21 - Clinical Pharmacology

Chapter 317. Concepts in Pharmacotherapy

Introduction

Drugs are selected based on characteristics of the drug (eg, efficacy, safety profile, route of administration, route of elimination, dosing frequency, cost) and of the patient (eg, age, sex, likelihood of pregnancy, ethnicity, other genetic determinants). Risks and benefits of the drug are also assessed; every drug poses some risk.

Response to a drug depends partly on the patient's characteristics and behaviors (eg, consumption of foods or supplements; adherence to a dosing regimen; differences in metabolism due to age, sex, race, genetic polymorphisms, or hepatic or renal insufficiency), coexistence of other disorders, and use of other drugs. Drug errors (eg, prescribing an inappropriate drug, misreading a prescription, administering a drug incorrectly) can also affect response.

Adherence to a Drug Regimen

Adherence (compliance) is the degree to which a patient follows a treatment regimen. For drugs, adherence requires that the prescription is obtained promptly and the drug is taken as prescribed in terms of dose, dosing interval, and duration of treatment. Patients should be told to alert their physician if they stop or alter the way they take a drug, but they rarely do so.

Only about half of patients who leave a physician's office with a prescription take the drug as directed. The most common reasons for nonadherence are

• Frequent dosing

• Denial of illness

• Poor comprehension of the benefits of taking the drug

• Cost

Many other reasons contribute to nonadherence (see Table 317-1).

Children are less likely than adults to adhere to a treatment regimen. Adherence is worst with chronic disorders requiring complex, long-term treatment (eg, juvenile diabetes, asthma). Parents may not clearly understand prescription instructions and, within 15 min, forget about half the information given by the physician.

[**Table 317-1.** Causes of Nonadherence]

The elderly adhere to treatment regimens as well as other adults. However, factors that decrease adherence (eg, inadequate finances, use of multiple drugs or drugs that must be taken several times a day) are more common among the elderly (see p. 3097). Cognitive impairment may further decrease adherence. Sometimes a prescriber must be creative by picking a drug that is easier to use even though it may not be the first choice. For example, a clonidine patch applied weekly by a visiting nurse or family member may be tried for hypertension in patients who cannot adhere to a more preferable daily regimen of oral drugs.

The most obvious result of nonadherence is that the disorder may not be relieved or cured. Nonadherence is estimated to result in 125,000 deaths due to cardiovascular disorders each year in the US. If patients took their drugs as directed, up to 23% of nursing home admissions, 10% of hospital admissions, many physician visits, many diagnostic tests, and many unnecessary treatments could be avoided. In some cases, nonadherence can actually lead to worsening of disease. For example, missed

doses or early cessation of antibiotic or antiviral therapy may lead to resistant organisms.

Pharmacists and nurses may detect and help solve adherence problems. For example, a pharmacist may note that a patient does not obtain refills or that a prescription is being refilled too soon. In reviewing prescription directions with the patient, a pharmacist or nurse may uncover a patient's misunderstandings or fears and alleviate them. Physicians can alter complicated or frequent dosing or substitute safe, effective, but less expensive drugs. Communication among all health care practitioners that provide care for a patient is important.

Drug Errors

Drug errors contribute to morbidity. They are estimated to cost the US health care system up to $177 billion (depending on definitions) annually. Drug errors may involve

- The wrong choice of a drug or a prescription for the wrong dose, frequency, or duration
- An error in reading the prescription by the pharmacist so that the wrong drug or dose is dispensed
- An error in reading the label of the drug container by the caregiver so that the wrong drug or dose is given
- Incorrect instructions to the patient
- Incorrect administration by a clinician, caregiver, or patient
- Incorrect storage of a drug by the pharmacist or patient, altering the drug's potency
- Use of outdated drug, altering the drug's potency
- Confusion of the patient so that the drug is taken incorrectly

Errors in prescribing are common, especially for certain populations. The elderly (see Ch. 308, especially Table 308-3 on p. 3094), women of childbearing age, and children are particularly at risk. Drug interactions particularly affect those taking many drugs. To minimize risk, clinicians should know all drugs being taken—including those prescribed by others and OTC drugs—and keep a complete problem list. Patients should be encouraged to write and update a list of their current drugs and dosages and bring the list to every health care appointment or emergency department visit. If there is any doubt as to which drugs are being used, patients should be instructed to bring all their drugs to their health care appointments for review.

Prescriptions must be written as clearly as possible. The names of some drugs are similar and, if not written clearly, cause confusion. Changing some traditional but easily confused notations may also help reduce errors. For example, "qd" (once/day) may be confused with "qid" (4 times/day). Writing "once/day" or "once a day" is preferred. Electronically transmitted or computer-printed prescriptions can avoid problems with illegible handwriting or inappropriate abbreviations.

Drugs may be given incorrectly, especially in institutions. A drug may be given to the wrong patient, at the wrong time, or by the wrong route. Certain drugs must be given slowly when given IV, and some drugs cannot be given simultaneously. When an error is recognized, it should be reported immediately to a clinician, and a pharmacist should be consulted. Bar codes and computerized pharmacy systems may help decrease the incidence of drug errors.

A pharmacist should store drugs in a manner that ensures their potency. Mail-order pharmacies should follow procedures to ensure proper transportation. Storage by patients is often suboptimal. If stored incorrectly, drugs are likely to decrease in potency long before the stated expiration date. Labeling should clearly state whether a drug needs to be stored in the refrigerator or kept cool, needs to be kept out of excessive heat or sun, or otherwise requires special storage. On the other hand, unnecessary precautions decrease adherence and waste the patient's time. For example, unopened insulin should be

refrigerated, but a bottle in use can be stored safely outside the refrigerator for a relatively long time if not exposed to excessive heat and sun.

Use of outdated drugs is common. Outdated drugs are likely to be ineffective and some (eg, aspirin, tetracycline) can be harmful if used when outdated.

Most commonly, drug error results from a patient's confusion about how to take drugs. Patients may take the wrong drug or dose. Dosing instructions for each drug, including why the drug has been prescribed, should be completely explained to patients and given in writing when possible. They should be advised to ask their pharmacist for additional advice about taking their drugs. Packaging should be convenient but safe. If children will not have access to the drug and patients may have difficulty opening the container, drugs do not need to be provided in childproof containers.

Drug Interactions

Drug interactions are changes in a drug's effects due to recent or concurrent use of another drug or drugs (drug-drug interactions) or due to ingestion of food (drug-nutrient interactions —see p. 7).

A drug interaction may increase or decrease the effects of one or both drugs. Clinically significant interactions are often predictable and usually undesired (see Table 317-2). Adverse effects or therapeutic failure may result. Rarely, clinicians can use predictable drug-drug interactions to produce a desired therapeutic effect. For example, coadministration of lopinavir and ritonavir to patients with HIV infection results in altered metabolism of lopinavir and increases serum lopinavir concentrations and effectiveness.

