PHARMACOLOGY CONCEPTS

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Pharmacology Concepts

Instructional Objectives

Upon completion of this course, the motivated learner will be able to:

1. Recognize the definitions of pharmacokinetics and pharmacodynamics.
2. Choose the drug information reference that is most appropriate to answer a given question.
3. Recognize desirable characteristics of professional journals.
4. List three limitations of the PDR.
5. List the site of absorption for most drugs.
6. Recognize the purpose of enteric coating.
7. List alternatives for patients unable to swallow enteric-coated tablets or capsules.
8. Calculate a loading dose when given a patient weight, desired drug serum concentration, and drug volume of distribution.
9. List two characteristics of drugs that influence the ability of the drug to be removed by dialysis.
10. Choose the correct course of action in monitoring phenytoin therapy in a patient with decreased serum albumin.
11. Recognize the physiologic purpose of drug metabolism.
12. List the organ responsible for most drug metabolism.
13. List two types of drug metabolism that occur in the liver.
14. Choose the most appropriate drug to prescribe in a patient with liver disease, given the available drugs' metabolic pathways.
15. List two routes by which drugs can be eliminated.
16. List two reasons that adjusting a dose according to a patient's renal function is important.
17. Calculate a patient's creatinine clearance given the patient's age, weight, height, and serum creatinine.
18. List three mechanisms by which drugs act in the body.
19. Recognize correct uses of the terms "agonist" and "antagonist."
20. Recognize correct uses of the terms "potency" and "efficacy."
21. List two determinants, according to receptor theory, of a drug's effect on the body.
22. List five mechanisms of drug interactions.
23. Choose the best course of action when faced with a potential drug interaction.
24. List three lethal drug interactions.
25. Match a given federal drug law with the event that inspired it.
26. List requirements for generic drug approval.
27. List who is authorized to "schedule" drugs and to register prescribers of controlled substances.
28. Recognize correct use of the term "orphan drug."
29. List six steps in the drug development process in chronological order.
30. List three shortcomings of the drug development process.

Purpose and Goals

With an astounding range and number of medications that must be safely administered to patients, it is essential for professionals to understand pharmacology concepts. This is the goal of this course. Pharmacokinetics, pharmacodynamics and drug interactions will be explained. Common prescribing issues and the history of drug laws will also be covered.

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Introduction

The number of prescription medications currently available is astounding, and the U.S. Food and Drug Administration (FDA) approves many new drugs each year. For example, in 1996, 62 new drugs were approved. It is impossible to be familiar with the details of all available medications. Fortunately, there are many drug information sources available that provide detailed information about specific drugs, and there are certain pharmacologic concepts that can be applied to many different medications.

Two such concepts are **pharmacokinetics** and **pharmacodynamics**. Pharmacokinetics can be thought of as the **body's action on the drug,** while pharmacodynamics can be thought of as the **drug's action on the body.** Pharmacokinetic parameters include drug **absorption** into the body, **distribution** of the drug throughout the body, and **metabolism** and **elimination** of the drug from the body. Although the chemistry and dosage form of the drug itself can affect its pharmacodynamics and pharmacokinetics, disease states and other patient factors can also determine how the body handles the drug (i.e. pharmacokinetics) and the drug's effect on the patient (i.e. pharmacodynamics). Understanding both pharmacokinetic and pharmacodynamic concepts is meaningful in drug dosing and administration, and also in the management of **drug interactions.**

Other important concepts related to medication use include **drug law** and **the drug development process.** Although these topics may seem unimportant, they influence drug safety, efficacy, and availability, and thus are of interest to health care providers.

All of these concepts were probably discussed in a pharmacology class you took in school. It is likely that the clinical applicability of these topics was not readily apparent, either because at the time you had little clinical experience, or because the instructor did not explain their practical significance. As each pharmacology concept is discussed, it will be applied to a common clinical situation.

Drug Information Sources

Journals

One common way for health care providers to keep up to date on new drugs, as well as to learn about the therapeutic use of older drugs, is through professional journals. There are literally thousands of journals available. One must take care in choosing which journals to follow, and in interpreting the articles within those journals.

You are probably familiar with nursing journals that focus on traditional practice such as RN, Nursing, and American Journal of Nursing. This latter journal is published by the American Nurses Association and is notable for its monthly "Drug Watch" and "New Drugs" sections. There are also specialty journals for advanced practice nurses such as Nurse Practitioner. Nursing journals geared toward nurse anesthetists (e.g. AANA Journal), school health nurses, surgical nurses, critical care nurses, and nurses practicing in other specialized settings (e.g., *Journal of Neuroscience Nursing*) are also available. Despite the wide selection of nursing journals, advanced practice nurses should also consider reading medical journals on a regular basis. Journals such as *New England Journal of Medicine, Annals of Internal Medicine, and Journal of the American Medical Association (JAMA)* publish clinical studies of interest to a variety of medical specialties. In addition, expert panels often publish practice guidelines in these two journals. One example is the American College of Gastroenterology's practice guideline for the medical treatment of peptic ulcer disease, published in the February 28th, 1996, issue of *JAMA*.

Cost is an important consideration in choosing journals to which to subscribe. Sometimes, a subscription to a journal published by a professional organization is free to members. You are probably also familiar with "throw-away journals" – ones that come in the mail to your home or clinic unsolicited, free of charge.

These journals are free because they are paid for by advertisements. You will notice that such journals contain many glossy pages of drug advertisements. The presence of advertisements in a journal does not necessarily reflect poorly on the information contained in the journal; many of these publications contain useful, unbiased

reviews of diseases and therapeutics.

In addition to the subject matter covered, another important consideration is the quality of the information provided. Journals that contain peer-reviewed articles provide the most reliable, unbiased information. Peer review means that an article has been sent to medical experts for comment before publication. After expert reviewers make suggestions for improvement, the article is sent back to the original author for changes. The journal's editor or editorial board then decides if and when the article should be published. Sometimes, articles are rejected without being sent to the expert reviewers if the editorial staff does not feel the subject matter is appropriate for the journal.

How does one know if an article has been peer-reviewed? Often, journals will put a special symbol at the end of an article to designate that it has been through the peer review process. An explanation of such symbols is usually found on one of the first pages of each issue. Another way to find out if an article has been reviewed is to look at the instructions to authors, which if not found in each issue, are usually published in the January, June, and/or December issues. These instructions usually explain which type of submission is subject to review. You can also look for statements to this effect on one of the first pages of each issue.

Examples include, "All manuscripts are subject to review by qualified consultants and the editors..." from the journal *Pharmacotherapy*, or *American Journal of Nursing* "is a peer-reviewed journal."

Other journals will specifically designate articles as "peer-reviewed" on the first page of the article or in the table of contents. Even when an article goes through the peer review process, quality cannot be absolutely assured. Unfortunately, there are many examples of review articles that contain inaccurate information, and of clinical studies containing falsified data. For this reason, it is always appropriate to question anything that does not seem correct.

The **Letters** section of a journal is a forum for readers to question and comment on what they have read in the journal. In some journals, such as the British journal *Lancet*, letters to the editor go through the peer review process just as articles do. In addition to serving as a mechanism by which readers can engage in discussion, the letters section of many journals also serves as a place to publish clinical observations, small studies, and short reviews of topics of limited scope.

One last consideration in evaluating the quality of a journal article is the funding for the article, and the employer of the author of the article. Often, clinical trials are conducted by, or funded by, a pharmaceutical manufacturer. Such an affiliation does not invalidate the results of the study. In fact, experts at the FDA guide manufacturers seeking FDA-approval for a new drug. It is in the manufacturer's best interest to adhere to FDA guidelines in designing a clinical trial and ensuring its integrity. Once a drug has been given FDA approval, manufacturers often supply their drug free of charge to independent investigators. These clinicians might want to perform additional studies on the drug to clarify the incidence of an adverse effect, compare the new drug to an old drug, or to find a new use for the drug. Just because the manufacturer has supplied the drug free of charge, the results of the study are not automatically suspect. In addition to funding clinical studies, pharmaceutical manufacturers sometimes sponsor review articles and continuing education programs published in journals. Again, this does not mean the information is incorrect or misleading, but sometimes such reviews will focus excessively on the pharmaceutical company's product. Readers should always be cognizant of industry involvement in any study or review.

Textbooks

You are probably familiar with at least one pharmacology textbook, and perhaps shudder at the thought of it! Most pharmacology textbooks are written specifically for nursing, pharmacy, or medical students. Unfortunately, textbooks designed to meet the unique needs of nurse practitioners are virtually non-existent. In addition, many textbooks focus extensively on the mechanism of action on drugs, but do not extensively cover the therapeutic use of the medications. Textbooks of therapeutics cover the gaps left by most pharmacology textbooks. Examples include *Applied Therapeutics: the Clinical Use of Drugs; Pharmacotherapy: a Pathophysiologic Approach;* and *Textbook of*

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Therapeutics: Drug and Disease Management. One caveat about textbooks is that the information contained in them can become out-of-date in the rapidly changing world of drug information. Most textbooks are published approximately every 3-5 years. They are very useful if supplemented with more current information from journals and newsletters.

