Pharmacology: A Self-instructional Approach

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NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The editors and the publisher of this work have made every effort to ensure that the drug dosage schedules herein are accurate and in accord with the standards accepted at the time of publication. Readers are advised, however, to check the product information sheet included in the package of each drug they plan to administer to be certain that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in regard to new or infrequently used drugs.

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Preface

This self-instructional pharmacology text presents basic principles of pharmacology in a logical sequence that allows the learner to participate actively in the learning process while proceeding through the content at an individual pace, thus allowing concentration on more difficult concepts. The programmed, test-retest format provides flexibility in sequence, sequential disclosure of information, repeatability of information, active response, and positive reinforcement and facilitates "mastery" learning. Information is presented in relatively small segments, each one leading in logical sequence to the next. After each step, the learner responds and is immediately informed of the accuracy of understanding. In many instances, the response component of each frame has been designed to facilitate higher-level cognitive processes, including discrimination, drawing inferences, and applying concepts and principles.

The text is presented in ten major modules, according to specific drug classifications based upon how particular drugs affect body systems and components. Within each major module, there may be one or more submodules, depending upon the nature of the content. Basically, each major module contains an introduction and rationale, prerequisite learning, objectives, one or more pretests and posttests (including answers), and one or more learning programs. The objectives serve as guides to learning and convey to the learner the behavioral expectations—what the learner should be able to do as a result of the instruction—which are tested. Prerequisite tests are designed to assess the learner's entering competencies and to identify content that needs to be reviewed prior to attempting a particular module of instruction. Pretests and answers are included for each module and/or submodule. These tests are designed to assess the learner's present level of knowledge of the information contained in each learning program and to serve as a guide to learning. The pretest items correlate with the stated objectives. Each learning program consists of a series of hierarchically ordered, linearly sequenced information-response-feedback frames. The

learner reads the information, responds, and checks for accuracy of response, thus receiving immediate, positive reinforcement. The posttest that follows each learning program is designed to assess the extent to which the learner has mastered the content and to reinforce learning. Posttest items correspond to the stated objectives and are alternate forms of pretest items.

All names and situations contained in the text are fictitious and are included only to personalize or illustrate information and to provide external motivation. Any similarity to living people is purely coincidental.

The content of the text has been field-tested. The original prototype materials were used and evaluated by undergraduate nursing students at the University of Iowa College of Nursing over a three-year period. Revision of the text has been based upon student feedback, input from faculty of the College of Nursing, and the reviewers provided by McGraw-Hill.

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How to Use this Text

The text is designed to be self-instructing and to facilitate "mastery learning." You will become actively involved in the learning process. Information is presented in relatively short segments, organized hierarchically so that each segment builds upon the preceding one. It is organized in ten major modules of instruction, each of which may be further subdivided into one or more submodules, depending on the nature of the content. The basic components of each module are an introduction and rationale, prerequisite learning necessary for understanding of the content, a prerequisite test and answer key, specific behavioral objectives, a pretest and answer key, a learning program, and a posttest and answer key.

The Introduction and Rationale Each major module is introduced with a brief description of its contents and its importance, which is designed to establish a frame of reference for the information that follows.

Prerequisite Learning Following the introduction and rationale, the vocabulary relevant to the particular module and the background knowledge needed for understanding the information in the learning program(s) are delineated. You may need to review these in order to achieve mastery of the content. A glossary is presented near the end of the text.

The Prerequisite Test The prerequisite tests are designed to assess your present level of knowledge of the background information that is necessary for an adequate understanding of the content contained in the particular module and to determine the concepts and principles that you need to review before proceeding with the unit. Answers to the prerequisite test items follow the test form.

The Objectives Specific behavioral objectives are stated for each module and submodule, which alert you to important aspects of the content and serve as a guide to study, pointing out what you will be able to do upon completion of a particular learning program.

The Pretest Pretests are designed to determine your present knowledge of the content contained in each module and submodule. They will help assess whether you need to complete the particular learning program and cue in the important aspects contained within the learning program. Pretest items are based upon the stated objectives. Answers to the pretest items follow the test form.