In therapeutic duplication, 2 drugs with similar properties are taken at the same time and have additive effects. For example, taking a benzodiazepine for anxiety and another benzodiazepine at bedtime for insomnia may have a cumulative effect, leading to toxicity.

Drug interactions involve

• Pharmacodynamics

• Pharmacokinetics

In **pharmacodynamic interactions**, one drug alters the sensitivity or responsiveness of tissues to another drug by having the same (agonistic) or a blocking (antagonistic) effect. These effects usually occur at the receptor level but may occur intracellularly.

In **pharmacokinetic interactions**, a drug usually alters absorption, distribution, protein binding, metabolism, or excretion of another

[**Table 317-2.** Some Drugs with Potentially Serious Drug Interactions*]

drug. Thus, the amount and persistence of available drug at receptor sites change. Pharmacokinetic interactions alter magnitude and duration, not type, of effect. They are often predicted based on knowledge of the individual drugs or detected by monitoring drug concentrations or clinical signs.

Minimizing drug interactions: Clinicians should know all of their patients' current drugs, including drugs prescribed by other clinicians and all OTC drugs, herbal products, and nutritional supplements. Asking patients relevant questions about diet and alcohol consumption is recommended. The fewest drugs in the lowest doses for the shortest possible time should be prescribed. The effects, desired and undesired, of all drugs taken should be determined because these effects usually include the spectrum of drug interactions. If possible, drugs with a wide safety margin should be used so that any unforeseen interactions do not cause toxicity.

Patients should be observed and monitored for adverse effects, particularly after a change in treatment; some interactions (eg, effects that are influenced by enzyme induction) may take ≥ 1 wk to appear. Drug interactions should be considered as a possible cause of any unexpected problems. When unexpected clinical responses occur, prescribers should determine serum concentrations of selected drugs being taken, consult the literature or an expert in drug interactions, and adjust the dosage until the desired effect is produced. If dosage adjustment is ineffective, the drug should be replaced by one that does not interact with other drugs being taken.

Pharmacogenetics

Pharmacogenetics involves variations in drug response due to genetic makeup.

The activity of drug-metabolizing enzymes often varies widely among healthy people, making metabolism highly variable. Drug elimination rates vary up to 40-fold. Genetic factors and aging seem to account for most of these variations.

Pharmacogenetic variation (eg, in acetylation, hydrolysis, oxidation, or drug-metabolizing enzymes) can have clinical consequences (see Table 317-3). For example, if patients metabolize certain drugs rapidly, they may require higher, more frequent doses to achieve therapeutic concentrations; if patients metabolize certain drugs slowly, they may need lower, less frequent doses to avoid toxicity, particularly of drugs with a narrow margin of safety. For example, patients with inflammatory bowel disease who require azathioprine therapy are now routinely tested for thiopurine methyltransferase (TPMT) genotype to determine the most appropriate starting dose for drug therapy. Most genetic differences cannot be predicted before drug therapy, but for an increasing number of drugs (eg, carbamazepine, clopidogrel, warfarin), changes in effectiveness and risk of toxicity have been specifically associated with certain genetic variations. Also, many environmental and developmental factors can interact with each other and with genetic factors to affect drug response (see Fig. 317-1).

Placebos

Placebos are inactive substances or interventions, most often used in controlled studies for comparison with potentially active drugs.

The term placebo (Latin for "I will please") initially referred to an inactive, harmless substance given to patients to make them feel better by the power of suggestion. More recently, sham interventions (eg, mock electrical stimulation or simulated surgical procedures in clinical trials) have also been considered placebos. The term is sometimes used for an active drug that is given solely for its placebo effect on a disorder in which the drug is inactive (eg, an antibiotic for patients with viral illness).

Effects: Placebos, although physiologically inactive, may have substantial effects—good and bad. These effects seem to be related to anticipation that the drug will work; anticipation of *adverse* effects is sometimes called the nocebo effect. The placebo effect typically occurs with subjective responses (eg, pain, nausea) rather than objective ones (eg, rate of healing of leg ulcers, infection rate of burn wounds).

The magnitude of the response varies with many factors, including the

- Expressed confidence of the clinician ("this is going to make you feel a lot better" vs "there is a chance this might help")

- Certainty of the patient's beliefs (effect is larger when patients are sure they are receiving an active drug than when they know there is a chance they are getting a placebo)

- Type of placebo (eg, injectable drugs have a larger effect than oral ones)

[**Fig. 317-1.** Genetic, environmental, and developmental factors that can interact, causing variations in drug response among patients.]

[Table 317-3. Examples of Pharmacogenetic Variations]

Not everyone responds to placebos, and it is not possible to predict who will respond; correlations between personality characteristics and response to placebos have been theorized but not well established. However, people who have dependent personalities and who want to please their clinicians may be more likely to report beneficial effects; those with histrionic personalities may be more likely to report any effect, good or bad.

Use in clinical trials: Many clinical trials compare an active treatment with a placebo. The apparent effects of the placebo are then subtracted from the apparent effects of the active treatment to identify the true treatment effect; to be meaningful, a clinically and statistically significant difference is required. In some studies, the placebo relieves the disorder in a high percentage of patients, making it more difficult to show the active treatment's efficacy.

Use in clinical practice: Rarely today, when a clinician determines that patients have a mild, self-limited disorder for which an active drug does not exist or is not indicated (eg, for nonspecific malaise or tiredness), a placebo may be prescribed. The reasoning is that the placebo satisfies patients' demands for treatment without exposing them to potential adverse effects and often makes them feel better—due to the placebo effect or spontaneous improvement.

Ethical considerations: In clinical studies, the ethical consideration is whether a placebo should be given at all. When effective treatment exists (eg, opioid analgesics for severe pain), it is typically considered unethical to deprive study participants of treatment by giving a placebo; in such cases, control groups are given an active treatment. Because participants acknowledge in advance that they may be given a placebo, there is no concern about deception.

However, when a placebo is given in medical practice, patients are not told they are receiving an inactive treatment. This deception is controversial. Some clinicians argue that it is prima facie (Latin for "at first view") unethical and, if discovered, may damage the clinician-patient relationship. Others suggest that it is more unethical to not give something that may make patients feel better. Giving an active treatment solely for placebo effect may be further considered unethical because it exposes patients to actual adverse effects (as opposed to nocebo adverse effects).

Drug Development

Promising compounds can be identified by mass screening of hundreds or thousands of molecules for biologic activity. In other cases, knowledge of the specific molecular pathophysiology of various diseases allows for rational drug design via computer modeling or modification of existing pharmaceutical agents.

During **early development**, potentially useful compounds are studied in animals to evaluate desired effects and toxicity. Compounds that seem effective and safe are candidates for human studies. A protocol describing the clinical study must be approved by an appropriate institutional research board (IRB) and the FDA, which then issues an investigational new drug (IND) exemption permit. At this point, the patent time period for the compound begins, which usually provides the owner with exclusive rights for the next 20 yr; however, the drug cannot be sold until it is approved by the FDA.