Newsletters

Newsletters are very timely and are usually published weekly, biweekly, or monthly. A popular newsletter that focuses on new drugs is *The Medical Letter on Drugs and Therapeutics*. This biweekly newsletter is usually about four pages in length, and usually contains two or three reviews of new drugs. In addition to new drugs, it also periodically reviews drug classes (e.g. drugs for hypertension; drugs for parasitic infections; drugs for HIV infection), drug adverse effects (e.g., drugs that cause psychiatric symptoms; safety of calcium channel blockers), and therapeutic use of drugs (e.g., advice for travelers; choice of antibiotics). In addition to drugs, *The Medical Letter* also occasionally covers dietary supplements (St. John's Wort; vitamins), devices, vaccines, and diagnostic tests.

Two other useful bi-monthly newsletters are *Internal Medicine Alert* and *Journal Watch*. These newsletters contain reviews of articles recently published in major medical journals. In addition to article reviews, *Internal Medicine Alert* also reviews new drugs. These newsletters are a cost-effective alternative to subscribing to several medical journals. You can obtain those articles that appear to be of particular interest to your practice at a local medical library.

General Drug Information References

There are several comprehensive drug reference books that provide information on dosing and administration, adverse effects, precautions, use in special populations, interactions, and mechanism of action. One of the most popular is *Drug Facts and Comparisons*. A unique feature of this reference is that it contains many tables that compare drugs within a particular class on the basis of half-life, indication, duration of effect, adverse effects, and elimination. Although specific drug prices are not available, it does compare the cost of drugs in relative terms. Both a hardback version and a loose-leaf version are available. Although the loose-leaf version is slightly more expensive, monthly updates are included in the price.

The *American Hospital Formulary Service* (*AHFS*) is published by the American Society of Health-System Pharmacists and contains evaluative, comprehensive monographs on drug classes, supplemented by specific information on particular drugs within each class. *AHFS* contains fairly detailed information on the therapeutic use, administration, and stability of drugs. It is also a good source of information on vaccines. It is published annually, with periodic supplements.

The *USP DI Volume I-Drug Information for the Health Care Professional (USPDI* Volume I) contains information that is similar to that contained in *Drug Facts and Comparisons* and *AHFS*. Like *AHFS*, it is published annually, and monthly supplements are available. Like *Drug Facts and Comparisons,* it contains tables that compare drugs within a class. It is organized in a fashion similar to that of *AHFS* (i.e., monographs of drug classes supplemented by shorter sections highlighting specific information on individual drugs), but is less comprehensive; however, its sections on precautions in geriatric and dental patients are unique. Helpful features include *Patient Monitoring* and *Patient Consultation,* which are included for many drugs. The *Patient Consultation* section is not written in lay language, but instead is meant to be a guide to the health care professional in what to tell patients about their medication. *USPDI Volume I* also lists drug/laboratory test interactions. This reference now includes monographs on the treatment of specific diseases.

The *Physicians' Desk Reference (PDR)* is one of the most highly regarded drug information references, not only among health care professionals, but to the lay public as well. It is often referred to as the "Physicians' Drug Bible" and other terms of reverence by the media. This distinction is questionable considering the myriad of more comprehensive drug information sources available. The *PDR* is nothing more than a collection of package inserts. The package insert is the official FDA-approved prescribing information for a drug, and must be attached to the bottle of a prescription

drug when it leaves its manufacturer. The package insert is meant to provide information to the prescriber, but unfortunately, the *PDR* is found in many bookstores, available for purchase and misinterpretation by lay persons. The *PDR* does not include prescribing information for all drugs – only those that the manufacturer pays to include. Because the prescribing information for a drug contains only information that has been submitted to the FDA by the manufacturer and subsequently approved by the FDA, it does not contain information on unlabeled, or non-FDA-approved, uses for drugs. It also does not contain much information on the use of drugs in special populations such as pediatrics, geriatrics, or lactating or pregnant women.

Specialized Drug References

Pediatrics

For detailed information on drug use in special populations, it is best to rely on specialized references. Drug use in pediatric patients is especially problematic for the clinician because most medications, even those that are commonly used in children, have not received FDA approval for use in children, and have not been studied in children to the extent that they have in adults. Two references that are indispensable to health care professionals dealing with children are *Pediatric Dosage Handbook*, published by the American Pharmaceutical Association, and the *Harriet Lane Handbook*, which is written by experts at Johns Hopkins Hospital. The *Harriet Lane Handbook* provides pediatric drug doses, but has several limitations. Compared to the *Harriet Lane Handbook*, *Pediatric Dosage Handbook* covers more medications, and is more comprehensive; it contains detailed drug information such as adverse effects and interactions, and is referenced. *Pediatric Dosage Handbook* is updated yearly, while the *Harriet Lane Handbook* is published every three years.

Unborn children and breastfeeding infants are unique pediatric populations. *Drugs in Pregnancy and Lactation* focuses solely on drug effects on the fetus and nursing infant, and is the most comprehensive reference available on this topic. Quarterly updates are available between editions.

Antimicrobials

For information on the treatment of infectious diseases, the pocket-sized *The Sanford Guide to Antimicrobial Therapy* is indispensable. This reference is also sometimes referred to as "The Chinese Book," due to its cover design. It contains tables of recommended empiric therapy for various infections; antimicrobial spectra of activity; drug interactions and adverse effects of antimicrobials; dosage of antimicrobials in renal failure; and immunization information. It is published in May of each year. Although pharmaceutical representatives sometimes distribute it free of charge, it is independently prepared and published. At only $7, it is a real bargain.

Drug Interactions

Drug interactions are a confusing aspect of drug prescribing and therapeutic monitoring. Most general drug information references mention drug interactions, but do not give detailed information, an explanation of the clinical importance of the interaction, or suggestions for management of the interaction. Fortunately, three references, *Drug Interaction Analysis and Management, Evaluations of Drug Interactions,* and *Drug Interaction Facts* provide these details. All three are loose-leaf binders. *Evaluations of Drug Interactions* is updated six times a year, and the other two are updated quarterly. All three references generally contain the same information, although most clinicians have a preference for one over the others.

Information for Patients

A trip to the local bookstore will reveal many drug information references available to lay persons; however, many are inappropriate, either because they are not specifically written for patients (e.g. the *PDR*), or because they contain inaccurate or alarming information. Fortunately, several reliable references contain drug monographs that can be reproduced for patients. *Medication Teaching Manual,* published by the American Association of Health-System Pharmacists; *Patient Drug Facts,* which is updated quarterly and published by the same company that publishes *Drug Facts and Comparisons and Drug Interaction Facts;* and *USPDI Volume II – Advice for the Patient (USP DI Volume II)* are all useful teaching tools.

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The Internet

Often, patients get their drug information from the Internet. Although the Internet has the potential to be a very powerful means of patient education, it is also a forum for misinformation and unscrupulous dealers of "miracle cures" for every disease known to man. Persons purporting to be physicians and other health care professionals answer questions posed by patients and offer advice on a variety of medical conditions.

Many web pages are maintained by government organizations, professional associations, universities, hospitals, and others that provide accurate, useful information about drugs. A comprehensive listing of such web pages is beyond the scope of this article, but there are two notable web sites of importance to health care providers. The Centers for Disease Control (www.cdc.gov) offers recommendations for vaccinations and malaria prophylaxis for international travelers, as well as other communicable disease information. Another government agency, the Food and Drug Administration (www.fda.gov), alerts health care providers to important problems with medications [e.g., the interaction between sildenafil (Viagra) and nitrates] and drug recalls [e.g. mibefradil (Posicor), dexfenfluramine (Redux), and fenfluramine (Pondimin)]. The FDA web page also offers limited information for the lay public on general topics (e.g., the drug development process) and specific topics of great public interest (e.g., what to do if one has taken Redux or Pondimin in the past). Beginning in January 1998, this web page also began to offer consumer information on newly approved drugs.

Pharmacists, Drug Information Centers, Poison Centers

Pharmacists are the health care professionals specifically trained to be drug experts. They are available in retail pharmacies, hospitals, and other health care settings for consultation about patient-specific drug related problems. In addition, pharmacists staff drug information centers, found in most university teaching hospitals and other larger hospitals. Drug information centers have access to specialized references, journals, and electronic databases not readily available in other settings. In addition, these centers usually keep a file of previous questions and answers. The pharmacists that staff these centers are well versed in the current medical literature, and are skilled at resolving medication-related problems without actually seeing the patient. Because they do not have access to the patient's chart, medication profile, or medical record, the pharmacist might ask for information such as the patient's medications, allergies, past medical history, current medical problems, age, weight, height, serum creatinine, and liver function. If you are calling about an adverse reaction to a medication, the pharmacist will need to know how many doses of the medication were taken before the reaction occurred; when it occurred in relation to the taking the dose; and its severity and duration.

