TOXICOKINETICS

Characterization (Quantitation) of the time course of disposition (ADME) of xenobiotics in the whole organism.

“a substance gets into the body and what happens to it in the body".

Absorption, Distribution, Metabolism, and Excretion

**T**he basis of toxicology involves the absorption, distribution, metabolism, and excretion (ADME) of a toxicant. Knowledge of these processes is important to evaluate risk of exposure to toxins

**Absorption**

Absorption may occur through the alimentary tract, skin, lungs, via the eye, mammary gland, or uterus, as well as from sites of injection. Toxic effects may be local, but the toxicant must be dissolved and absorbed to some extent to affect the cell. Solubility is the primary factor affecting absorption. Insoluble salts and ionized compounds are poorly absorbed, whereas lipid-soluble substances are generally readily absorbed, even through intact skin. For example, barium is toxic, but barium sulphate can be used for intestinal contrast radiography because of low absorption.

**Distribution**

Distribution or translocation of a toxicant is via the bloodstream to reactive sites, including storage depots. The liver receives the portal circulation and is the organ most commonly involved with intoxication (and detoxification). The selective deposit of foreign chemicals in various tissues depends on receptor sites. Ease of chemical distribution depends largely on its water solubility. Polar or aqueous-soluble agents tend to be excreted by the kidneys; lipid-soluble chemicals are more likely to be excreted via the bile and accumulate in fat depots. The highest concentration of a toxin within an animal is not necessarily found in the organ or tissue on which it exerts its maximal effect (the target organ). Lead may be found in highest concentrations in bone, which is neither a site for toxic effects nor a reliable tissue for toxicologic interpretation. Knowledge of the translocation characteristics of toxicants is necessary for proper selection of organs for analysis.

**Metabolism**

Metabolism or biotransformation of toxicants by the body is an “attempt to detoxify.” In some instances, metabolized xenobiotic agents are more toxic than the original compound. This is referred to as lethal synthesis. Metabolism of many organophosphorous insecticides produces metabolites more toxic than the initial (or parent) compounds (eg, parathion to paroxan).

There are two phases of metabolism. Phase I includes oxidation, reduction, and hydrolysis mechanisms. These reactions, catalyzed by hepatic enzymes, generally convert foreign compounds to derivatives for Phase II reactions. Products of Phase I, however, may be excreted as such, if polar solubility permits translocation. Phase II principally involves conjugation or synthesis reactions. Common conjugates include glucuronides, acetylation products, and combinations with glycine. Metabolism of xenobiotic agents seldom follows a single pathway. Usually, a fraction is excreted unchanged, and the rest is excreted or stored as metabolites. Significant differences in metabolic mechanisms exist between species. For example, because cats lack forms of glucuronyl transferase, their ability to conjugate compounds such as morphine and phenols is compromised. Increased tolerance to subsequent exposures of a toxicant, in some instances, is due to enzyme induction initiated by the previous exposure.

**Excretion**

Excretion of most toxicants and their metabolites is by way of the kidneys. Some excretion occurs in the digestive tract and some via milk. Many polar and high-molecular-weight compounds are excreted into the bile. An enterohepatic cycle occurs when these compounds are excreted from the liver via bile, reabsorbed from the intestine, and returned to the liver. Milk is also an excretion pathway for some toxicants. The excretion rate may be of primary concern, because some toxicants can cause violative residues in food-producing animals. The route of administration, dose, and condition of the animal—to name a few factors—can have a profound effect on excretion rates. Toxicants are removed in the kidney by glomerular filtration, tubular excretion by passive diffusion, and active tubular secretion. The damage to the kidney from the excretion of xenobiotics is specific to the anatomic location where the excretion occurs. Excretion sites are proximal tubules, glomeruli, medulla, papilla, and loop of Henle. The proximal convoluted tubule is the most common site of toxicant-induced injury.

The important Phase I enzymes present in the kidney are cytochrome P450, prostaglandin synthase, and prostaglandin reductase. The Phase I enzyme cytochrome P450 is present in the kidney at 10% of the level of the liver. Important Phase II enzymes present in the kidneys are UDP-glucuronosyltransferases (UGT), sulfotransferases, and glutathione-S-transferase.