Phase 1 evaluates safety and toxicity in humans. Different amounts of the compound are given to a small number (often 20 to 80) of healthy, young, usually male volunteers to determine the dose at which toxicity first appears.

Phase 2 determines whether the compound is active against the target disorder. The compound is given to up to about 100 patients for treatment or prevention of the target disorder. An additional goal is to determine an optimal dose-response range.

Phase 3 evaluates the drug's effect in larger (often hundreds to thousands of people), more heterogeneous populations in an attempt to duplicate the drug's proposed clinical use. This phase also compares the drug with existing treatments, a placebo, or both. Studies may involve many practicing

physicians and multiple research sites. The purpose is to verify efficacy and detect effects—good and bad—that may not have been observed during phases 1 and 2.

When sufficient data have been collected to justify and request approval of the drug, a new drug application (NDA) is submitted to the FDA. The process from early development to approval of a drug may sometimes take up to 10 yr.

Phase 4 studies occur after the drug is approved and marketed. They are ongoing and involve large populations. Often, special subpopulations (eg, pregnant women, children, the elderly) are studied. Phase 4 also includes ongoing reporting of adverse effects. Some drugs approved by the FDA after phase 3 have been withdrawn from the market after newly recognized and serious adverse effects have occurred in phase 4.

Chapter 318. Pharmacokinetics

Introduction

Pharmacokinetics, sometimes described as what the body does to a drug, refers to the movement of drug into, through, and out of the body—the time course of its absorption, bioavailability, distribution, metabolism, and excretion. Pharmacodynamics (see p. 3181), described as what a drug does to the body, involves receptor binding, postreceptor effects, and chemical interactions. Drug pharmacokinetics determines the onset, duration, and intensity of a drug's effect. Formulas relating these processes summarize the pharmacokinetic behavior of most drugs (see Table 318-1).

Pharmacokinetics of a drug depends on patient-related factors as well as on the drug's chemical properties. Some patient-related factors (eg, genetic makeup, sex, age) can be used to predict pharmacologic response of populations. For example, the half-life of some drugs, especially those that require both metabolism and excretion, may be remarkably long in the elderly (see Fig. 318-1). In fact, physiologic changes that occur with aging affect many aspects of pharmacokinetics (see p. 3090). Other factors are related to individual physiology. The effects of some individual factors (eg, renal failure, obesity, hepatic failure, dehydration) can be reasonably predicted, but other factors are idiosyncratic and thus have unpredictable effects. Because of individual differences, drug administration must be based on each patient's needs—traditionally, by empirically adjusting dosage until the therapeutic objective is met. This approach is frequently inadequate because it can delay optimal response or result in adverse effects. Knowledge of pharmacokinetic principles helps prescribers adjust dosage more accurately and rapidly.

Absorption

Drug absorption is determined by the drug's physicochemical properties, formulation, and route of administration. Dosage forms (eg, tablets, capsules, solutions), consisting of the drug plus other ingredients, are formulated to be given by various routes (eg, oral, buccal, sublingual, rectal, parenteral, topical, inhalational).

[**Table 318-1.** Formulas Defining Basic Pharmacokinetic Parameters]

[**Fig. 318-1.** Comparison of pharmacokinetic outcomes for diazepam in a younger man (A) and an older man (B).]

Regardless of the route of administration, drugs must be in solution to be absorbed. Thus, solid forms (eg, tablets) must be able to disintegrate and deaggregate.

Unless given IV, a drug must cross several semipermeable cell membranes before it reaches the systemic circulation. Cell membranes are biologic barriers that selectively inhibit passage of drug molecules. The membranes are composed primarily of a bimolecular lipid matrix, which determines membrane permeability characteristics. Drugs may cross cell membranes by passive diffusion, facilitated passive diffusion, active transport, or pinocytosis. Sometimes various globular proteins embedded in the matrix function as receptors and help transport molecules across the membrane.

Passive diffusion: Drugs diffuse across a cell membrane from a region of high concentration (eg, GI fluids) to one of low concentration (eg, blood). Diffusion rate is directly proportional to the gradient but also depends on the molecule's lipid solubility, size, degree of ionization, and the area of absorptive surface. Because the cell membrane is lipoid, lipid-soluble drugs diffuse most rapidly. Small molecules tend to penetrate membranes more rapidly than larger ones.

Most drugs are weak organic acids or bases, existing in un-ionized and ionized forms in an aqueous environment. The un-ionized form is usually lipid soluble (lipophilic) and diffuses readily across cell membranes. The ionized form has low lipid solubility (but high water solubility—ie, hydrophilic) and high electrical resistance and thus cannot penetrate cell membranes easily. The proportion of the unionized form present (and thus the drug's ability to cross a membrane) is determined by the pH and the drug's

pK_a(acid dissociation constant). The pK_a is the pH at which concentrations of ionized and un-ionized forms are equal. When the pH is lower than the pK_a, the un-ionized form of a weak acid predominates, but the ionized form of a weak base predominates. Thus, in plasma (pH 7.4), the ratio of un-ionized to ionized forms for a weak acid (eg, with a pK_a of 4.4) is 1:1000; in gastric fluid (pH 1.4), the ratio is reversed (1000:1). Therefore, when a weak acid is given orally, most of the drug in the stomach is un-ionized, favoring diffusion through the gastric mucosa. For a weak base with a pK_a of 4.4, the outcome is reversed; most of the drug in the stomach is ionized. Theoretically, weakly acidic drugs (eg, aspirin) are more readily absorbed from an acid medium (stomach) than are weakly basic drugs (eg, quinidine). However, whether a drug is acidic or basic, most absorption occurs in the small intestine because the surface area is larger and membranes are more permeable (see Oral Administration on p. 3174).

Facilitated passive diffusion: Certain molecules with low lipid solubility (eg, glucose) penetrate membranes more rapidly than expected. One theory is facilitated passive diffusion: A carrier molecule in the membrane combines reversibly with the substrate molecule outside the cell membrane, and the carrier-substrate complex diffuses rapidly across the membrane, releasing the substrate at the interior surface. In such cases, the membrane transports only substrates with a relatively specific molecular configuration, and the availability of carriers limits the process. The process does not require energy expenditure, and transport against a concentration gradient cannot occur.

Active transport: Active transport is selective, requires energy expenditure, and may involve transport against a concentration gradient. Active transport seems to be limited to drugs structurally similar to endogenous substances (eg, ions, vitamins, sugars, amino acids). These drugs are usually absorbed from specific sites in the small intestine.

Pinocytosis: In pinocytosis, fluid or particles are engulfed by a cell. The cell membrane invaginates, encloses the fluid or particles, then fuses again, forming a vesicle that later detaches and moves to the cell interior. Energy expenditure is required. Pinocytosis probably plays a small role in drug transport, except for protein drugs.