For accidental or deliberate poisonings, and exposure to toxic chemicals, contact your regional poison center. Pharmacists and nurses who are usually certified in poison information staff these centers. They are your best source for information in these situations. Even if you have a handbook, textbook, or other source of poisoning information, these references are notoriously inaccurate and even dangerous.

Pharmacokinetics

Pharmacokinetics describes the body's action on the drug and includes the concepts of absorption, distribution, metabolism and elimination.

Absorption

Almost all orally administered drugs are absorbed in the small intestine. Before a drug can be absorbed, it must first dissolve in the watery, alkaline fluid in the intestinal lumen. (Remember – "like dissolves like.") Drugs that are water soluble, such as those that carry a positive or negative electric charge, dissolve in the intestinal fluid. Once dissolved, the drug can pass through the lipid-rich intestinal mucosa into the bloodstream if the drug is sufficiently fat-soluble to pass through. (Remember – "oil and water don't mix.") Thus, for drugs that are well absorbed, a certain balance exists between water solubility and lipid solubility.

The antibiotic vancomycin (Vancocin^{R}) is an example of a drug that is too water soluble to be absorbed in the small intestine. Even though vancomycin is available in capsule form, it is not

effective for treatment of systemic infections when administered orally; the capsules are effective only for a type of infectious diarrhea called pseudomembranous colitis. At the other extreme is atovaquone (Mepron®), a drug used to treat Pneumocystis pneumonia (PCP) in patients intolerant to sulfa drugs. Atovaquone is very lipid soluble, and thus is poorly soluble in the watery environment of the small intestine. Taking atovaquone with a fatty meal increases its ability to dissolve in the intestine, and thus increases the amount of atovaquone that is absorbed. Thus, it is very important to instruct patients to take atovaquone with meals.

In contrast to atovaquone, the absorption of certain other medications can be **decreased** by food. Lists of food/drug interactions can be found in Drug Topics' *Red Book,* as well as review articles in the medical, pharmacy, and nursing literature. When interpreting such information, it is important to keep in mind the distinction between **rate** and **extent** of absorption. When the rate of drug absorption is slowed by food, there is usually no consequence. However, when food decreases the extent of drug absorption (amount of drug absorbed), a decrease in clinical effect might be seen.

For example, the extent of captopril (Capoten®) absorption is decreased by food; only 30-55% of the given dose is absorbed when it is taken on a full stomach. It can be said that the **bioavailability** of captopril is decreased by 30-50% when it is taken with food. Bioavailability describes that amount of drug that actually reaches the blood stream.

Because most drugs are absorbed in the small intestine, a problem results if the drug is degraded in the stomach before it can reach the small intestine. Drugs that are susceptible to degradation in the acidic environment of the stomach are often formulated with a protective enteric coating. Enteric coating protects the drug from stomach acid, but dissolves in the alkaline environment of the small intestine, releasing the drug. Administration of enteric-coated products can be problematic if a patient cannot swallow a tablet or capsule. For example, erythromycin products are formulated as tablets protected by an enteric coasting (Ery-Tab®), or as capsules containing enteric-coated beads (Eryc®). Erythromycin enteric-coated tablets should not be crushed because the enteric coating will be disrupted, allowing stomach acid to destroy the drug. Fortunately, erythromycin is available as a suspension containing a form of erythromycin called erythromycin ethylsuccinate (E.E.S.®), an ester of erythromycin that is stable in the acidic stomach contents. When dosing erythromycin ethyl succinate, one must remember that 400 mg of erythromycin ethylsuccinate is equivalent to 250 mg of erythromycin.

Omperazole (Prilosec®) is another example of a product formulated as a capsule containing enteric-coated beads. For patients who cannot swallow the capsules whole, the beads can be dispersed in a tablespoon of applesauce. If administration down a nasogastric, gastrostomy, or orogastric tube is necessary, the beads can be dispersed in an acidic beverage such as orange, apple, grape, grapefruit, prune, pineapple, or tomato juice. On the other hand, if a patient has a jejunostomy tube or Dobhoff, which goes directly into the small intestine, enteric coating is unnecessary; a drug administered by this route will bypass the stomach. In such cases, the beads can be dissolved in a liquid with a pH greater than 4.5, such as an antacid (e.g. Maalox®), water, saline, or milk for easy administration down the tube.

Distribution

Once a drug is absorbed, it is distributed throughout the body. Unfortunately, drugs do not "know" where they are needed; the drugs' lipid solubility and ability to bind to plasma and tissue proteins determine where the drug is distributed. For example, drugs that are very fat-soluble distribute widely throughout the body's fat stores. Such drugs are said to have a large **volume of distribution** (Vd).

In addition to fat-soluble drugs, drugs that are highly bound to tissues also have large Vds. Digoxin (Lanoxin®) is an example of a drug that is highly bound to tissues (heart and other muscles) and thus has a large Vd. Some drugs stay mainly within the vascular space. Such drugs are said to have a small Vd. Drugs with a small Vd are usually water-soluble, are not highly bound to tissues, and/or are highly bound to plasma proteins such as albumin. One can think of highly protein bound drugs as being "trapped" within the

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vascular space. An example of a drug with a small Vd is warfarin (Coumadin^{R}), which is about 90% bound to serum albumin.

What is the clinical significance of a drug's Vd and extent of protein binding? A drug's Vd can be used to predict whether a drug is removed by hemodialysis. Such information is important because if a drug is significantly removed by dialysis, its dosing schedule should be such that a dose of the drug is administered **after** the dialysis session. Drugs with small Vds that are **not** highly bound to serum proteins, such as penicillins and most cephalosporin antibiotics, can be removed by dialysis because a significant amount of unbound drug is in the plasma compartment, available for removal. On the days that the patient is dialyzed (usually two or three days each week), a dose of these drugs should be administered **after** dialysis. On the other hand, if a drug has a large Vd (e.g. digoxin), it will not be removed by dialysis, and the timing of the dose in relation to dialysis is unimportant. Drugs that are highly bound to serum proteins (e.g. warfarin) are also poorly removed by dialysis, even though their Vds are usually small. Hemodialysis cannot be used to treat poisonings caused by drugs with large Vds or drugs that are highly protein bound.

How does one know if a drug's Vd is large or small? Such information is available in common references such as the *Physicians' Desk Reference* (*PDR*), *Drug Information Facts and Comparisons,* and *American Hospital Formulary Service.* A drug's Vd is considered small if it is close to that of the plasma volume (about 4% of body weight).

For comparison, the Vd of digoxin is 7 L/kg. Obviously, Vd is **not** a physiologic volume; a 100 kg man does not contain 700 liters of fluid! To understand what volume of distribution is, imagine that there is a hole in the ground filled with water, and you want to know how much water is in the hole. You have no means to measure the depth of the hole, but you do have 1 mg of Drug X in your hand. You dump 1 mg of Drug X in the water, then send a sample of the water to the laboratory for analysis. The laboratory reports that the concentration of Drug X in the hole is 0.1 mg/L. This means that the hole contains 10 liters of water (i.e., 1 mg divided by 10 liters is 0.1 mg/mL). Volume of distribution is therefore just a proportionality constant that relates the dose of a medication to the serum concentration it produces.

The difference between a drug distributing into a hole full of water and a drug distributing throughout the body is that the drug does not distribute evenly throughout the body; a drug can concentrate in fat, bind to tissue proteins, or stay bound to serum proteins. A drug that concentrates in fat or other tissues will produce a very low plasma concentration, and will have a volume of distribution that greatly exceeds any possible physiologic volume; therefore, Vd is simply the volume into which the drug **appears** to disperse based on its resulting serum concentration.

Because Vd relates the dose of a drug to the serum concentration it produces, another practical use of Vd is calculation of a drug dose needed to produce a given serum drug concentration.

For example, if the desired serum concentration of digoxin is 1-2 ng/mL, its Vd is 7 L/kg, and the patient weighs 70 kg, the dose of digoxin needed to produce the desired serum concentration is 0.49 mg to 0.98 mg.

Calculations:

70 kg x 7L/kg = 490 L x 1 mcg/L = 490 mcg, or 0.49 mg, and 490 L x 2 mcg/L = 980 mcg, or 0.98 mg.

