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CHAPTER 1

PHARMACOKINETICS

The Dynamics of Drug Absorption, Distribution, and Elimination

Grant R. Wilkinson

To produce its characteristic effects, a drug must be present in appropriate concentrations at its sites of action. Although obviously a function of the amount of drug administered, the concentrations of active, unbound (free) drug attained also depend upon the extent and rate of its absorption, distribution (which mainly reflects relative binding to plasma and tissue proteins), metabolism (biotransformation), and excretion. These disposition factors are depicted in Figure 1–1 and are described in this chapter.

PHYSICOCHEMICAL FACTORS IN TRANSFER OF DRUGS ACROSS MEMBRANES

The absorption, distribution, metabolism, and excretion of a drug all involve its passage across cell membranes. Mechanisms by which drugs cross membranes and the physicochemical properties of molecules and membranes that influence this transfer are, therefore, important. The determining characteristics of a drug are its molecular size and shape, degree of ionization, relative lipid solubility of its ionized and nonionized forms, and its binding to tissue proteins.

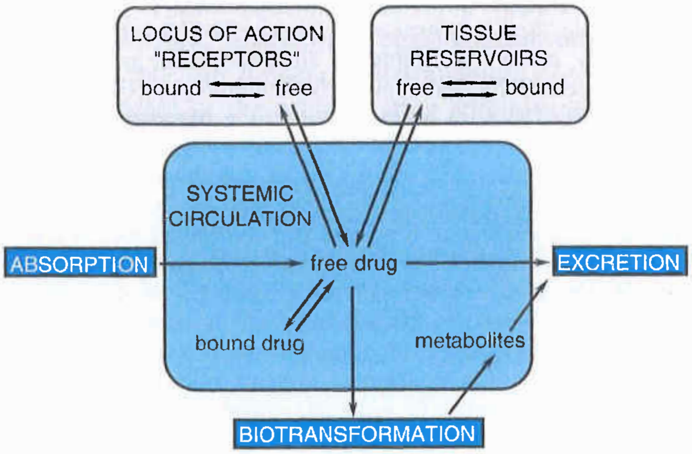

***Figure 1–1.** Schematic representation of the interrelationship of the absorption, distribution, binding, metabolism, and excretion of a drug and its concentration at its locus of action.*

When a drug permeates a cell, it obviously must traverse the cellular plasma membrane. Other barriers to drug movement may be a single layer of cells (intestinal epithelium) or several layers of cells (skin). Despite such structural differences, the diffusion and transport of drugs across these various boundaries have many common characteristics, since drugs in general pass through cells rathe than between them. The plasma membrane thus represent the common barrier.

Cell Membranes. The plasma membrane consists of a bilaye of amphipathic lipids, with their hydrocarbon chains oriente inward to form a continuous hydrophobic phase and their hydrophilic heads oriented outward. Individual lipid molecules i the bilayer vary according to the particular membrane and ca move laterally, endowing the membrane with fluidity, flexibility high electrical resistance, and relative impermeability to highl polar molecules. Membrane proteins embedded in the bilaye serve as receptors, ion channels, or transporters to elicit electr cal or chemical signaling pathways and provide selective targe for drug actions.

Most cell membranes are relatively permeable to wat either by diffusion or by flow resulting from hydrostatic or o motic differences across the membrane, and bulk flow of wat can carry with it drug molecules. Such transport is the maj mechanism by which drugs pass across most capillary endoth lial membranes. However, proteins and drug molecules bou to them are too large and polar for this type of transport to o cur; thus, transcapillary movement is limited to unbound dru Paracellular transport through intercellular gaps is sufficient large that passage across most capillaries is limited by blo glomerular membranes in the kidney. Important exceptions exist in such capillary diffusion, however, since "tight" intercellular junctions are present in specific tissues and paracellular transport in them is limited. Capillaries of the central nervous system (CNS) and a variety of epithelial tissues have tight junctions (*see* below). Although bulk flow of water can carry with it small, water-soluble substances, if the molecular mass of these compounds is greater than 100 to 200 daltons, such transport is limited. Accordingly, most large lipophilic drugs must pass through the cell membrane itself by one or more processes.