Oral Administration

To be absorbed, a drug given orally must survive encounters with low pH and numerous GI secretions, including potentially degrading enzymes. Peptide drugs (eg, insulin) are particularly susceptible to degradation and are not given orally. Absorption of oral drugs involves transport across membranes of the epithelial cells in the GI tract. Absorption is affected by

- Differences in luminal pH along the GI tract
- Surface area per luminal volume
- Blood perfusion
- Presence of bile and mucus
- The nature of epithelial membranes

The oral mucosa has a thin epithelium and rich vascularity, which favor absorption; however, contact is usually too brief for substantial absorption. A drug placed between the gums and cheek (buccal administration) or under the tongue (sublingual administration) is retained longer, enhancing absorption.

The stomach has a relatively large epithelial surface, but its thick mucous layer and short transit time limit absorption. Because most absorption occurs in the small intestine, gastric emptying is often the rate-limiting step. Food, especially fatty food, slows gastric emptying (and rate of drug absorption), explaining why taking some drugs on an empty stomach speeds absorption. Drugs that affect gastric emptying (eg, parasympatholytic drugs) affect the absorption rate of other drugs. Food may enhance the extent of absorption for poorly soluble drugs (eg, griseofulvin), reduce it for drugs degraded in the stomach (eg, penicillin G), or have little or no effect.

The small intestine has the largest surface area for drug absorption in the GI tract, and its membranes are more permeable than those in the stomach. For these reasons, most drugs are absorbed primarily in the small intestine, and acids, despite their ability as un-ionized drugs to readily cross membranes, are absorbed faster in the intestine than in the stomach. The intraluminal pH is 4 to 5 in the duodenum but becomes progressively more alkaline, approaching 8 in the lower ileum. GI microflora may reduce absorption. Decreased blood flow (eg, in shock) may lower the concentration gradient across the intestinal mucosa and reduce absorption by passive diffusion.

Intestinal transit time can influence drug absorption, particularly for drugs that are absorbed by active transport (eg, B vitamins), that dissolve slowly (eg, griseofulvin), or that are polar (ie, with low lipid solubility; eg, many antibiotics).

Most drugs are given orally as tablets or capsules primarily for convenience, economy, stability, and patient acceptance. Because solid drug forms must dissolve before absorption can occur, dissolution rate determines availability of the drug for absorption. Dissolution, if slower than absorption, becomes the rate-limiting step. Manipulating the formulation (ie, the drug's form as salt, crystal, or hydrate) can change the dissolution rate and thus control overall absorption.

Parenteral Administration

Drugs given IV enter the systemic circulation directly. However, drugs injected IM or sc must cross one or more biologic membranes to reach the systemic circulation. If protein drugs with a molecular mass > 20,000 g/mole are injected IM or sc, movement across capillary membranes is so slow that most absorption occurs via the lymphatic system. In such cases, drug delivery to systemic circulation is slow and often incomplete because of 1st-pass metabolism (metabolism of a drug before it reaches systemic circulation) by proteolytic enzymes in the lymphatics.

Perfusion (blood flow/gram of tissue) greatly affects capillary absorption of small molecules injected IM or sc. Thus, injection site can affect absorption rate. Absorption after IM or sc injection may be delayed or erratic for salts of poorly soluble bases and acids (eg, parenteral form of phenytoin) and in patients with poor peripheral perfusion (eg, during hypotension or shock).

Controlled-Release Forms

Controlled-release forms are designed to reduce dosing frequency for drugs with a short elimination half-life and duration of effect. These forms also limit fluctuation in plasma drug concentration, providing a more uniform therapeutic effect. Absorption rate is slowed by coating drug particles with wax or other water-insoluble material, by embedding the drug in a matrix that releases it slowly during transit through the GI tract, or by complexing the drug with ion-exchange resins. Most absorption of these forms occurs in the large intestine. Crushing or otherwise disturbing a controlled-release tablet or capsule can often be dangerous.

Transdermal controlled-release forms are designed to release the drug for extended periods, sometimes for several days. Drugs for transdermal delivery must have suitable skin penetration characteristics and high potency because the penetration rate and area of application are limited.

Many non-IV parenteral forms are designed to sustain plasma drug concentrations. Absorption of antimicrobials can be extended by using their relatively insoluble salt form (eg, penicillin G benzathine) injected IM. For other drugs, suspensions or solutions in non-aqueous vehicles (eg, crystalline suspensions for insulin) are designed to delay absorption.

Bioavailability

Bioavailability refers to the extent to and rate at which the active moiety (drug or metabolite) enters systemic circulation, thereby accessing the site of action.

Bioavailability of a drug is largely determined by the properties of the dosage form (which depend partly

on its design and manufacture), rather than by the drug's physicochemical properties, which determine absorption potential. Differences in bioavailability among formulations of a given drug can have clinical significance; thus, knowing whether drug formulations are equivalent is essential.

Chemical equivalence indicates that drug products contain the same compound in the same amount and meet current official standards; however, inactive ingredients in drug products may differ.

Bioequivalence indicates that the drug products, when given to the same patient in the same dosage regimen, result in equivalent concentrations of drug in plasma and tissues.

Therapeutic equivalence indicates that drug products, when given to the same patient in the same dosage regimen, have the same therapeutic and adverse effects.

Bioequivalent products are expected to be therapeutically equivalent. Therapeutic non-equivalence (eg, more adverse effects, less efficacy) is usually discovered during long-term treatment when patients who are stabilized on one formulation are given a nonequivalent substitute.

Sometimes therapeutic equivalence is possible despite differences in bioavailability. For example, the therapeutic index (ratio of the minimum toxic concentration to the median effective concentration) of penicillin is so wide that efficacy and safety are usually not affected by the moderate differences in plasma concentration due to bioavailability differences in penicillin products. In contrast, for drugs with a relatively narrow therapeutic index, bioavailability differences may cause substantial therapeutic nonequivalence.

Causes of low bioavailability: Orally administered drugs must pass through the intestinal wall and then through the portal circulation to the liver; both are common sites of 1st-pass metabolism (metabolism of a drug before it reaches systemic circulation). Thus, many drugs may be metabolized before adequate plasma concentrations are reached. Low bio-availability is most common with oral dosage forms of poorly water-soluble, slowly absorbed drugs.

Insufficient time for absorption in the GI tract is a common cause of low bioavailability. If the drug does not dissolve readily or cannot penetrate the epithelial membrane (eg, if it is highly ionized and polar), time at the absorption site may be insufficient. In such cases, bioavailability tends to be highly variable as well as low.

Age, sex, physical activity, genetic pheno-type, stress, disorders (eg, achlorhydria, mal-absorption syndromes), or previous GI surgery (eg, bariatric surgery) can also affect drug bioavailability.

Chemical reactions that reduce absorption can reduce bioavailability. They include formation of a complex (eg, between tetracycline and polyvalent metal ions), hydrolysis by gastric acid or digestive enzymes (eg, penicillin and chloramphenicol palmitate hydrolysis), conjugation in the intestinal wall (eg, sulfoconjugation of isoproterenol), adsorption to other drugs (eg, digoxin to cholestyramine), and metabolism by luminal microflora.