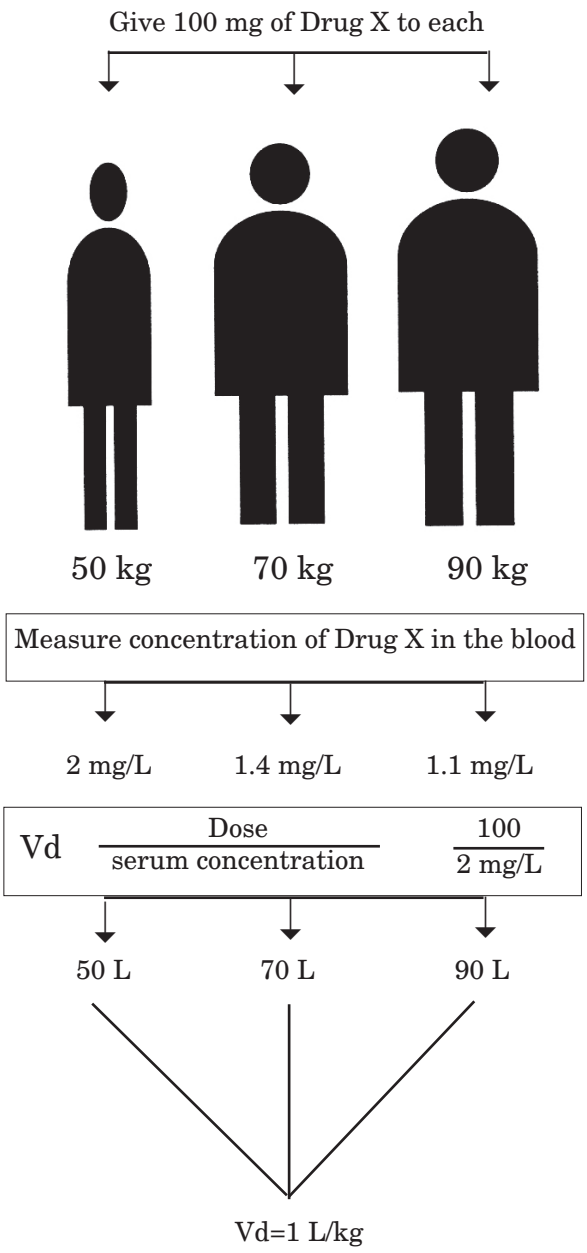
(There are 100 micrograms in one milligram.)

For convenience, the higher dose can be rounded to 1 mg. If tablets are used, one must consider that only about 75% of a digoxin dose administered by oral tablets is absorbed, and so the dose must be increased by 25%. Such **loading doses** of digoxin are usually administered in three divided doses, six hours apart. This is so that response to each dose can be evaluated before giving the next.

In this case, 625mcg (two 250 mcg tablets plus a 125 mcg tablet) would be given orally, followed by two doses of 312.5 mcg (one 250 mcg tablet and a half 125 mcg tablet) each. Calculation of a **maintenance dose** of digoxin will be explained under "elimination."

In addition to volume of distribution, a drug's extent of protein binding can also be found in the references listed above. The fact that highly protein bound drugs are poorly removed by dialysis has already been mentioned. Highly (> 80%) protein bound drugs can be problematic in patients with liver disease, kidney

SUMMARY: VOLUME OF DISTRIBUTION



When calculating volume of distribution, we are assuming that the body is one big container of water, and that the drug distributes throughout it uniformly; however, we know that the body is comprised of blood vessels, fat, bone, connective tissue, and various organs. We also know that drugs distribute into these "compartments" differently depending on the drug's ability to

1. bind to plasma proteins,
2. dissolve in fat, and
3. distribute into and bind to various tissues and organs.

If a drug binds extensively to serum albumin, its volume of distribution will approximate the blood volume. If it is very fat soluble, the volume of distribution may exceed any physiologic volume because there will be a very low concentration measurable in the blood.

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disease, alcoholism, cancer, or malnourishment because these patients typically have low serum albumin levels.

What happens if a patient has an abnormally low albumin level, due to either liver or kidney disease? In these patients, proportionately less of the drug will be bound to albumin, and a greater percentage of the drug will be floating free in the bloodstream. Keeping in mind that only free, unbound drug is able to leave the blood stream and enter tissues, a patient with low serum albumin will experience a greater effect from a given dose of a highly albumin-bound drug than if the patient had a normal albumin.

Examples of drugs that must be dosed cautiously in patients with low serum albumin include warfarin and phenytoin (Dilantin[R]). Even though phenytoin serum levels are usually monitored, these levels measure the total concentration (bound plus unbound) of phenytoin. A patient with a low serum albumin can have a total phenytoin concentration that is within the normal range with an abnormally high free (unbound) concentration.

Thus, in patients with low serum albumin who are taking phenytoin, the free phenytoin level should be used to monitor therapy.

A final consideration regarding drug distribution is that drugs that are fat-soluble are able to enter the brain more readily than more water-soluble drugs. This is because the endothelial cells that make up the capillaries in the brain are packed closely together; there are no water-filled channels between the capillary endothelial cells in the brain as there are in other tissues.

These special capillaries are called the **blood-brain barrier.** Its function is to keep potentially harmful substances out of the brain. Lipid soluble drugs can traverse the lipid-rich capillary endothelial cells relatively well.

For example, the beta-blocker propranolol (Inderal[R]), a beta-blocker, is more lipid soluble than atenolol (Tenormin[R]). This difference in lipid solubility is thought to explain the difference in adverse effect profiles of the two drugs: propranolol is more likely to cause fatigue, depression, and other central nervous system effects.

Metabolism

Drug metabolism is the process by which the body changes the chemical structure of a drug to make it more water-soluble and thus more easily eliminated in the urine or bile. It is a common misconception that the purpose of drug metabolism is to inactivate the drug. Metabolism can inactivate a drug, but as will be discussed, some drugs are metabolized to more toxic or more active drugs. Understanding drug metabolism is paramount in understanding patients' response to medications as well as drug interactions.

One of the most common types of drug metabolism is **oxidation**, also called **phase I metabolism.** This is usually achieved through the **cytochrome P450 (CYP450)** enzymes in the liver. There are several different CYP450 enzymes that are important in human drug metabolism. The CYP450 enzymes are named using numbers and letters, and are referred to as isoenzymes. CYP450 isoenzymes involved in human drug metabolism include CYP3A, CYP2D6, CYP1A2, CYP2B6, CYP2C19, CYP2E1, and CYP2C9. Important features of selected isoenzymes will be discussed.

The isoenzyme CYP2D6 is genetically absent in about 7-10% of Caucasians, while Blacks and Asians are slightly less likely to have this genetic aberration. Patients without CYP2D6 can accumulate antipsychotics, certain antidepressants, and other drugs metabolized by this isoenzyme. Therefore, such patients are at increased risk for adverse effects from medications metabolized by CYP2D6.

Unfortunately, a test that clinicians can use to identify patients who lack CYP2D6 is not currently available, although the technology exists to do this in research settings. Although lack of CYP2D6 can increase the risk of adverse effects from certain drugs, patients who lack this enzyme actually have a decreased response to codeine. This is because codeine is metabolized by CYP2D6 to morphine, which is responsible in part for codeine's analgesic effect.

Another clinically important isoenzyme is CYP3A, which is responsible for the metabolism of a large number of commonly used medications. It is found in the gastrointestinal tract as well as the liver. Calcium channel blockers, cisapride (Propulsid[R]), astemizole (Hismanal[R]), certain antidepressants [sertraline

(Zoloft[R]), nefazodone (Serzone[R])], some benzodiazepines [triazolam (Halcion[R]), alprazolam (Xanax[R])], carbamazepine (Tegretol[R]), protease inhibitors used to treat HIV, and many other medications are metabolized by this enzyme. Although a genetic absence of this enzyme has not been identified, it is probable that there is variation among individuals in their amount of CYP3A, and thus variation in inter-individual responses to a given dose of a medication.

CYP1A2 is an enzyme that is found in greater amounts in smokers and in people who eat a lot of grilled foods. This is because hydrocarbon substances produced from burning organic matter increase the body's production of this isoenzyme. This process is called induction. Theophylline is an example of a drug metabolized by CYP1A2. Smokers therefore require more theophylline than non-smokers to achieve the same therapeutic effect and blood level.

Other isoenzymes of clinical importance include CYP2C9, which metabolizes non-steroidal anti-inflammatory drugs, phenytoin, and warfarin; and CYP2E1, which metabolizes acetaminophen and alcohol. Alcohol induces CYP2E1 and thereby can cause problems for alcohol drinkers who take acetaminophen.

Acetaminophen is usually a very safe product when taken as directed. It is largely devoid of adverse effects and drug interactions. However, even when taken in recommended doses, acetaminophen is metabolized by CYP2E1 to a toxic metabolite. Fortunately, the liver is able to detoxify this dangerous by-product through a type of metabolism called **conjugation,** or **phase II metabolism.**

In conjugation, the liver attaches a large water-soluble molecule to a drug or drug metabolite. In the case of acetaminophen, the liver attaches glutathione to acetaminophen's toxic metabolite, rendering it harmless. Problems can occur, however, when the amount of toxic acetaminophen metabolite produced exceeds the liver's glutathione stores.