Passive Membrane Transport. Drugs cross membranes either by passive processes or by mechanisms involving the active participation of components of the membrane. In the former, the drug molecule usually penetrates by passive diffusion along a concentration gradient by virtue of its solubility in the lipid bilayer. Such transfer is directly proportional to the magnitude of the concentration gradient across the membrane, the lipid:water partition coefficient of the drug, and the cell surface area. The greater the partition coefficient, the higher is the concentration of drug in the membrane and the faster is its diffusion. After a steady state is attained, the concentration of the unbound drug is the same on both sides of the membrane if the drug is a nonelectrolyte. For ionic compounds, the steady-state concentrations will be dependent on differences in pH across the membrane, which may influence the state of ionization of the molecule on each side of the membrane and on the electrochemical gradient for the ion.

Weak Electrolytes and Influence of pH. Most drugs are weak acids or bases that are present in solution as both the nonionized and ionized species. The nonionized molecules are usually lipid-soluble and can diffuse across the cell membrane. In contrast, the ionized molecules are usually unable to penetrate the lipid membrane because of their low lipid solubility.

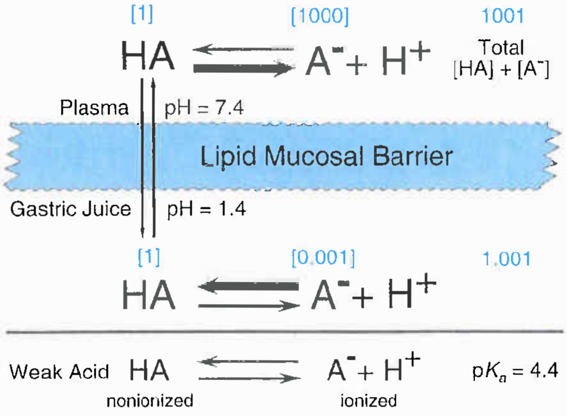

Figure 1–2. Influence of pH on the distribution of a weak acid between plasma and gastric juice, separated by a lipid barrier.

Therefore, the transmembrane distribution of a weak electrolyte usually is determined by its pK_a and the pH gradient across the membrane. The pK_a is the pH at which half of the drug (weak electrolyte) is in its ionized form. To illustrate the effect of pH on distribution of drugs, the partitioning of a weak acid ($pK_a = 4.4$) between plasma (pH = 7.4) and gastric juice (pH = 1.4) is depicted in Figure 1–2. It is assumed that the gastric mucosal membrane behaves as a simple lipid barrier that is permeable only to the lipid-soluble, nonionized form of the acid. The ratio of nonionized to ionized drug at each pH is readily calculated from the Henderson–Hasselbalch equation. Thus, in plasma, the ratio of nonionized to ionized drug is 1:1000; in gastric juice, the ratio is 1:0.001. These values are given in brackets in Figure 1–2. The total concentration ratio between the plasma and the gastric juice would therefore be 1000:1 if such a system came to a steady state. For a weak base with a pK_a of 4.4, the ratio

each pH. Accordingly, at steady state, an acidic drug will accumulate on the more basic side of the membrane and a basic drug on the more acidic side—a phenomenon termed *ion trapping*. These considerations have obvious implications for the absorption and excretion of drugs, as discussed more specifically below. The establishment of concentration gradients of weak electrolytes across membranes with a pH gradient is a purely physical process and does not require an active transport system. All that is necessary is a membrane preferentially permeable to one form of the weak electrolyte and a pH gradient across the membrane. The establishment of the pH gradient is, however, an active process.

Carrier-Mediated Membrane Transport. While passive diffusion through the bilayer is dominant in the disposition of most drugs, carrier-mediated mechanisms also can play an important role. *Active transport* is characterized by a requirement for energy, movement against an electrochemical gradient, saturability, selectivity, and competitive inhibition by cotransported compounds. The term *facilitated diffusion* describes a carrier-mediated transport process in which there is no input of energy and therefore enhanced movement of the involved substance is down an electrochemical gradient. Such mechanisms, which may be highly selective for a specific conformational structure of a drug, are involved in the transport of endogenous compounds whose rate of transport by passive diffusion otherwise would be too slow. In other cases, they function as a barrier system to protect cells from potentially toxic substances.