Assessing bioavailability: Bioavailability is usually assessed by determining the

• Maximum (peak) plasma drug concentration

• Peak time (when maximum plasma drug concentration occurs)

• Area under the plasma concentration-time curve (AUC—see Fig. 318-2)

[**Fig. 318-2.** Representative plasma concentration-time relationship after a single oral dose of a hypothetical drug.]

Plasma drug concentration increases with extent of absorption; the peak is reached when drug elimination rate equals absorption rate. Bioavailability determinations based on the peak plasma

concentration can be misleading because drug elimination begins as soon as the drug enters the bloodstream. Peak time is the most widely used general index of absorption rate; the slower the absorption, the later the peak time. The most reliable measure of a drug's bioavailability is AUC. AUC is directly proportional to the total amount of unchanged drug that reaches systemic circulation. Drug products may be considered bio-equivalent in extent and rate of absorption if their plasma concentration curves are essentially superimposable.

For drugs excreted primarily unchanged in urine, bioavailability can be estimated by measuring the total amount of drug excreted after a single dose. Ideally, urine is collected over a period of 7 to 10 elimination half-lives for complete urinary recovery of the absorbed drug. After multiple dosing, bioavailability may be estimated by measuring unchanged drug recovered from urine over a 24-h period under steady-state conditions.

Distribution

After a drug enters the systemic circulation, it is distributed to the body's tissues. Distribution is generally uneven because of differences in blood perfusion, tissue binding (eg, because of lipid content), regional pH, and permeability of cell membranes.

The entry rate of a drug into a tissue depends on the rate of blood flow to the tissue, tissue mass, and partition characteristics between blood and tissue. Distribution equilibrium (when entry and exit rates are the same) between blood and tissue is reached more rapidly in richly vascularized areas, unless diffusion across cell membranes is the rate-limiting step. After equilibrium, drug concentrations in tissues and in extracellular fluids are reflected by the plasma concentration. Metabolism and excretion occur simultaneously with distribution, making the process dynamic and complex.

For interstitial fluids of most tissues, drug distribution rate is determined primarily by perfusion. For poorly perfused tissues (eg, muscle, fat), distribution is very slow, especially if the tissue has a high affinity for the drug.

Volume of distribution: The apparent volume of distribution is the theoretical volume of fluid into which the total drug administered would have to be diluted to produce the concentration in plasma. For example, if 1000 mg of a drug is given and the subsequent plasma concentration is 10 mg/L, that 1000 mg seems to be distributed in 100 L (dose/volume = concentration; 1000 mg/x L = 10 mg/L; therefore, x = 1000 mg/10 mg/L = 100 L). Volume of distribution has nothing to do with the actual volume of the body or its fluid compartments but rather involves the distribution of the drug within the body. For drugs that are highly tissue-bound, comparatively little of a dose remains in the circulation to be measured; thus, plasma concentration is low and volume of distribution is high. Drugs that remain in the circulation tend to have a low volume of distribution. Volume of distribution provides a reference for the plasma concentration expected for a given dose but provides little information about the specific pattern of distribution. Each drug is uniquely distributed in the body. Some drugs distribute mostly into fat, others remain in ECF, and others are bound extensively to specific tissues.

Many acidic drugs (eg, warfarin, aspirin) are highly protein-bound and thus have a small apparent volume of distribution. Many basic drugs (eg, amphetamine, meperidine) are extensively taken up by tissues and thus have an apparent volume of distribution larger than the volume of the entire body.

Binding: The extent of drug distribution into tissues depends on the extent of plasma protein and tissue binding. In the bloodstream, drugs are transported partly in solution as free (unbound) drug and partly as reversibly bound to blood components (eg, plasma proteins, blood cells). Of the many plasma proteins that can interact with drugs, the most important are albumin, α1-acid glycoprotein, and lipoproteins. Acidic drugs are usually bound more extensively to albumin; basic drugs are usually bound more extensively to α1-acid glyco-protein, lipoproteins, or both.

Only unbound drug is available for passive diffusion to extravascular or tissue sites where the pharmacologic effects of the drug occur. Therefore, the unbound drug concentration in systemic circulation typically determines drug concentration at the active site and thus efficacy.

At high drug concentrations, the amount of bound drug approaches an upper limit determined by the number of available binding sites. Saturation of binding sites is the basis of displacement interactions among drugs (see Drug-Receptor Interactions on p. 3181).

Drugs bind to many substances other than proteins. Binding usually occurs when a drug associates with a macromolecule in an aqueous environment but may occur when a drug is partitioned into body fat. Because fat is poorly perfused, equilibration time is long, especially if the drug is highly lipophilic.

Accumulation of drugs in tissues or body compartments can prolong drug action because the tissues release the accumulated drug as plasma drug concentration decreases. For example, thiopental is highly lipid soluble, rapidly enters the brain after a single IV injection, and has a marked and rapid anesthetic effect; the effect ends within a few minutes as the drug is redistributed to more slowly perfused fatty tissues. Thiopental is then slowly released from fat storage, maintaining subanesthetic plasma levels; these levels may become significant if doses of thiopental are repeated, causing large amounts to be stored in fat. Thus, storage in fat initially shortens the drug's effect but then prolongs it.

Some drugs accumulate within cells because they bind with proteins, phospholipids, or nucleic acids. For example, chloroquine concentrations in WBCs and liver cells can be thousands of times higher than those in plasma. Drug in cells is in equilibrium with drug in plasma and moves into plasma as the drug is eliminated from the body.

Blood-brain barrier: Drugs reach the CNS via brain capillaries and CSF. Although the brain receives about one sixth of cardiac output, distribution of drugs to brain tissue is restricted because the brain's permeability characteristics differ from those of other tissues. Although some lipid-soluble drugs (eg, thiopental) enter the brain readily, polar compounds do not. The reason is the blood-brain barrier, which consists of the endothelium of brain capillaries and the astrocytic sheath. The endothelial cells of brain capillaries, which appear to be more tightly joined to one another than those of most capillaries, slow the diffusion of water-soluble drugs. The astrocytic sheath consists of a layer of glial connective tissue cells (astrocytes) close to the basement membrane of the capillary endothelium. With aging, the blood-brain barrier may become less effective, allowing increased passage of compounds into the brain.

Drugs may enter ventricular CSF directly via the choroid plexus, then passively diffuse into brain tissue from CSF. Also in the choroid plexus, organic acids (eg, penicillin) are actively transported from CSF to blood.

The drug penetration rate into CSF, as for other tissue cells, is determined mainly by the extent of protein binding, degree of ionization, and lipid-water partition coefficient of the drug. The penetration rate into the brain is slow for highly protein-bound drugs and nearly nonexistent for the ionized form of weak acids and bases. Because the CNS is so well perfused, the drug distribution rate is determined primarily by permeability.