The Learning Program Each learning program consists of a series or hierarchical frames of information. Each frame presents information relative to the content of the particular module and/or submodule and then asks you to respond by making a distinction, filling in a blank, labeling, drawing an inference, or responding in some manner in order to reinforce the particular concept, fact, or principle conveyed. Correct responses follow. Each correct response should be covered until you have written your response. If you are able to give a correct response, proceed to the next frame. You should concentrate on each frame until you are able to give a correct response. This immediate feedback and reinforcement of correct response is one of the important features of programmed instruction. The learning program allows you to proceed at your own pace through the content, moving quickly through areas that present no difficulty and more slowly where content is more difficult for you.

The Posttest At the conclusion of each learning program there is a posttest. The posttest items correlate with the stated objectives and are alternate forms of the pretest items. Each posttest is designed to determine your level of mastery of the content contained in the learning program and to reinforce learning. The posttest is taken upon completion of each learning program. It is suggested that if you do not obtain 90 to 100 percent accuracy, you should work through the program a second time, concentrating on difficult areas, and then retake the posttest.

Test Items Tests include matching, completion, true or false, and multiple true/false questions. You may not be familiar with the multiple true/false item. Each foil in a multiple true/false question is preceded by T (True) and F (False). You are to mark each foil as you would the "traditional" true or false item. This type of test item

has been included because it has been found that such items are more reliable than complex multiple-choice items.[1]

Procedure For this self-instructional text to be most effective, you should follow the procedure listed below. Any shortcuts will reduce your chances of mastering the content.

1. Read the introduction to the text.
2. Read the module introduction and rationale.
3. Look up any vocabulary words with which you are not familiar in the glossary at the back of the text.
4. Review cognitive knowledge prerequisites.
5. Take the prerequisite test and check your answers with the answer key.
6. Review any concepts or principles that have been identified through the prerequisite test about which you are unsure.
7. Read the objectives for the module or submodule.
8. Take the pretest and check your answers with the answer key. If you obtain 90 to 100 percent on the pretest, you may want to skip the particular learning program and proceed to the next one.
9. Proceed to the learning program. Cover the correct response below the first frame with a marker.
10. Carefully read the frame of information and write your response. Then uncover the correct response.
11. If your response is correct, proceed to the next frame. If your response is incorrect, review the information in order to find out why.
    Respond once again, and then proceed to the next frame. Proceed through the learning program in this manner.
12. Take the posttest at the end of the learning program and check your answers with the answer key.
13. If you obtain the mastery level, proceed to the next module or submodule and repeat the procedure.
14. If you do not obtain the 90 to 100 percent competency level, work through the learning program a second time and retake the posttest.

If you follow these instructions, you will be assured of mastering the pharmacology content contained in this text.

[1] Mark A. Albanese, Thomas H. Kent, Douglass A. Whitney, "A Comparison of the Difficulty, Reliability, and Validity of Complex Multiple Choice, Multiple Choice, Multiple Response, and Multiple True-False Items," The University of Iowa, July 1977.

Introduction

Pharmacology, the interaction between drugs and living systems, is a dynamic field of study. Drug therapy, the use of substances that can interact with and affect human protoplasm to diagnose, cure, mitigate, treat, or prevent disease, is constantly changing because of the discovery of new drugs through laboratory research. Nursing care relating to drug therapy requires sound, current, basic knowledge of drug action and interaction, side effects and toxic reactions, dosage and route of administration, therapeutic use, and conditions that contraindicate the use of particular drugs. Concepts and principles of anatomy, physiology, and chemistry must be integrated and applied in order to facilitate adequate understanding of these concepts. The nurse's role in drug therapy involves all components of the nursing process—assessment, planning, intervention, and evaluation—in order to provide essential health care that facilitates a high level of wellness. It includes moral, ethical, legal, and educational responsibilities.