This occurs in three situations:

1. when alcohol induces CYP2E1, increasing the production of the toxic metabolite and overwhelming glutathione stores;
2. when an overdose of acetaminophen is taken; and
3. when a person is malnourished and does not have adequate glutathione stores to detoxify even a normal acetaminophen dose.

This explains why manufacturers of nonprescription acetaminophen-containing products recently added a warning to the label concerning use in patients who consume more than three alcoholic beverages per day.

Interestingly, alcohol and many other medications can be metabolized in more than one way. In addition to metabolism by CYP1E2, alcohol can be metabolized by alcohol dehydrogenase, an enzyme found in both the stomach and the liver. Other examples of drugs with dual mechanisms of metabolism include warfarin, which is metabolized by CYP2C9 and to a lesser extent by CYP3A and CYP1A2; theophylline, which is metabolized by CYP1A2 and CYP3A4; and tricyclic antidepressants, which are metabolized to various extents by CYP1A2, CYP3A4, and CYP2D6. Such dual metabolism should be considered when evaluating drug interactions.

Because the liver is the major site of drug metabolism, liver disease can affect drug metabolism. Usually, phase I metabolism is affected to a greater extent than phase II metabolism. For this reason, drug metabolism should be considered when choosing a medication for a patient with liver disease. For example, most benzodiazepines, including diazepam (Valium[R]), chlordiazepoxide (Librium[R]), and clonazepam (Klonopin[R]) are eliminated through phase I metabolism, but lorazepam is metabolized through phase II metabolism. Lorazepam is therefore a better choice in a patient with liver disease.

Elimination

Once a drug is rendered water-soluble through metabolism, it can be eliminated in the urine or bile. Ethinyl oestradiol, an ingredient of most oral contraceptives, is eliminated in the bile after undergoing a conjugation reaction. The conjugated metabolite can either be eliminated in the feces, or changed back into ethinyl oestradiol by intestinal bacteria and reabsorbed. This cycle is known as enterohepatic recirculation, and is analogous to recycling aluminium soda cans.

In contrast to ethinyl oestradiol, most drugs and their metabolites are eliminated in the urine.

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This poses a problem for patients with renal failure. Fortunately, most drug information references contain recommendations on drug dosage adjustments for various degrees of renal impairment.

A patient's degree of renal impairment is measured by the patient's creatinine clearance. Creatinine is a by-product of muscle breakdown and is produced and eliminated by the kidneys at a constant rate.

Equation 1

$$CrCl = \frac{(140\text{-age})(wt)}{72 \times SCr}$$

(Multiply by 0.85 for females)

Where CrCl is creatinine clearance, SCr is serum creatinine in mg/dL, and wt is weight in kilograms.

If the patient is overweight, the patient's ideal body weight should be used. Ideal body weight is calculated as follows:

IBW = 50 kg + 2.3 kg for every inch over five feet (for men)

-or-

IBW = 45.5 kg + 2.3 kg for every inch over five feet (for women)

Creatinine clearance can be measured by a 24-hour urine collection, or estimated using **Equation 1**:

Once the patient's creatinine clearance is calculated, the proper dose can be ascertained. Without using this equation, health care professionals often overestimate renal function in the elderly, and do not adjust drug doses to match the ability of geriatric patients to eliminate drugs. Notice that in the equation for creatinine clearance, age is inversely proportional to creatinine clearance (i.e. renal function). Even in the absence of overt renal disease, an 80-year-old patient has a decreased ability to eliminate medications, simply because her kidneys are eighty years old! The following example illustrates that adjusting the dose of ranitidine can decrease the risk of adverse effects, decrease drug cost, and enhance dosing convenience as seen in **Equation 2**:

Equation 2

An 80-year-old female weighs 45.5 kg and is 5'5" tall. Her serum creatinine is 1.1 mg/dL.

Calculating:

$$\frac{(140\text{-}80)\,(45.5\text{kg})}{72(1.1)} \times (0.85) = 29 \text{ mL/min.}$$

The patient is complaining of heartburn and the plan is to prescribe ranitidine (Zantac®). According to *Facts and Comparisons,* the dose of ranitidine in patients with gastroesophageal reflux disease (GERD) is 150 mg twice a day; however, this reference recommends that the dose be decreased to 150 mg daily for patients with a creatinine clearance less than 50 mL/min. If tolerated, the dosing frequency can be increased to every twelve hours if necessary.

For some drugs, there are specific formulas for calculating the appropriate dose of a medication based on renal function. Calculation of a loading dose of digoxin has already been illustrated. The following shows how a loading dose and maintenance dose of digoxin can be calculated for this 80-year-old female as seen in **Equation 3**:

Twenty percent of 478 mcg is 96 mcg, increased by 25% (assuming the patient will be taking tablets) is 120 mcg.

In contrast to ranitidine and digoxin, which can be used even in patients with very poor renal elimination provided the dose is properly adjusted, some medications cannot be used safely in patients with renal dysfunction. These medications have toxic

Equation 3

Loading dose =

(45.5 kg)(7L/kg)(1.5 ng/L) = 478 mcg

The daily **maintenance dose** is a percentage of the total loading dose.

The equation is:

$$\frac{CrCl}{5} + 14 = \text{percentage of digoxin eliminated per day.}$$

Thus, $\frac{29}{5} + 14 =$ 20%, or 96 mcg

metabolites that are eliminated so slowly by the kidney that they accumulate.

Examples include nor-meperidine, the neurotoxic metabolite of meperidine (Demerol^{R}), and the metabolites of nitrofurantoin (Macrodantin^{R}), which can accumulate and cause peripheral neuropathy. Drugs that are metabolized in the liver to inactive, non-toxic metabolites can generally be used safely in patients with renal dysfunction without dosage adjustment.

Although most general drug references contain information about drug dosing in renal failure, the American College of Physicians *Drug Dosing in Renal Failure* is an excellent source of this information for prescribers.

For some drugs, there are no definitive guidelines on dosing in renal failure. Two such drugs are morphine and non-steroidal anti-inflammatory drugs (NSAIDs). Morphine is metabolized in the liver to morphine 6-glucuronide, which crosses the blood brain barrier more readily than morphine and binds more readily to opiate receptors than does morphine. Normally, the kidneys eliminate this active metabolite, and so it accumulates in patients with impaired renal function. Morphine therefore must be dosed cautiously in these patients. NSAIDs must also be dosed cautiously in renal failure. Although NSAIDs are metabolized in the liver to an inactive conjugated metabolite, this inactive metabolite can accumulate in renal disease and spontaneously convert back into the active NSAID while it floats through the bloodstream. NSAIDs can further impair renal function by decreasing renal blood flow. In addition, NSAIDs can contribute to bleeding in patients with end-stage renal disease by further impairing platelet function, which is already compromised in such patients. These effects of NSAIDs in renal disease, as well as the effects of morphine 6-glucuronide, are pharmacodynamic effects.

Pharmacodynamics

Mechanisms of Drug Action

Thus far, the pharmacology concepts discussed have focused on what the body does to the drug. Pharmacodynamics explains how drugs act on the body to produce therapeutic effects as well as adverse effects.

Central to modern pharmacologic thought is **receptor theory.** Receptors are proteins found on cell membranes. When drugs bind to these receptors, a chain reaction is triggered within the cell, resulting in a response or change in the cell's function.

For example, if a patient is having an asthma attack and is given a dose of albuterol (Proventil^{R}), the albuterol binds to Beta-2 receptors in the bronchial smooth muscle. This binding triggers a series of reactions that cause the muscle to relax so that the patient can breathe. Because albuterol binds to the receptor and causes a reaction, it is an **agonist**. On the other hand, some drugs bind to receptors but do not cause a reaction. They are said to be **antagonists** at this receptor because they occupy the receptor without causing a reaction. Naloxone (Narcan^{R}) is an antagonist at μ-opiate receptors and thus acts to prevent μ-agonists such as morphine from acting, and so is used to treat narcotic overdose.

Some drugs bind to receptors in a manner that is in-between an agonist and an antagonist; these are **partial agonists.** Tramadol (Ultram^{R}) is a partial agonist at μ-receptors. When it binds to μ-receptors, it does not elicit as great an effect as morphine because tramadol is only a partial agonist. Partial agonists have a **ceiling** effect; this means that by increasing the dose, there is a point that is reached where increasing the dose further does not result in increased efficacy. Another consideration is that if a partial agonist is prescribed with an agonist, the partial agonist can block or minimize the agonist's effect by competing for receptor sites. Some drugs are **agonist/antagonists.** This means that they are antagonists or partial agonists at some receptors, but are agonists at others. For example, pentazocine (Talwin^{R}) is an antagonist at μ-receptors, but is an agonist at kappa opiate receptors.