Metabolism

The liver is the principal site of drug metabolism. Although metabolism typically inactivates drugs, some drug metabolites are pharmacologically active—sometimes even more so than the parent compound. An inactive or weakly active substance that has an active metabolite is called a prodrug, especially if designed to deliver the active moiety more effectively.

Drugs can be metabolized by oxidation, reduction, hydrolysis, hydration, conjugation, condensation, or isomerization; whatever the process, the goal is to make the drug easier to excrete. The enzymes involved in metabolism are present in many tissues but generally are more concentrated in the liver. Drug metabolism rates vary among patients. Some patients metabolize a drug so rapidly that therapeutically effective blood and tissue concentrations are not reached; in others, metabolism may be so slow that usual doses have toxic effects. Individual drug metabolism rates are influenced by genetic factors, coexisting disorders (particularly chronic liver disorders and advanced heart failure), and drug interactions (especially those involving induction or inhibition of metabolism).

For many drugs, metabolism occurs in 2 phases. Phase I reactions involve formation of a new or modified

functional group or cleavage (oxidation, reduction, hydrolysis); these reactions are nonsynthetic. Phase II reactions involve conjugation with an endogenous substance (eg, glucuronic acid, sulfate, glycine); these reactions are synthetic. Metabolites formed in synthetic reactions are more polar and more readily excreted by the kidneys (in urine) and the liver (in bile) than those formed in nonsynthetic reactions. Some drugs undergo only phase I or phase II reactions; thus, phase numbers reflect functional rather than sequential classification.

Rate: For almost all drugs, the metabolism rate in any given pathway has an upper limit (capacity limitation). However, at therapeutic concentrations of most drugs, usually only a small fraction of the metabolizing enzyme's sites are occupied, and the metabolism rate increases with drug concentration. In such cases, called first-order elimination (or kinetics), the metabolism rate of the drug is a constant fraction of the drug remaining in the body (rather than a constant amount of drug per hour); ie, the drug has a specific half-life. For example, if 500 mg is present in the body at time zero, after metabolism, 250 mg may be present at 1 h and 125 mg at 2 h (illustrating a half-life of 1 h). However, when most of the enzyme sites are occupied, metabolism occurs at its maximal rate and does not change in proportion to drug concentration; ie, a fixed amount of drug is metabolized per unit time (zero-order kinetics). In this case, if 500 mg is present in the body at time zero, after metabolism, 450 mg may be present at 1 h and 400 mg at 2 h (illustrating a maximal clearance of 50 mg/h and no specific half-life). As drug concentration increases, metabolism shifts from first-order to zero-order kinetics.

Cytochrome P-450: The most important enzyme system of phase I metabolism is cytochrome P-450 (CYP450), a microsomal superfamily of isoenzymes that catalyze the oxidation of many drugs. The electrons are supplied by NADPH-CYP450 reductase, a flavo-protein that transfers electrons from NADPH (the reduced form of nicotinamide adenosine dinucleotide phosphate) to CYP450. CYP450 enzymes can be induced or inhibited by any drugs and substances, helping explain many drug interactions in which one drug enhances the toxicity or reduces the therapeutic effect of another drug. For examples of drugs that interact with specific enzymes, see
Table 318-2 (see also Drug Interactions on p. 3167).

With aging, the liver's capacity for metabolism through the CYP450 enzyme system is reduced by ≥ 30% because liver volume and hepatic blood flow are decreased. Thus, drugs that are metabolized through this system reach higher levels and have prolonged half-lives in the elderly (see Fig. 318-1). Because neonates have partially developed liver microsomal enzyme systems, they also have difficulty metabolizing many drugs.

Conjugation: Glucuronidation, the most common phase II reaction, is the only one that occurs in the liver microsomal enzyme system. Glucuronides are secreted in bile and eliminated in urine. Thus, conjugation makes most drugs more soluble and easily excreted by the kidneys. Amino acid conjugation with glutamine or glycine produces conjugates that are readily excreted in urine but not extensively secreted in bile. Aging does not affect glucuronidation. However, in neonates, conversion to glucuronide is slower, sometimes with serious effects.

Conjugation may also occur through acetylation or sulfoconjugation. Sulfate esters are polar and readily excreted in urine. Aging does not affect these processes.

Excretion

The kidneys, which excrete water-soluble substances, are the principal organs of excretion. The biliary system contributes to excretion to the degree that drug is not reabsorbed from the GI tract. Generally, the contribution of intestine, saliva, sweat, breast milk, and lungs to excretion is small, except for exhalation of volatile anesthetics. Excretion via breast milk, although not important to the mother, may affect the breastfeeding infant (see
Table 268-4 on p. 2706).

Hepatic metabolism often makes drugs more polar and thus more water soluble. The resulting metabolites are then more readily excreted.

Renal excretion: Renal filtration accounts for most drug excretion. About one fifth of the plasma

reaching the glomerulus is filtered through pores in the glomerular endothelium; nearly all water and most electrolytes are passively and actively reabsorbed from the renal tubules back into the circulation. However, polar compounds, which include most drug metabolites, cannot diffuse back into the circulation and are excreted unless a specific transport mechanism exists for their reabsorption (eg, as for glucose, ascorbic acid, and B vitamins). With aging, renal drug excretion decreases (see Ch. 308, especially Table 308-1 on p. 3091); at age 80, clearance is typically reduced to half of what it was at age 30.

The principles of transmembrane passage govern renal handling of drugs. Drugs bound to plasma proteins remain in the circulation;

[**Table 318-2.** Common Substances that Interact with Cytochrome P-450 Enzymes]

only unbound drug is contained in the glomerular filtrate. Un-ionized forms of drugs and their metabolites tend to be reabsorbed readily from tubular fluids.

Urine pH, which varies from 4.5 to 8.0, may markedly affect drug reabsorption and excretion by determining whether a weak acid or base is in an un-ionized or ionized form (see p. 3173). Acidification of urine increases reabsorption and decreases excretion of weak acids and decreases reabsorption of weak bases. Alkalinization of urine has the opposite effect. In some cases of overdose, these principles are used to enhance the excretion of weak bases or acids; eg, urine is alkalinized to enhance excretion of acetylsalicylic acid. The extent to which changes in urinary pH alter the rate of drug elimination depends on the contribution of the renal route to total elimination, the polarity of the unionized form, and the molecule's degree of ionization.

Active tubular secretion in the proximal tubule is important in the elimination of many drugs. This energy-dependent process may be blocked by metabolic inhibitors. When drug concentration is high, secretory transport can reach an upper limit (transport maximum); each substance has a characteristic transport maximum.

Anions and cations are handled by separate transport mechanisms. Normally, the anion secretory system eliminates metabolites conjugated with glycine, sulfate, or glucuronic acid. Anions compete with each other for secretion. This competition can be used therapeutically; eg, probenecid blocks the normally rapid tubular secretion of penicillin, resulting in higher plasma penicillin concentrations for a longer time. In the cation transport system, cations or organic bases (eg, pramipexole, dofetilide) are secreted by the renal tubules; this process can be inhibited by cimetidine, trimethoprim, prochlorperazine, megestrol, or ketoconazole.