This self-instructional approach to pharmacology conveys information based upon major drug classifications according to their specific effects upon the body systems. At least one prototype drug is identified for each drug group within a major classification. Students will be able to draw meaningful inferences about other drugs in the same classification.

Drugs are chemical substances used in the diagnosis, cure, mitigation, treatment, or prevention of disease or infection. Drug molecules react with the molecules of cells and tissues. A drug may mimic, facilitate, or antagonize cell function at specific receptor sites. Drugs act at a specific receptor site either extracellularly, intracellularly, or on cell membrane. An example of a drug that acts at an extracellular site would be Metamucil, which stimulates peristalsis but does not act directly on body cells. Drugs such as penicillin act on the cellular membrane by inhibiting cell wall synthesis. Some antibiotics alter membrane permeability. Chlorothiazide diuretics act on one of the mechanisms in the membrane that trans-

ports material in and out of the cell. At the intracellular sites, drugs may act on enzyme molecules necessary for the production and deactivation of the neurotransmitter, causing the enzyme molecules to break apart so that activity is inhibited. Sulfonamides act in this manner. Salicylates may affect the neurotransmitter release or reuptake mechanism. Antineoplastic drugs may act on components such as DNA, RNA, or ribosomes within the cell.

In order for a drug to reach the tissues with which it reacts to produce a pharmacological effect, its molecules must be able to move from the point at which it enters the body to the site of its action. Similarly, a drug reaches the organ responsible for its breakdown and elimination by being able to pass through biological membranes. These events are important in relation to the pharmacologic action of a drug, because they determine the quantity of drug that reaches the site of action and the length of time that it is available to exert its therapeutic effect.

The concentration that the drug reaches in the reacting tissues at any time after it is administered depends on its rate of absorption, distribution, biotransformation, and excretion, which vary from moment to moment. The level of concentration depends upon the balance between these four processes.

Absorption Absorption is the process by which the drug is transferred from the site of entry into the body to the circulating fluids. With the exception of locally acting drugs, all drugs must reach the bloodstream to be carried to their receptors. Absorption is largely influenced by (1) the form of the drug—gas, solution, suspension, solid, or enteric-coated; (2) the concentration of the drug; (3) the method of administration—oral, parenteral, sublingual, inhalation, rectal; (4) circulation to the site of absorption; and (5) the nature of the absorbing surface.

For rapid absorption of a solid drug, the drug must possess a certain degree of solubility in water and in lipids. The solid drug must first partially dissolve in the aqueous gastrointestinal fluids and then transfer to the lipid gastrointestinal cells for absorption. Drugs transfer into cells from a solution and do not enter cells as solid particles. If a drug has a very slow rate of dissolution in aqueous gastrointestinal fluids, it may be absorbed slowly even though it is highly soluble in lipid. The higher the concentration of a drug, the more rapidly it will be absorbed. This holds true with circulation to the site of absorption. The more vascular areas of the body, such as the lungs and oral cavity, have a more rapid rate of absorption. The nature of the absorbing surface is of utmost importance. Membranes in the body consist of a double layer of lipid molecules, which have proteins located within them. Drugs soluble in lipid and drugs

bound to protein can pass through the membrane. Cell membranes also contain pores through which some water-soluble drugs, depending on their molecular size, may enter the cell.

Distribution After a drug is absorbed into the bloodstream, it must be distributed through the body to the reception site in order to have a therapeutic effect. There are a number of factors that influence the distribution of drugs. These include blood flow, the ease of penetration of an organ, the blood-brain barrier, placental transfer, the recycling mechanism, tissue binding, and protein binding. Tissues that have a rich vascular bed, or in which vasodilation is common, receive larger amounts of drug than do tissues where blood flow is limited. The degree of lipid solubility, ionization, and structure of capillary membranes determine the ease of penetration at the reception site.

It has been suggested that because the cells of brain capillary membranes are joined together so tightly, there are no pores, and because the surface of each capillary in the brain is covered with a thick lipid sheath, a barrier exists to prevent the distribution of many drugs into this area of the body.

