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information about pharmaceutical and medicinal agents; also, a guide to the professional responsibilities of the pharmacist as the drug information specialist of the health team . . . A textbook and reference work for pharmacists, physicians, and other practitioners of the pharmaceutical and medical sciences.

AUTHORS

The 133 chapters of this edition of *Remington* were written by the editors, by members of the Editorial Board, and by the authors listed on pages xi to xv.

Director

Philip P Gerbino 1995-2005

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CHAPTER 57

Drug Absorption, Action, and Disposition

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Although drugs differ widely in their pharmacodynamic effects and clinical applications; in penetration, absorption, and usual route of administration; in distribution among the body tissues; and in disposition and mode of termination of action, there are certain general principles that help explain these differences. These principles have both pharmaceutic and therapeutic implications. They facilitate an understanding of both the features that are common to a class of drugs and the differences among the members of that class.

For a drug to act it must be absorbed, transported to the appropriate tissue or organ, penetrate to the responding cell surface or subcellular structure, and elicit a response or alter ongoing processes. The drug may be distributed simultaneously or sequentially to a number of tissues, bound or stored, metabolized to inactive or active products, or excreted. The history of a drug in the body is summarized in Figure 57-1. Each of the processes or events depicted relates importantly to therapeutic and toxic effects of a drug and to the mode of administration, and drug design must take each into account. Since the effect elicited by a drug is its *raison d'être, drug action,* and *effect* are discussed first in the text that follows, even though they are preceded by other events.

DRUG ACTION AND EFFECT

The word *drug* imposes an action-effect context within which the properties of a substance are described. The description of necessity must include the pertinent properties of the recipient of the drug. Thus, when a drug is defined as an analgesic, it is implied that the recipient reacts to a noxious stimulus in a certain way, called pain. (Studies indicate that pain is not simply the *perception* of a certain kind of stimulus but rather, a *reaction* to the perception of a variety of kinds of stimuli or stimulus patterns.) Both because the pertinent properties are locked into the complex and somewhat imprecise biological context and because the types of possible response are many, descriptions of the properties of drugs tend to emphasize the qualitative features of the effects they elicit. Thus, a drug may be described as having analgesic, vasodepressor, convulsant, antibacterial, etc, properties. The specific effect (or use) categories into which the many drugs may be placed are the subject of Chapters 64 through 89 and are not elaborated upon in this chapter. However, the description of a drug does not end with the enumeration of the responses it may elicit. There are certain intrinsic properties of the drug-recipient system that can be described in quantitative terms and that are essential to the full description of the drug and to the validation of the drug for specific uses. Under *Definitions and Concepts* below, certain general terms are defined in qualitative language; under *Dose-Effect Relationships,* the foundation is laid for an appreciation of some of the quantitative aspects of pharmacodynamics.

DEFINITIONS AND CONCEPTS

In the field of pharmacology, the vocabulary that is unique to the discipline is relatively small, and the general vocabulary is that of the biological sciences and chemistry. Nevertheless, there are a few definitions that are important to the proper understanding of pharmacology. It is necessary to differentiate among action, effect, selectivity, dose, potency, and efficacy.

ACTION VS EFFECT—The *effect* of a drug is an *alteration of function* of the structure or process upon which the drug acts. It is common to use the term *action* as a synonym for effect. However, action precedes effect. *Action* is the *alteration of condition* that brings about the effect.

The final effect of a drug may be far removed from its site of action. For example, the diuresis subsequent to the ingestion of ethanol does not result from an action on the kidney but instead from a depression of activity in the region of the hypothalamus, which regulates the release of antidiuretic hormone from the posterior pituitary gland. The alteration of hypothalamic function is, of course, also an effect of the drug, as is each subsequent change in the chain of events leading to diuresis. The action of ethanol was exerted only at the initial step, each subsequent effect being then the action to a following step.

MULTIPLE EFFECTS—No known drug is capable of exerting a single effect, although a number are known that appear to have a single mechanism of action. Multiple effects may derive from a single mechanism of action. For example, the inhibition of acetylcholinesterase by physostigmine will elicit an effect at every site where acetylcholine is produced, is potentially active, and is hydrolyzed by cholinesterase. Thus, physostigmine elicits a constellation of effects.

A drug also can cause multiple effects at several different sites by a single action at only one site, providing that the function initially altered at the site of action ramifies to control other functions at distant sites. Thus, a drug that suppresses steroid synthesis in the liver may not only lower serum cholesterol, impair nerve myelination and function, and alter the condition of the skin (as a consequence of cholesterol deficiency) but also may affect digestive functions (because of a deficiency in bile acids) and alter adrenocortical and sexual hormonal balance.

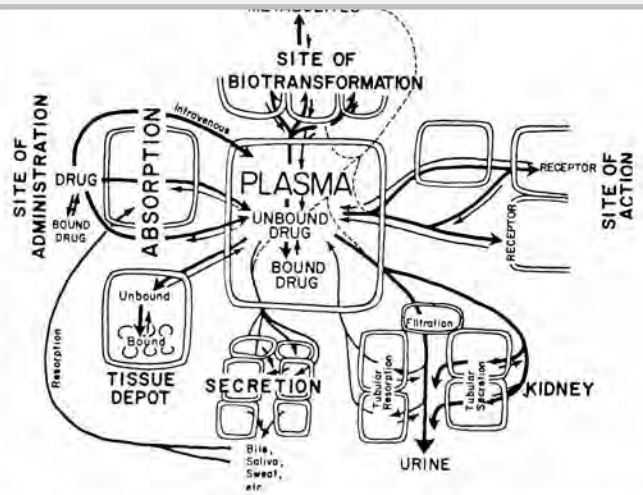

Figure 57-1. The absorption, distribution, action, and elimination of a drug (arrows represent drug movement). Intravenous administration is the only process by which a drug may enter a compartment without passing through a biological membrane. Note that drugs excreted in bile and saliva may be resorbed.

