The Importance of Tissue Distribution in Pharmacokinetics

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In evoking pharmacological and toxicological responses, drugs generally combine either reversibly or irreversibly with action sites on intrastitial macromolecules or organelles, and thereby cause alterations of physico-chemical or biochemical processes in the living animal. These alterations can be evoked by a number of mechanisms. Drugs can either mimic or block the action of normally occurring substances by combining with receptor sites. Drugs can alter the localization of normally occurring substances by interfering with transport mechanisms or changing the number of storage sites. Drugs can change the concentrations of normally occurring substances in tissues by reacting with them directly or by altering the activities of enzymes that catalyze their formation or destruction.

Regardless of the mechanism of drug action, the drug must first reach its site of action in adequate concentrations to produce its effect. With reversibly acting drugs, the amount of drug combined with the action site is dependent on the concentration of unbound drug in the fluid immediately surrounding the action site, the so-called biophase. Unfortunately, the concentration of unbound drug at these sites is seldom known. Most estimates of the concentration of unbound drug at these sites are based on the concentration of unbound drug in blood plasma, the physiological medium of exchange between all tissues. In making these estimates, the investigator assumes that the unbound concentrations of the drug in the plasma and at the locus of action are the same. But this assumption is invalid in a number
of instances. Polar compounds slowly transverse membranes such as the blood–brain barrier; thus the levels of quaternary ammonium compounds and sulfonic acid derivatives can be considerably lower in brain than in plasma. Some compounds can be metabolized so rapidly in plasma that their rates of diffusion from their receptor sites determine their duration of action; for example, the pharmacological effects of succinylcholine can still be observed even after the drug has been virtually cleared from plasma (Kalow, 1962). Other polar compounds can be concentrated in tissues by active transport systems; for example, the levels of certain amino acids can be greater within cells than in interstitial fluid.

On the other hand, lipid-soluble compounds readily pass through lipoid membrane barriers and can be concentrated only slightly or not at all by active transport systems; thus, within a short time after the administration of a lipid-soluble compound, its free concentration at the locus of action becomes virtually identical to its free concentration in plasma. Since the pH is usually slightly lower within cells than it is in plasma, however, the unbound concentrations of lipid-soluble weak acids and bases in cells differ slightly from those in plasma (Waddell and Butler, 1959). For example, the concentration of phenobarbital is slightly lower in brain than in plasma (Waddell and Butler, 1957). Moreover, hyperventilation of the lungs or breathing atmospheres containing CO₂ can alter the distribution of phenobarbital by changing the pH of the blood plasma.

The distribution of most drugs, however, is governed by their reversible combinations with proteins and other constituents in blood and tissues. The concentration of unbound drug, therefore, can be considerably lower than either the total plasma level or the total tissue level of the drug. In fact, determination of the tissue to plasma level ratios of the drugs frequently gives a wrong impression of the extent of binding, because drugs are usually bound to both tissue and plasma proteins.

Some drugs are strongly bound to tissue even though the tissue to plasma ratios are low. For example, calculations made from the results of Burns et al. (1953) showed that about 98% of the phenylbutazone in plasma is bound to proteins and that about 95% of the drug in liver and kidney is bound. If Burns et al. (1953) had determined only the tissue to plasma ratios of the drug they might have concluded that the drug was not appreciably bound since these ratios approached values that might be expected with drugs that are distributed with body water.

On the other hand, a drug can be highly bound to plasma proteins even when the tissue to plasma ratios are high. For example, Dingell et al. (1964) found that 90 min after the intravenous administration of imipramine (20 mg/kg) to rabbits, the drug levels were about 12 μg/g in brain and 0.6 μg/