As mentioned previously, drugs do not "know" where in the body they need to go to exert their effect. It was explained that a drug's lipid solubility, protein binding, and tissue binding all influence where the drug goes. The type and number of receptors found in various tissues also influences where a drug will exert its effects. For example, albuterol acts in the lungs and heart because Beta-2 receptors are found there. Its desired therapeutic effect is in the lungs, but albuterol's binding to Beta-2

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receptors in the heart can also cause increased heart rate.

Another concept central to the receptor theory is that the greater the drug dose, the greater the number of receptors occupied, and the greater the pharmacologic effect. Simply stated, the greater the drug dose, the greater the effect. This is the opposite of the "theory of infinitesimals" a fundamental tenant of homeopathy. Homeopathy is a philosophy that emerged in the 1800s and is enjoying renewed popularity today as a form of self-medication. Homeopathic medicines are extremely dilute because of the belief that medicines become stronger the more dilute they are made. In fact, homeopathic medicines are so dilute that sometimes not even a single molecule of the labeled active ingredient can be found in the bottle!

Although most drugs act by binding to receptors, there are other mechanisms by which drugs act. For example, NSAIDs reduce inflammation by inhibiting an enzyme called cyclooxygenase, which is found in most body tissues and produces inflammatory chemicals. Inhibition of this enzyme also leads to decreased renal blood flow and platelet dysfunction. Another drug that acts by inhibiting an enzyme is the anti-diabetic agent acarbose (Precose^{R}). This medication inhibits alpha-glucosidase, an intestinal enzyme necessary for the absorption of glucose.

Yet another mechanism of drug action involves binding of substances in the gastrointestinal tract. Cholestyramine (Questran^{R}) and colestipol (Colestid^{R}) act by binding bile salts in the intestine, thus reducing the pool of bile salts from which cholesterol is made. Antacids also act directly in the gastrointestinal tract by neutralizing stomach acid.

Potency versus Efficacy

Terminology regarding drug action is often misused. The terms "potency" and "efficacy" are often used interchangeably, but in fact are two very different characteristics.

Potency refers to how much of a drug is required to produce a given effect. For example, the analgesic effect of ibuprofen 400 mg is approximately equivalent to that of ketoprofen 25 mg. It can be said that ketoprofen is more potent because less is required to produce the same effect. However, both drugs show equal **efficacy** as analgesics – they are both capable of producing the same analgesic effect. On the other hand, morphine is a more effective analgesic than either ibuprofen or ketoprofen because it is more effective for severe cancer pain than NSAIDs such as ketoprofen or ibuprofen. Among narcotic analgesics, it can be said that morphine is a more effective analgesic than propoxyphene, found in Darvocet^{R} and Darvon^{R}. No matter how much ibuprofen, ketoprofen, or propoxyphene is given, they can never match the pain relief that can be provided by morphine.

Drug Interactions

The mechanisms of drug interaction fall into one of five categories:

1. interference with drug absorption,
2. change in drug distribution,
3. increased or decreased metabolism,
4. increased or decreased elimination, or
5. enhancement of or interference with drug action.

It is important to understand that most drug interactions do not contraindicate the concomitant use of medications that have the potential to interact, although important exceptions will be discussed. Most drug interactions can be managed if clinicians understand their mechanism. Management of drug interactions is usually a matter of identifying the consequence of the drug interaction, and monitoring the patient for increased or decreased drug effect, as appropriate. Another important concept is that not all patients who take medications that can potentially interact will experience an adverse outcome because of the interaction. There are factors that influence the likelihood of a drug interaction causing a clinically important effect.

For example, not all drugs within a certain class have the same propensity to be involved in an interaction. The closely related antibiotics doxycycline and tetracycline can both complex with calcium, zinc, aluminium, and magnesium found in antacids and dietary supplements. Although calcium-containing dairy products can complex with and inactivate tetracycline, doxycycline is not affected.

In fact, tetracycline should be taken one hour before or two hours after meals to maximize the extent of tetracycline absorption, but it is recommended that

doxycycline be taken with milk or food to minimize stomach upset.

The extent of absorption of the quinoline antibiotics (ciprofloxacin, levofloxacin, sparfloxacin, others) is also decreased by complexation with divalent cations. "Hidden" sources of divalent cations include sucralfate (Carafate®), which contains aluminum, and the magnesium-containing ACE inhibitor quinapril (Accupril®).

In some cases, it is wise to assume that all drugs in a class are capable of causing an interaction. An example is the bile acid resins cholestyramine and colestipol, used to lower cholesterol. As explained previously, these drugs act by binding bile acids in the intestine. Unfortunately, they are not selective in their binding activity and can bind to drugs, thus decreasing the extent of drug absorption. When the drug interaction references discussed previously are consulted, one finds that for some drugs, one bile acid resin is listed as interacting with a given drug while the other is not. In addition, there are only a limited number of medications listed as interacting. This is because not all drugs have been tested for interaction with the bile acid resins. Given the mechanism of action of the bile acid resins, it is prudent to assume that both can bind to medications and decrease the extent of drug absorption. Unless there is specific information that the resin does not interact with a given drug, patients should be instructed to separate other medications from the resin as far as possible. However, separating the doses will not completely eliminate the interaction with all medications, and patients should be monitored for decreased therapeutic response.

Another mechanism of drug interaction is alteration of drug distribution. Some drugs, including sulfamethoxazole/trimethoprim (Bactrim®, Septra®), displace highly protein bound drugs (e.g. warfarin, phenytoin) from protein binding sites, increasing their free fraction and therapeutic effect. Other medications can displace drugs from tissue binding sites, thus increasing serum levels. Digoxin can be displaced from its binding sites in the heart by the calcium channel blockers diltiazem and verapamil.

The most common mechanism of drug interaction involves the inhibition or induction of metabolism. When one drug inhibits an enzyme required for metabolism of another drug, the serum concentration of the other drug increases. The likelihood of a patient suffering an adverse effect from inhibition or induction of drug metabolism depends on several factors. One is the serum concentration of the medication.

For example, if a patient taking theophylline is prescribed clarithromycin (Biaxin®), an inhibitor of CYP3A, the resulting increase in theophylline concentration might not be clinically significant if the patient's baseline theophylline concentration is low.

Another important consideration is that theophylline is one of several drugs with "dual" metabolism. CYP1A2 is also involved in theophylline metabolism, and so the increase in theophylline concentration might be especially great if the patient is also taking a CYP1A2 inhibitor such as fluvoxamine (Luvox®). Fluvoxamine is an antidepressant of the selective serotonin reuptake inhibitor class (SSRIs). Although there are several SSRIs available with similar efficacy and side effects, they have different propensities to inhibit the CYP450 isoenzymes.

For example, paroxetine (Paxil®) and fluoxetine (Prozac®) are both SSRIs, but paroxetine is an inhibitor of CYP2D6, while fluoxetine is an inhibitor of CYP3A. Citalopram (Celexa®) does not inhibit either of these isoenzymes. Thus, the risk of a drug interaction depends on which medication within a drug class the patient is taking.

Finally, a patient's individual sensitivity to the effects of a given medication in part determines the consequences of a drug interaction. Increasing or decreasing a drug dose in anticipation of an interaction is rarely appropriate. Patients should simply be monitored for increased adverse effects, and drug serum levels should be monitored if appropriate. The dose of the affected drug can then be adjusted if necessary. The vigilance with which the patient must be monitored is dependent in part upon the potential seriousness of the interaction.

Unfortunately, there are several life-threatening drug interactions due to enzyme inhibition. Drugs that inhibit CYP3A should never be used in patients taking cisapride or astemizole, because elevated levels of these two medications can lead to lethal ventricular arrhythmia.

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This contraindication results not only from the seriousness of the consequences of the interaction (i.e., death), but also from the inability to monitor the patient for the interaction before it actually occurs.

Another absolute contraindication is the use of sildenafil (Viagra[R]) in patients taking any form of nitrate (e.g., nitroglycerin, isosorbide dinitrate, etc.). Sildenafil inhibits the enzyme responsible for nitrate metabolism, and thus can cause profound, refractory hypotension and death due to high nitrate concentrations.

Enzyme induction has already been discussed. In addition to smoking, rifampin, omeprazole (Prilosec[R]), phenobarbital, and phenytoin (Dilantin[R]) are all inducers of CYP1A2. CYP3A, CYP2E1, and CYP2C9 are also subject to induction by medications, but a complete list of these inducers is beyond the scope of this discussion.