Although a single action can give rise to multiple effects, most drugs exert multiple actions. The various actions may be related, as for example, the sympathomimetic effects of phenylephrine that accrue to its structural similarity to norepinephrine and its ability to exert sympathetic responses, or the actions may be unrelated, as with the actions of morphine to interfere with the release of acetylcholine from certain autonomic nerves, block some actions of 5-hydroxytryptamine (serotonin), and release histamine. Many drugs bring about immunological (allergic or hypersensitivity) responses that bear no relation to the other pharmacodynamic actions of the drug.

SELECTIVITY—Despite the potential most drugs have for eliciting multiple effects, one effect is generally more readily elicitable than another. This differential responsiveness is called *selectivity*. It usually is considered to be a property of the drug, but it is also a property of the constitution and biodynamics of the recipient subject or patient.

Selectivity may come about in several ways. The subcellular structure (receptor) with which a drug combines to initiate one response may have a higher affinity for the drug than that for some other action. Atropine, for example, has a much higher affinity for muscarinic receptors that subserve the function of sweating than it does for the nicotinic receptors that subserve voluntary neuromuscular transmission, so that suppression of sweating can be achieved with only a tiny fraction of the dose necessary to cause paralysis of the skeletal muscles. A drug may be distributed unevenly, so that it reaches a higher concentration at one site than throughout the tissues generally; chloroquine is much more effective against hepatic than intestinal (colonic) amebiasis because it reaches a much higher concentration in the liver than in the wall of the colon. An affected function may be much more critical to, or have less reserve in, one organ than in another, so that a drug will be predisposed to elicit an effect at the more critical site. Some inhibitors of dopa decarboxylase (which is also 5-hydroxytryptophan decarboxylase) depress the synthesis of histamine more than that of either norepinephrine or 5- hydroxytryptamine (serotonin), even though histidine decarboxylase is less sensitive to the drug, simply because histidine decarboxylase is the only step and, hence, is rate-limiting in the biosynthesis of histamine. Dopa decarboxylase is not rate limiting in the synthesis of either norepinephrine or 5-hydroxytryptamine until the enzyme is nearly completely inhibited. Another example of the determination of selectivity by the diuretic drugs. An inhibition of only 1% in the tubular resorption of glomerular filtrate usually will double urine flow, since 99% of the glomerular filtrate is normally resorbed. Aside from the question of the possible concentration of diuretics in the urine, a drug-induced reduction of 1% in sulfhydryl enzyme activity in tissues other than the kidney usually is not accompanied by an observable change in function. Selectivity also can be determined by the pattern of distribution of inactivating or activating enzymes among the tissues and by other factors.

DOSE—Even the uninitiated person knows that the dose of a drug is the amount administered. However, the appropriate dose of a drug is not some unvarying quantity, a fact sometimes overlooked by pharmacists, official committees, and physicians. The practice of pharmacy is entrapped in a system of fixed-dose formulations, so that fine adjustments in dosage are often difficult to achieve. Fortunately, there is usually a rather wide latitude allowable in dosages. It is obvious that the size of the recipient individual should have a bearing upon the dose, and the physician may elect to administer the drug on a body-weight or surface-area basis rather than as a fixed dose. Usually, however, a fixed dose is given to all adults, unless the adult is exceptionally large or small. The dose for infants and children often is determined by one of several formulas that take into account age or weight, depending on the age group of the child and the type of action exerted by the drug. Infants, relatively, are more sensitive to many drugs, often because systems involved in the inactivation and elimination of the drugs may not be developed fully in the infant.

The nutritional condition of the patient, the mental outlook, the presence of pain or discomfort, the severity of the condition being treated, the presence of secondary disease or pathology, and genetic and many other factors affect the dose of a drug necessary to achieve a given therapeutic response or to cause an untoward effect (Chapter 61). Even two apparently well-matched normal persons may require widely different doses for the same intensity of effect. Furthermore, a drug is not always employed for the same effect and, hence, not in the same dose. For example, the dose of a progestin necessary for an oral contraceptive effect is considerably different from that necessary to prevent spontaneous abortion, and a dose of an estrogen for the treatment of the menopause is much too small for the treatment of prostatic carcinoma.

From the above, it is evident that the wise physician knows that *the dose of a drug* is not a rigid quantity but rather that which is necessary and can be tolerated and individualizes the regimen accordingly. The wise pharmacist also recognizes that official or manufacturer's recommended doses are sometimes quite narrowly defined and should serve only as a useful guide rather than as an imperative.

POTENCY AND EFFICACY—The *potency* of a drug is the reciprocal of dose. Thus, it will have the units of persons/unit weight of drug or body weight/unit weight of drug, etc. Potency generally has little utility other than to provide a means of comparing the relative activities of drugs in a series, in which case *relative potency*, relative to some prototypic member of the series, is a parameter commonly used among pharmacologists and in the pharmaceutical industry.

Whether a given drug is more potent than another has little bearing on its clinical usefulness, provided that the potency is not so low that the size of the dose is physically unmanageable or the cost of treatment is higher than with an equivalent drug. If a drug is less potent but more selective, it is the one to be preferred. Promotional arguments in favor of a more potent drug thus are irrelevant to the important considerations that should govern the choice of a drug. However, it sometimes occurs that drugs of the same class differ in the maximum intensity of effect; that is, some drugs of the class may be less efficacious than others, irrespective of how large a dose is used.

Efficacy connotes the property of a drug to achieve the desired response, and *maximum efficacy* denotes the maximum achievable effect. Even huge doses of codeine often cannot achieve the relief from severe pain that relatively small doses

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