Nonionized drugs readily pass through membranes of the placenta and enter fetal circulation from the maternal circulation. Such drugs can exert toxic effects on the fetus and may induce congenital anomalies.

The recycling of alkaline drugs delays the amount of distribution to the target site and increases the time that the drug remains effective in the body. The molecules of an alkaline drug remain largely nonionized in the blood's slightly alkaline pH. In this form, they can readily cross lipid membranes between tissues. Thus, they can flow from capillaries surrounding the gastric mucosa into the stomach, where the acidic pH causes the basic drug molecules to ionize. In this form, they are no longer free to diffuse through the lipid membrane and are trapped. Thus the stomach acts as a "sink" for basic drugs. When the molecules move by normal gastrointestinal motility into the alkaline environment of the small intestine, they again become nonionized and are reabsorbed into the bloodstream. The drug molecules are then carried again to the liver and heart and circulate throughout the body, reaching the gastric mucosa once again. The cycle may be repeated another time. Alkaline drugs require longer periods of time, up to several days, to reach the therapeutic blood level desired, and after being discontinued, they require several more days to disappear from the body. Therefore, there are dangers of overdosing and interactions with other drugs for several days after the alkaline drug has been discontinued.

Some drugs, on reaching a storage tissue in the body, will bind to

a specific site within it and be trapped or stored. An adequate priming dose is necessary to saturate the binding site for a therapeutic effect to ensue. Binding of drugs decreases the concentration of free drug in circulation and prevents the drug from reaching its site of action in full concentration. The drug will remain at the binding site until it is released and becomes unbound again. The stored drug is in equilibrium with the amount of drug contained in plasma and is released as plasma levels of the drug are reduced. Tissue binding delays drug distribution, and hence, the drug action is prolonged. Calcified tissues, and especially adipose tissue, are areas where tissue binding is common. Probably the most common site of drug binding is protein albumin. The most common drugs that bind to albumin are weak acids, because they ionize well in the slightly alkaline pH of the blood and are attached to the large number of electrical charges on the albumin molecule. Basic drugs tend to be in the nonionized form. They have little electrical charge when in the blood and usually do not bind with albumin. As with tissue binding, the binding of a drug to albumin is a reversible reaction. The drug is released from the protein to replace the drug that has been utilized at target sites or metabolized. Thus, while drug concentration is decreasing in the plasma, the equilibrium ratio between bound and unbound drug is maintained. The opposite is also true. When concentration of the drug increases within the blood system, as when a second dose is administered, more of the drug becomes bound to the albumin.

There are a number of effects of protein binding on drug action. Protein binding maintains a stable level of unbound drug in the blood, so that shifts in concentration of drug available for action do not occur between doses. As protein binding slows the rate at which the drug is utilized, drug action is prolonged. This maintains the unbound drug level within the therapeutically effective level longer than would otherwise be expected. Protein binding also reduces the potential for drug toxicity. Even if the drug dosage is increased, the possibility that toxic levels of unbound drug will occur is reduced, since a given percentage of it becomes bound. The advantage of a highly protein-bound drug, the anticonvulsant Dilantin, for example, is that a daily dose can be given at one time, and its unbound drug serum concentration will usually remain within therapeutic levels for the entire 24-hour period.

A dangerous interaction occurs when two or more highly bound drugs are administered together. The two drugs compete for binding sites on the albumin molecules, and the equilibrium of each drug is altered. For example, if a person is stabilized on long-term anticoagulant therapy with a coumarin derivative drug and then is given another protein-bound drug, such as phenylbutazone, for an

inflammatory disorder, the effects of the coumarin drug can result in bleeding. Readjustment in dosage will be necessary whenever combinations of protein-bound drugs are given.