An important distinction between enzyme inhibition and induction is their onset of effect. Inhibition begins with the first dose of the inhibitor, while induction usually requires several weeks because additional enzymes must be made. Keeping the expected time course of an interaction in mind is important in monitoring patients for a need for dosage adjustment. In addition, for short courses of medications, such as antibiotics, the course of medication administration might be over before a change in therapeutic effect is seen. The effect of a course of a macrolide antibiotic on theophylline levels is one example. Although erythromycin and clarithromycin inhibit theophylline metabolism, they are an exception to the rule that inhibition begins with the first dose of the inhibitor; due to their unique mechanism of inhibition, it can take several days for theophylline levels to begin to increase.

You will remember the example of doxycycline and tetracycline illustrated that not all drugs in the same class exhibit the same drug interactions. The macrolide antibiotics erythromycin, clarithromycin, and azithromycin pose another example: while clarithromycin and azithromycin are inhibitors of theophylline metabolism, azithromycin is actually an inducer of theophylline metabolism, and so the decrease in theophylline metabolism caused by azithromycin is seen after completion of a 5-day course of the antibiotic.

Interference with drug elimination is the final pharmacokinetic-based mechanism of drug interaction. Antibiotics enhance elimination of oral contraceptives, and pose a risk of therapeutic failure (i.e., pregnancy). The enterohepatic recirculation of ethinyl estradiol is interrupted when an antibiotic given to treat an infection kills normal gut bacteria, allowing the ethinyl estradiol metabolite to be eliminated in the feces rather than converted back into active drug and reabsorbed. Although the risk of unwanted pregnancy is extremely low, it is prudent to inform oral contraceptive users taking an antibiotic of this risk. Use of an alternate form of contraception until the next cycle is reasonable, especially if the antibiotic course is longer than ten days. When antibiotics are taken long-term, such as for treatment of acne, the gut flora become resistant to the antibiotic, and unwanted pregnancy is probably not a concern.

In addition to pharmacokinetic-based drug interactions, pharmacodynamic interactions can also occur. Narcotic analgesics provide an example of such an interaction. Morphine is an agonist at m-opiate receptors, through which morphine exerts its analgesic effect. Certain other narcotics, including pentazocine (Talwin[R]) and butorphanol (Stadol[R]) exert their analgesic effect through kappa opiate receptors, but are antagonists at m-opiate receptors. They can thereby block the analgesic effects of morphine and other m-opiate agonists (codeine, hydrocodone, hydromorphone, oxycodone) if used together.

This discussion of drug interactions serves as a general overview of drug interaction mechanisms and management. For specific information on over 25,000 drug interactions, specialized drug interaction references are essential.

Federal Drug Law

The citizens of the United States believe that medications should be safe, effective, and accessible to all who need them, but inaccessible to those who might misuse them. They also support the development of new medications. Federal drug laws reflect these values and are designed to protect the public health. Examining the events that influenced the development of these laws

clarifies the intent of the laws, and gives a unique perspective on what health care, and even life, in the United States would be like if these laws were ever repealed.

Pure Food and Drug Act of 1906

This law was passed due to concerns about danger from medicines containing impurities. This law was designed to ensure that a product's label was truthful in regard to the identity of its ingredients, its purity, and its potency. A shortcoming of this law was that it did not require labeling of products' potency, purity and ingredients – only that this information must be true if it were included on the label. To avoid prosecution, manufacturers simply did not include this information on their products! Unfortunately, the law did nothing to protect the public from false claims about products' efficacy.

In 1911, the U.S. Supreme Court decided that because the law did not address false efficacy claims, a product that claimed to cure cancer did not violate this law, even though the manufacturer was aware that the product did not cure cancer. In 1912, the Pure Food and Drug Act was amended to prohibit false efficacy claims, but required the government to prove that the manufacturer knew that the claim was false. Clearly, this law was inadequate to protect the public health.

Food, Drug, and Cosmetic Act of 1938

It took an incident known as the sulfanilamide tragedy of 1937 to spur the passage of this law, which was the first to require that drugs must be safe for use as labeled, and that they must be approved by the FDA prior to marketing. The sulfanilamide tragedy occurred when a new antimicrobial, sulfanilamide, was found to dissolve easily in an attractive, sweet-tasting fluid. The resulting sulfanilamide solution was marketed without any toxicity testing, and caused 107 deaths. The attractive, sweet-tasting solvent was diethylene glycol, commonly used today as antifreeze. Unbelievably, there was no law that prohibited the sale of this deadly product on the basis that it was unsafe. The FDA was able to remove the product from the market on the basis that it was labeled untruthfully – it was labeled as an elixir (an alcohol-containing solution), but it contained no alcohol. The passage of the Federal Food, Drug, and Cosmetic Act was obviously an improvement over the Pure Food and Drug Act.

Durham-Humphrey Amendment of 1951 (Prescription Drug Amendment)

Prior to enactment of this law, many drugs were being sold over the counter that were not safe for independent use by lay persons. This amendment to the Food, Drug, and Cosmetic Act established two classes of medication: prescription and nonprescription. Nonprescription drugs must have labels that contain "adequate directions for use," meaning, "directions under which the layman can use a drug safely and for the purposes for which it is intended."

Conversely, prescription drugs are not safe to use except under medical supervision, and thus do not need to be labeled in this manner. Prescription drugs must carry the legend "Caution: Federal law prohibits dispensing without a prescription," and the directions typed on the label by the pharmacist constitute "adequate directions for use."

For prescription drugs, the FDA-approved prescribing information, or package insert, is a legal document that contains "adequate information for use" and is intended for the prescriber, not the patient. The prescribing information is included with each bottle of a prescription drug when it is shipped from the manufacturer.

As discussed previously, selected package inserts are also reproduced in the *PDR*.

Kefauver-Harris Amendment of 1962 (Drug Efficacy Amendment)

The next time that the Food, Drug, and Cosmetic Act was amended, it was in response to the thalidomide tragedy of the late 1950's. Thalidomide, which was a popular European tranquilizer, was used experimentally in the United States, but was never FDA-approved. While the manufacturer was collecting additional safety data requested by the FDA, it was confirmed that the drug was associated with a type of limb defect, phocomelia (seal limbs). Fortunately, the number of birth defects caused by the drug was low in the U.S. because the drug had never been approved here, but the incident

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called attention to the drug approval process, and the Drug Efficacy Amendment was enacted.

DESI Review

The Food, Drug, and Cosmetic Act of 1938 established that drugs must be safe, and the Kefauver-Harris Amendment in 1962 established that drugs must also be efficacious for their intended use. But what about drugs that were already on the market before these laws were passed?

In response to the passage of the Kefauver-Harris amendment, the FDA began the Drug Efficacy Study Implementation (DESI). The DESI review was necessary because the Kefauver-Harris Amendment was retroactive; the thousands of drugs marketed between 1938 and 1962 had to be proven efficacious.

For nonprescription drug products, the FDA decided that it would be reasonable to review only active ingredients, rather than each individual product.

There was much controversy during this process in regard to generic drugs. Should generic drugs automatically be cleared for marketing if their corresponding brand name product had already been deemed safe and effective? After several Supreme Court decisions, it was decided that manufacturers of generic drugs marketed between 1938 and 1962 needed only to submit an Abbreviated New Drug Application (ANDA) to the FDA. An ANDA does not contain safety and efficacy information; it only contains information on the manufacturing process, ingredients, bioavailability, and bioequivalence of the generic product. Bioequivalence means that the serum levels produced by the generic product match those of the innovator product. Some deviation in serum levels is allowed, as long as the difference is not deemed clinically important. In contrast, generic products marketed after 1962 were required to submit safety and efficacy data, as did the original brand name products via a New Drug Application (NDA).

Drug Price Competition and Patent-Term Restoration Act of 1984 (Waxman-Hatch Amendment)

Collecting data to complete an NDA is an expensive, time-consuming process. The FDA's requirement that manufacturers of generic drugs marketed after 1962 submit an NDA for FDA approval placed a financial burden on the generic drug manufacturers. The Waxman-Hatch Amendment streamlined the FDA-approval process for generic drugs by requiring that manufacturers of generic drugs submit only an ANDA instead of an NDA. Thus, generic drugs became more readily available. This law also provided patent extensions to manufacturers of new drug products. By protecting new drugs from competition from generic versions, patent extensions provide an incentive for manufacturers to develop new drugs. This gives pharmaceutical researchers time to profit from their innovation.

Orphan Drug Act of 1983

As you can imagine, developing a new drug and collecting data sufficient to prove that the drug is safe and effective is a very expensive process, costing hundreds of millions of dollars. Some diseases are so rare and affect so few people that a company might not ever recoup the money it spent bringing the drug to market. The Orphan Drug Act provides tax incentives and patent extensions to companies willing to manufacture such drugs. The designation of "orphan drug" has little implication for health care professionals, but is often misinterpreted as meaning that the drug is experimental, difficult to obtain, or not FDA-approved.