The responsible transporter proteins often are expressed within cell membranes in a domain-specific fashion such that they mediate either drug uptake or efflux, and often such an arrangement facilitates vectorial transport across cells. Thus, in the liver, a number of basolaterally localized transporters with different substrate specificities are involved in the uptake of bile acids and amphipathic organic anions and cations into the hepatocyte, and a similar variety of ATP-dependent transporters in the canalicular membrane export such compounds into the these sites and also in the capillary endothelium of brain capillaries is P-glycoprotein, which is encoded by the multidrug resistance-1 (*MDR1*) gene, important in resistance to cancer chemotherapeutic agents (Chapter 52). P-glycoprotein localized in the enterocyte also limits the oral absorption of transported drugs since it exports the compound back into the intestinal tract subsequent to its absorption by passive diffusion.

DRUG ABSORPTION, BIOAVAILABILITY, AND ROUTES OF ADMINISTRATION

Absorption describes the rate at which a drug leaves its site of administration and the extent to which this occurs. However, the clinician is concerned primarily with a parameter designated as *bioavailability*, rather than absorption. *Bioavailability* is a term used to indicate the fractional extent to which a dose of drug reaches its site of action or a biological fluid from which the drug has access to its site of action. For example, a drug given orally must be absorbed first from the stomach and intestine, but this may be limited by the characteristics of the dosage form and/or the drug's physicochemical properties. In addition, drug then passes through the liver, where metabolism and/or biliary excretion may occur before it reaches the systemic circulation. Accordingly, a fraction of the administered and absorbed dose of drug will be inactivated or diverted before it can reach the general circulation and be distributed to its sites of action. If the metabolic or excretory capacity of the liver for the agent in question is large, bioavailability will be substantially reduced (the so-called *first-pass effect*). This decrease in availability is a function of the anatomical site from which absorption takes place; other anatomical, physiological, and pathological factors can influence bioavailability (*see* below), and the choice of the route of drug administration must be based on an understanding of these conditions.

Oral (Enteral) *versus* Parenteral Administration. Often there is a choice of the route by which a therapeutic agent may be given, and a knowledge of the advantages and disadvantages of the different routes of administration is then of primary importance. Some characteristics of the major routes employed for systemic drug effect are compared in Table 1–1.

Oral ingestion is the most common method of drug administration. It also is the safest, most convenient, and most economical. Disadvantages to the oral route include limited absorption of some drugs because of their physical characteristics (*e.g.*, water solubility), emesis as a result of irritation to the gastrointestinal mucosa, destruction of some drugs by digestive enzymes or low gastric pH, irregularities in absorption or propulsion in the presence of food or other drugs, and necessity for cooperation on the part of the patient. In addition, drugs in the gastrointestinal tract may be metabolized by the enzymes of the intestinal flora, mucosa, or the liver before they gain access to the general circulation.

The parenteral injection of drugs has certain distinct advantages over oral administration. In some instances, parenteral administration is essential for the drug to be delivered in its active form. Availability is usually more rapid, extensive, and predictable than when a drug is given by mouth. The effective dose therefore can be more accurately delivered. In emergency therapy and when a patient is unconscious, uncooperative, or unable to retain anything given by mouth, parenteral therapy may be a necessity. The injection of drugs, however, has its disadvantages: asepsis must be maintained; pain may accompany the injection; it is sometimes difficult for patients to perform the injections themselves if self-medication is necessary; and there is the risk of inadvertent administration of a drug when it is not intended. Expense is another consideration.

Oral Ingestion. Absorption from the gastrointestinal tract is governed by factors such as surface area for absorption, blood flow to the site of absorption, the physical state of the drug (solution, suspension, or solid dosage form), its water solubility, and concentration at the site of absorption. For drugs given in solid form, the rate of dissolution may be the limiting factor in their absorption, especially if they have low water solubility. Since most drug absorption from the gastrointestinal tract occurs *via* passive processes, absorption is favored when the drug is in the nonionized and more lipophilic form. Based on the pH-partition concept presented in Figure 1–2, it would be predicted that drugs that are weak acids would be better absorbed from the stomach (pH 1 to 2) than from the upper intestine (pH 3 to 6), and *vice versa* for weak bases. However, the epithelium of the stomach is lined with a thick mucous layer, and its surface area is small; by contrast, the villi of the upper intestine provide an extremely large surface area (~200 m^2). Accordingly, the rate of absorption of a drug from the intestine will be greater than that from the stomach even if the drug is predominantly ionized in the intestine and largely nonionized in the stomach. Thus, any factor that accelerates gastric emptying will be likely to increase the rate of drug absorption, while any factor that delays gastric emptying will probably have the opposite effect, regardless of the characteristics of the drug.

Drugs that are destroyed by gastric juice or that cause

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