Biliary excretion: Some drugs and their metabolites are extensively excreted in bile. Because they are transported across the biliary epithelium against a concentration gradient, active secretory transport is required. When plasma drug concentrations are high, secretory transport may approach an upper limit (transport maximum). Substances with similar physicochemical properties may compete for excretion.

Drugs with a molecular weight of > 300 g/mole and with both polar and lipophilic groups are more likely to be excreted in bile; smaller molecules are generally excreted only in negligible amounts. Conjugation, particularly with glucuronic acid, facilitates biliary excretion.

In the enterohepatic cycle, a drug secreted in bile is reabsorbed into the circulation from the intestine. Biliary excretion eliminates substances from the body only to the extent that enterohepatic cycling is incomplete—when some of the secreted drug is not reabsorbed from the intestine.

Chapter 319. Pharmacodynamics

Introduction

Pharmacodynamics, sometimes described as what a drug does to the body, involves receptor binding (including receptor sensitivity), postreceptor effects, and chemical interactions. Pharmacodynamics, with pharmacokinetics (what the body does to a drug—see p. 3172), helps explain the relationship between the dose and response, ie, the drug's effects. The pharmacologic response depends on the drug's binding to its target. The concentration of the drug at the receptor site influences the drug's effect.

A drug's pharmacodynamics can be affected by physiologic changes due to disorders, aging, or other drugs. Disorders that affect pharmacodynamic responses include genetic mutations, thyrotoxicosis, malnutrition, myasthenia gravis, Parkinson's disease, and some forms of insulin-resistant diabetes mellitus. These disorders can change receptor binding, alter the level of binding proteins, or decrease receptor sensitivity. Aging tends to affect pharmacodynamic responses through alterations in receptor binding or in postreceptor response (see
Table 308-2 on p. 3093). Pharmacodynamic drug-drug interactions result in competition for receptor binding sites or alter postreceptor response.

Drug-Receptor Interactions

Receptors are macromolecules involved in chemical signaling between and within cells; they may be located on the cell surface membrane or within the cytoplasm (see
Table 319-1). Activated receptors directly or indirectly regulate cellular biochemical processes (eg, ion conductance, protein phosphorylation, DNA transcription, enzymatic activity). Molecules (eg, drugs, hormones, neurotransmitters) that bind to a receptor are called ligands. A ligand may activate or inactivate a receptor; activation may increase or decrease a particular cell function. Each ligand may interact with multiple receptor subtypes. Few if any drugs are absolutely specific for one receptor or subtype, but most have relative selectivity. Selectivity is the degree to which a drug acts on a given site relative to other sites; selectivity relates largely to physicochemical binding of the drug to cellular receptors.

A drug's ability to affect a given receptor is related to the drug's affinity (probability of the drug occupying a receptor at any given instant) and intrinsic efficacy (intrinsic activity—degree to which a ligand activates receptors and leads to cellular response). A drug's affinity and activity are determined by its chemical structure.

Physiologic functions (eg, contraction, secretion) are usually regulated by multiple receptor-mediated mechanisms, and several steps (eg, receptor-coupling, multiple intracellular 2nd messenger substances) may be interposed between the initial molecular drug-receptor interaction and ultimate tissue or organ response. Thus, several dissimilar drug molecules can often be used to produce a desired response.

Ability to bind to a receptor is influenced by external factors as well as by intracellular regulatory mechanisms. Baseline receptor

[**Table 319-1.** Some Types of Physiologic and Drug-Receptor Proteins]

density and the efficiency of stimulus-response mechanisms vary from tissue to tissue. Drugs, aging, genetic mutations, and disorders can increase (up-regulate) or decrease (down-regulate) the number and binding affinity of receptors. For example, clonidine down-regulates α_2-receptors; thus, rapid withdrawal of clonidine can cause hypertensive crisis. Chronic therapy with β-blockers up-regulates β-receptor density; thus, severe hypertension or tachycardia can result from abrupt withdrawal. Receptor up-regulation and down-regulation affect adaptation to drugs (eg, desensitization, tachyphylaxis, tolerance, acquired resistance, postwithdrawal supersensitivity).

Ligands bind to precise molecular regions, called recognition sites, on receptor macromolecules. The binding site for a drug may be the same as or different from that of an endogenous agonist (hormone or neurotransmitter). Agonists that bind to an adjacent site or a different site on a receptor are sometimes

called allosteric agonists. Nonspecific drug binding also occurs—ie, at molecular sites not designated as receptors (eg, plasma proteins). Drug binding to such nonspecific sites prohibits the drug from binding to the receptor and thus inactivates the drug. Unbound drug is available to bind to receptors and thus have an effect.

Agonists and antagonists: Agonist drugs activate receptors to produce the desired response. Conventional agonists increase the proportion of activated receptors. Inverse agonists stabilize the receptor in its inactive conformation and act similarly to competitive antagonists (see p. 3183). Many hormones, neurotransmitters (eg, acetylcholine, histamine, norepinephrine), and drugs (eg, morphine, phenylephrine, isoproterenol) act as agonists.

Antagonists prevent receptor activation. Preventing activation has many effects. Antagonist drugs increase cellular function if they block the action of a substance that normally decreases cellular function. Antagonist drugs decrease cellular function if they block the action of a substance that normally increases cellular function.

Receptor antagonists can be classified as reversible or irreversible. Reversible antagonists readily dissociate from their receptor; irreversible antagonists form a stable, permanent or nearly permanent chemical bond with their receptor (eg, by alkylation). Pseudo-irreversible antagonists slowly dissociate from their receptor.

In competitive antagonism, binding of the antagonist to the receptor prevents binding of the agonist to the receptor. In noncompetitive antagonism, agonist and antagonist can be bound simultaneously, but antagonist binding reduces or prevents the action of the agonist. In reversible competitive antagonism, agonist and antagonist form short-lasting bonds with the receptor, and a steady state among agonist, antagonist, and receptor is reached. Such antagonism can be overcome by increasing the concentration of the agonist. For example, naloxone (an opioid receptor antagonist that is structurally similar to morphine), when given shortly before or after morphine, blocks morphine's effects. However, competitive antagonism by naloxone can be overcome by giving more morphine.

Structural analogs of agonist molecules frequently have agonist and antagonist properties; such drugs are called partial (low-efficacy) agonists, or agonist-antagonists. For example, pentazocine activates opioid receptors but blocks their activation by other opioids. Thus, pentazocine provides opioid effects but blunts the effects of another opioid if the opioid is given while pentazocine is still bound. A drug that acts as a partial agonist in one tissue may act as a full agonist in another.

Chemical Interactions

Some drugs produce effects without altering cellular function and without binding to a receptor. For example, most antacids decrease gastric acidity through simple chemical reactions; antacids are bases that chemically interact with acids to produce neutral salts. The primary action of cholestyramine, a bile acid sequestrant, is to bind bile acids in the GI tract.