Robinson-Patman Act of 1936 and Prescription Drug Marketing Act of 1987

The impetus for the passage of these laws was the concern about unfair competition and danger to the public health from prescription drugs distributed to the public outside of the safeguards of the normal drug distribution process. The Prescription Drug Marketing Act prohibits the sale of drug samples, and requires record keeping of sample disposition by pharmaceutical companies and sales representatives. Based on similar concerns, the sale of prescription drugs from hospital pharmacies to the general public is prohibited by the Robinson-Patman Act of 1936. Because hospitals acquire their medications at a substantial discount compared to retail pharmacies, a hospital pharmacy would pose unfair competition for retail pharmacies in the community if it sold its medications to the general public. Hospitals can only dispense drugs to inpa-

tients; emergency department patients; outpatients for use on the hospital premises; and hospital employees and their dependents. Patients being discharged from the hospital can take home enough medication to last for a "limited and reasonable time."

Controlled Substances Act

This law establishes a "closed" system for the distribution of drugs that are recognized as having the potential for addiction or abuse. A special division of the Department of Justice, the Drug Enforcement Administration (DEA), administers this law – not the FDA. Manufacturers, distributors (wholesalers, pharmacies), researchers, and prescribers of controlled substances must register with the federal DEA in order to be involved in this "closed" distribution system; however, it is the individual state boards governing the various health care professions that decide which professions can prescribe controlled substances in their states. For example, nurse practitioners can prescribe controlled substances in some states, but not in all states.

Controlled substances are classified into schedules based on their potential for abuse. Schedule I controlled substances have a high potential for abuse, and have no role in medical practice. Such substances include LSD, marijuana, and heroin. Controlled substances with low abuse potential are classified in schedule V. The U.S. Attorney General, upon recommendation by the U.S. Secretary of Health and Human Services, has the authority to decide which substances are placed in each schedule. In addition, each state has the authority to add drugs to each schedule, given local patterns of abuse. For example, in some states butorphanol (Stadol^{R}) was a schedule IV controlled substance for some time before it was scheduled by the U.S. Attorney General.

In some states, a pharmacist can sell certain schedule V medications without a prescription. Usually, the purchaser must sign a ledger and show proof of age, and can only purchase a certain quantity of the product within a certain period of time. In states in which nurse practitioners can prescribe controlled substances, they are usually limited to prescribing products in schedules V through III, and are often limited to prescribing a certain quantity, such as a 72-hour supply of a schedule III medication. State boards of nursing, medicine, and pharmacy, not the DEA, promulgate such rules and regulations.

Dietary Supplement Health and Education Act (DSHEA) of 1994

As time has passed, the laws regarding the quality and availability of drugs have become more and more restrictive. The federal laws have taken freedom away from consumers to make their own choices, and their own mistakes, regarding use of medications. With the increasing number of medications on the market, many with dangerous side effects and drug interactions, it is difficult to argue that the public at large is sufficiently educated to use most drugs safely without medical advice and supervision. It would also be difficult to contend that drug manufacturers have a right to mislead consumers about the potency, purity, or efficacy of a drug product.

However, due to pressure from the manufacturers of vitamins and other dietary supplements, as well as some consumers, the Dietary Supplement Health and Education Act (DSHEA) was passed. This amendment to the Food, Drug, and Cosmetic Act restricts the FDA's ability to regulate vitamins, minerals, herbs and other botanicals, amino acids, and other dietary supplements.

Unlike drugs, these products can be marketed without FDA-approval, and unlike drugs their potency, purity, safety, and efficacy do not have to be proven. Claims concerning the role of the product in affecting the structure or function of the human body (e.g. "improves well-being," or "for leg vein health") or in preventing a nutritional deficiency are allowed, but the manufacturer cannot claim that the product treats or cures any disease. The label on the product must carry the disclaimer, "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease." The FDA has the authority to remove such products from the market, but only if they can prove that the product is dangerous. Proponents feel that the DSHEA empowers patients to take responsibility for their own health, but the law is also a step backward in the government's ability to protect the public health.

Another problem with the

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DSHEA is that it makes the distinction between dietary supplements and drugs less clear. For example, both the prescription drug Mevacor® and the dietary supplement Cholestin® contain lovastatin, which is a cholesterol-lowering agent isolated from a particular strain of fungus. Mevacor® is FDA-approved to lower total and LDL cholesterol in patients with primary hypercholesterolemia, and to slow the progression of atherosclerosis in patients with coronary artery disease. Cholestin® is a nonprescription dietary supplement marketed to lower cholesterol. Because the product does not claim to cure or treat a disease, it is legally available without a prescription, despite the potential for adverse effects and drug interactions. It will be interesting to see how many other prescription drugs that are derived from plant or animal sources reach the nonprescription market in this manner.

The Drug Development Process

The permissiveness of the Dietary Supplement Health and Education Act is in sharp contrast to the requirements set forth by the FDA in order for a new drug to be approved. The first step in getting a potential drug to the marketplace is pre-clinical testing. The new drug is tested in animals to see if it has any effects that might be beneficial to humans. Animal toxicity data are also collected. If the activity of the drug appears promising, and its toxicity profile is acceptable, the manufacturer files an Investigational New Drug Application (INDA) with the FDA. The INDA includes all data collected thus far, and details the human experiments the manufacturer plans to undertake. It is at this point that the news media often get wind of a promising new drug, and health professionals are bombarded with questions from patients about the new medication! However, the medication is probably at least ten years away from pharmacy shelves, if the FDA allows the manufacturer to proceed with phase I clinical trials.

Phase I clinical studies include less than one hundred healthy volunteers. An exception to use of healthy volunteers for phase I studies would be very toxic medications such as cancer drugs, which are usually not administered to patients who do not have cancer. Phase I trials are basically pharmacokinetic studies. In addition, the dosage range for the drug is determined at this point, and study participants are screened for adverse effects. Next are phase II studies, involving several hundred actual patients. The drug's efficacy is assessed, and its adverse effects are further characterized. Phase III is the longest phase, lasting several years and involving several thousand patients. All through these three phases, the FDA, as well as Institutional Review Boards (IRBs) affiliated with the clinics or hospitals where the studies are conducted, are monitoring the studies closely to make certain that patients' rights and safety are the foremost concern, and that the study protocols are being followed to the letter. Once the clinical trials are completed, the manufacturer must file a New Drug Application (NDA), a document several hundred thousand pages in length containing all of the information known about the medication.

A panel of medical experts at the FDA then reviews the NDA, and makes a recommendation for or against drug approval. If FDA-approved, the drug is deemed safe and effective for use according to the prescribing information. This does not prohibit prescribers from prescribing the drug for an indication for which the drug is not FDA-approved, or from administering it in a manner that is not FDA-approved. For example, clotrimazole vaginal tablets are not FDA-approved for oral use, but are often prescribed by dentists to treat oral candidiasis (thrush).

Even after all of this testing, it is not uncommon for adverse effects and drug interactions not identified in the clinical trials to become evident after the drug is marketed. This is because in clinical trials, the drug is only administered to a few thousand patients for two or three years at most, so rare adverse effects and long-term safety and efficacy cannot assessed. It is also not possible to test for drug interactions between the new medication and every other medication available on the market. For this reason, manufacturers sometimes apply the same drug interaction concepts discussed in this program to predict which drugs might interact with the new drug. In addition, they test for interactions with drugs with which it might be commonly prescribed

in clinical practice. Post-marketing studies, called Phase IV studies, are sometimes done to clarify these issues. Considering all of this uncertainty concerning safety despite the rigorous, controlled testing required for drug approval, the empiric use of dietary supplements is very frightening indeed.

Of course, the rationale behind this lengthy and expensive process is to ensure that drugs are both safe and efficacious before being made available for general use, but qualified patients can have access to investigational drugs if they meet criteria for entry into clinical trials. Keep in mind that patients enrolled in clinical trials will likely be randomly assigned to either active treatment or a placebo, so there is a chance that the patient will not receive the study medication. This might seem cruel or inhumane, but use of a placebo or comparative treatment is necessary to truly ascertain the new drug's efficacy and safety. Sometimes, manufacturers have protocols through which a drug can be obtained for a patient even if he or she does not fit the inclusion criteria for the study.

The drug approval process strikes a delicate balance between protecting the public from unsafe or ineffective products while ensuring that medications are made available as soon as possible to those who need them. Although the system sometimes fails by not identifying a serious adverse effect or drug interaction before harm is done, or withholds an effective medication from which a patient might benefit, the complexity of drug pharmacokinetics and pharmacodynamics necessitates rigorous scientific scrutiny. By understanding general pharmacology concepts, nurse practitioners can be better equipped to identify and manage drug-related problems, even in the face of incomplete information. ◆

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