Biotransformation Biotransformation regulates the conversion of drug molecules into metabolites. A metabolite may be either less or more toxic, or less or more active, than the initial drug. The process of biotransformation involves chemical changes that are intended to make drugs more water-soluble to facilitate excretion of the drug by the kidneys. This process is carried on primarily by the enzyme system in the liver. The liver is an ideal site for biotransformation because of its unique pattern of blood flow. All drugs eventually reach the liver and are subject to biotransformation. The liver also possesses a vast number and variety of enzymes for carrying out the drug alteration process. The enzyme system responsible seems to be located in the hepatic endoplasmic reticulum, and the enzymes are generally called microsomal enzymes. Drug biotransformation is carried on in the liver by the chemical reactions: oxidation, reduction, hydrolysis, and conjugation. The rate of biotransformation varies from one individual to another. The same dose in one person may inactivate the drug so rapidly that the therapeutic dose cannot be reached, while in another person, the drug may be inactivated so slowly that toxic blood levels are reached.

The quantity and type of enzyme availability largely determine the rate of biotransformation. Genetic factors or abnormalities may determine enzyme availability. For example, the Japanese people rapidly metabolize the drug iosniazid, which is used in the treatment of tuberculosis, and therefore it is not effective. The enzyme system in infants has not been developed, and so drugs are not readily biotransformed. The enzyme systems degenerate with age, so that gradually, the older person's body biotransforms drugs less readily. Pathology, jaundice, and malnutrition may also be causes for decreased ability or availability of enzymes in the liver, thus slowing the rate of biotransformation. The rate is also slowed when two or more drugs are competing for the same enzyme.

Drugs, insecticides, and cigarette smoking stimulate the liver to increase its production of enzymes. This increases the rate of biotransformation and is the cause of the body's tolerance to certain drugs.

Excretion After drugs have gone through biotransformation, they pass out of the body through channels of excretion. The kidney is the major organ of excretion. Three processes are involved: (1) passive glomerular filtration, which depends on drug concentration in unbound form in the plasma; (2) active tubular secretion and

reabsorption; and (3) passive tubular diffusion. The rate of excretion will depend upon the maintenance of effective physiological mechanisms of distribution in the organs involved. Immaturity and degeneration will slow the rate of excretion. The rate at which the drug is presented to the kidney through vascular circulation and the rate of glomerular filtration will influence the rate of excretion of the drug from the body. The biologic half-life of a drug, which is the amount of time required for the plasma level concentration of the drug to decrease to 50 percent of the original concentration, will also influence excretion.

The lungs are the major organs of excretion for gaseous substances. Nonvolatile, water-soluble drugs can leave the body by sweat, tears, saliva, nasal excretion, and through the milk of lactating mothers. Some metabolites of drugs formed in the liver are excreted into the intestinal tract in the bile and then may be excreted in the feces.

Physiological Conditions that Modify the Effects of Drugs in the Body Body size is one of the most critical measurements for calculating effective drug levels in the body tissues. Therefore, stating dosage per kilogram of body weight is best.

Genetic factors have a marked influence on drug dosage. This is most often manifested in drug allergies and idiosyncracies. In some families, genes are present that will rapidly inactivate the drug, so that higher doses are necessary to have a therapeutic effect. Other families may lack the gene that inactivates the drug, so that the ordinary dose of a drug causes accumulation of toxic levels in the body and adverse reactions occur.

Age, either immaturity or degeneration of cells, has already been mentioned as an important variable. Types of food, emotional state, amount of fatigue, and the residual effects of previously administered drugs are other factors that modify drug effects. Food often delays absorption. Highly emotional states or fatigue may affect the results of central nervous system drugs. Those drugs that remain in the body tissues long after the drug has been discontinued may modify the response of a currently administered drug.

Pathological conditions also modify the effects of drugs. For example, diarrhea and vomiting decrease the gastrointestinal absorption of orally administered drugs. Gastric ulcers contraindicate the use of ulcergenic drugs. Intestinal spasms increase gastrointestinal absorption of orally administered drugs. Liver dysfunction increases the effects of many drugs.

These principles must be kept in mind as you carefully study *Pharmacology: A Self-instructional Approach.*

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