Dose-Response Relationships

Regardless of how a drug effect occurs—through binding or chemical interaction—the concentration of the drug at the site of action controls the effect. However, response to concentration may be complex and is often nonlinear. The relationship between the drug dose, regardless of route used, and the drug concentration at the cellular level is even more complex (see Ch. 318).

Dose-response data are typically graphed with the dose or dose function (eg, $\log_{10}$ dose) on the x-axis and the measured effect (response) on the y-axis. Because a drug effect is a function of dose and time, such a graph depicts the dose-response relationship independent of time. Measured effects are frequently recorded as maxima at time of peak effect or under steady-state conditions (eg, during continuous IV infusion). Drug effects may be quantified at the level of molecule, cell, tissue, organ, organ system, or organism.

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Fig. 319-1. Hypothetical dose-response curve.]

A hypothetical dose-response curve has features that vary (see Fig. 319-1): potency (location of curve along the dose axis), maximal efficacy or ceiling effect (greatest attainable response), and slope (change in response per unit dose). Biologic variation (variation

[
Fig. 319-2. Comparison of dose-response curves.]

in magnitude of response among test subjects in the same population given the same dose of drug) also occurs. Graphing dose-response curves of drugs studied under identical conditions can help compare the pharmacologic profiles of the drugs (see Fig. 319-2). This information helps determine the dose necessary to achieve the desired effect.

Dose-response, which involves the principles of pharmacokinetics and pharmacodynamics, determines the required dose and frequency as well as the therapeutic index for a drug in a population. The therapeutic index (ratio of the minimum toxic concentration to the median effective concentration) helps determine the efficacy and safety of a drug. Increasing the dose of a drug with a small therapeutic index increases the probability of toxicity or ineffectiveness of the drug. However, these features differ by population and are affected by patient-related factors (eg, pregnancy [see p. 2625], age [see p. 3091]).

Chapter 320. Adverse Drug Reactions

Introduction

Adverse drug reaction (ADR, or adverse drug effect) is a broad term referring to unwanted, uncomfortable, or dangerous effects that a drug may have. ADRs can be considered a form of toxicity; however, toxicity is most commonly applied to effects of overingestion (accidental or intentional—see p. 3323) or to elevated blood levels or enhanced drug effects that occur during appropriate use (eg, when drug metabolism is temporarily inhibited by a disorder or another drug). *Side effect* is an imprecise term often used to refer to a drug's unintended effects that occur within the therapeutic range. Because all drugs have the potential for ADRs, risk-benefit analysis (analyzing the likelihood of benefit vs risk of ADRs) is necessary whenever a drug is prescribed.

In the US, 3 to 7% of all hospitalizations are due to ADRs. ADRs occur during 10 to 20% of hospitalizations; about 10 to 20% of these ADRs are severe. Incidence of death due to ADRs is unknown; suggested rates of 0.5 to 0.9% may be falsely high because many of the patients included had serious and complex disorders.

Incidence and severity of ADRs vary by patient characteristics (eg, age, sex, ethnicity, coexisting disorders, genetic or geographic factors) and by drug factors (eg, type of drug, administration route, treatment duration, dosage, bioavailability). Incidence is probably higher and ADRs are more severe among the elderly (see p. 3092), although age per se may not be the primary cause. The contribution of prescribing and adherence errors to the incidence of ADRs is unclear (see p. 3166).

Etiology

Most ADRs are dose-related; others are allergic or idiosyncratic. Dose-related ADRs are usually predictable; ADRs unrelated to dose are usually unpredictable.

Dose-related ADRs are particularly a concern when drugs have a narrow therapeutic index (eg, hemorrhage with oral anticoagulants). ADRs may result from decreased drug clearance in patients with impaired renal or hepatic function or from drug-drug interactions.

Allergic ADRs are not dose-related and require prior exposure. Allergies develop when a drug acts as an antigen or allergen. After a patient is sensitized, subsequent exposure to the drug produces one of several different types of allergic reaction (see p. 1122). Clinical history and appropriate skin tests can sometimes help predict allergic ADRs.

Idiosyncrasy is an imprecise term used to classify unexpected ADRs that are not dose-related or allergic. They occur in a small percentage of patients given a drug. Idiosyncrasy has been defined as a genetically determined abnormal response to a drug, but not all idiosyncratic reactions have a pharmacogenetic cause. The term may become obsolete as specific mechanisms of ADRs become known.

Symptoms and Signs

ADRs are usually classified as mild, moderate, severe, or lethal (see Table 320-1). Symptoms and signs may manifest soon after the first dose or only after chronic use. They may obviously result from drug use or be too subtle to identify as drug-related. In the elderly, subtle ADRs can cause functional deterioration, changes in mental status, failure to thrive, loss of appetite, confusion, and depression.

[**Table 320-1.** Classification of Adverse Drug Reactions]

Allergic ADRs typically occur soon after a drug is taken but generally do not occur after the first dose; typically, they occur when the drug is given after an initial exposure. Symptoms include itching, rash, fixed-drug eruption, upper or lower airway edema with difficulty breathing, and hypotension.

Idiosyncratic ADRs can produce almost any symptom or sign and usually cannot be predicted.

Diagnosis

• Consideration of rechallenge

• Reporting of suspected ADRs to MedWatch

Symptoms that occur soon after a drug is taken are often easily connected with use of a drug. However, diagnosing symptoms due to chronic drug use requires a significant level of suspicion and is often complicated. Stopping a drug is sometimes necessary but is difficult if the drug is essential and does not have an acceptable substitute. When proof of the relationship between drug and symptoms is important, rechallenge should be considered, except in the case of serious allergic reactions.

Physicians should report most suspected ADRs to MedWatch (the FDA's ADR monitoring program), which is an early alert system. Only through such reporting can unexpected ADRs be identified and investigated. Med-Watch also monitors changes in the nature and frequency of ADRs. Forms for and information about reporting ADRs are available in the Physicians' Desk Reference, AMA Drug Evaluations, and FDA Drug Bulletin (mailed to all physicians at least yearly) and at www.fda.gov/medwatch; forms may also be obtained by calling 800-FDA-1088. Nurses, pharmacists, and other health care practitioners should also report ADRs.

Treatment

• Modification of dosage

• Discontinuation of drug if necessary

• Switching to a different drug

For dose-related ADRs, modifying the dose or eliminating or reducing precipitating factors may suffice. Increasing the rate of drug elimination is rarely necessary. For allergic and idiosyncratic ADRs, the drug usually should be withdrawn and not tried again. Switching to a different drug class is often required for allergic ADRs and sometimes required for dose-related ADRs.

Prevention

Prevention of ADRs requires familiarity with the drug and potential reactions to it. Computer-based analysis should be used to check for potential drug interactions; analysis should be repeated whenever drugs are changed or added. Drugs and initial dosage must be carefully selected for the elderly (see Ch. 308). If patients develop nonspecific symptoms, ADRs should always be considered before beginning symptomatic treatment.