caused by either a heroin overdose or pain medication, which may be fatal. The treatment of an opioid overdose includes the ABCs (airway, breathing, circulation) and the administration of naloxone, which is a competitive antagonist of opioids.

7. What are the drug-drug interactions to be concerned with regarding a particular medication?

Patients are often prescribed multiple medications, from either the same practitioner or different clinicians. Patients may not be aware of the drug-drug interactions; thus, the clinician must compile, as a component of good clinical practice, a current list of all medications (prescribed, over-the-counter, and herbal) taken by the patient. Thus, the student should be aware of the most common and dangerous interactions; once again, understanding the underlying mechanism allows for lifelong learning rather than short-term rote memorization of facts that are easily forgotten. For example, magnesium sulfate to stop preterm labor should not be used if the patient is taking a calcium-channel-blocking agent such as nifedipine. Magnesium sulfate acts as a competitive inhibitor of calcium, and by decreasing its intracellular availability it slows down smooth muscle contraction such as in the uterus. Calcium-channel blockers potentiate the inhibition of calcium influx and can lead to toxic effects, such as respiratory depression.

COMPREHENSION QUESTIONS

- I.1 Bioavailability of an agent is maximal when the drug has which of the following qualities?
- Highly lipid soluble
 - More than 100 Daltons in molecular weight
 - Highly bound to plasma proteins
 - Highly ionized
- I.2 An agent is noted to have a very low calculated volume of distribution (V_d). Which of the following is the best explanation?
- The agent is eliminated by the kidneys, and the patient has renal insufficiency.
 - The agent is extensively bound to plasma proteins.
 - The agent is extensively sequestered in tissue.
 - The agent is eliminated by zero-order kinetics.

- I.3 Which of the following describes the first-pass effect?
- A. Inactivation of a drug as a result of the gastric acids.
 - B. Absorption of a drug through the duodenum.
 - C. Drug given orally is metabolized by the liver before entering the circulation.
 - D. Drug given IV accumulates quickly in the central nervous system (CNS).
- I.4 A laboratory experiment is being conducted in which a mammal is injected with a noncompetitive antagonist to the histamine receptor. Which of the following best describes this agent?
- A. The drug binds to the histamine receptor and partially activates it.
 - B. The drug binds to the histamine receptor but does not activate it.
 - C. The drug binds to the receptor, but not where histamine binds, and prevents the receptor from being activated.
 - D. The drug irreversibly binds to the histamine receptor and renders it ineffective.
- I.5 A 25-year-old medical student is given a prescription for asthma, which the physician states has a very high therapeutic index. Which of the statements best characterizes the drug as it relates to the therapeutic index?
- A. The drug's serum levels will likely need to be carefully monitored.
 - B. The drug is likely to cross the blood-brain barrier.
 - C. The drug is likely to have extensive drug-drug interactions.
 - D. The drug is unlikely to have any serious adverse effects.
- I.6 A drug M is injected IV into a laboratory subject. It is noted to have high serum protein binding. Which of the following is most likely to be increased as a result?
- A. Drug interaction
 - B. Distribution of the drug to tissue sites
 - C. Renal excretion
 - D. Liver metabolism
- I.7 A bolus of drug K is given IV. The drug is noted to follow first-order kinetics. Which of the following describes the elimination of drug K?
- A. The rate of elimination of drug K is constant.
 - B. The rate of elimination of drug K is proportional to the patient's renal function.
 - C. The rate of elimination of drug K is proportional to its concentration in the patient's plasma.
 - D. The rate of elimination of drug K is dependent on a nonlinear relationship to the plasma protein concentration.