bonate alkalinizes the urine, raising the number of barbiturate ions in the renal filtrate. The ionized particles cannot pass easily through renal tubular membranes. Therefore, less drug is reabsorbed into the blood and more is excreted by the kidneys.

Client-Related Variables

Age

The effects of age on drug action are most pronounced in neonates, infants, and older adults. In children, drug action depends largely on age and developmental stage. During pregnancy, drugs cross the placenta and may harm the fetus. Fetuses have no effective mechanisms for metabolizing or eliminating drugs because their liver and kidney functions are immature. Newborn infants (birth to 1 month) also handle drugs inefficiently. Drug distribution, metabolism, and excretion differ markedly in neonates, especially premature infants, because their organ systems are not fully developed. Older infants (1 month to 1 year) reach approximately adult levels of protein binding and kidney function, but liver function and the blood–brain barrier are still immature.

Children (1 to 12 years) experience a period of increased activity of drug-metabolizing enzymes so that some drugs are rapidly metabolized and eliminated. Although the onset and duration of this period are unclear, a few studies have been done with particular drugs. Theophylline, for example, is cleared much faster in a 7-year-old child than in a neonate or adult (18 to 65 years). After approximately 12 years of age, healthy children handle drugs similarly to healthy adults.

In older adults (65 years and older), physiologic changes may alter all pharmacokinetic processes. Changes in the GI tract include decreased gastric acidity, decreased blood flow, and decreased motility. Despite these changes, however, there is little difference in absorption. Changes in the cardiovascular system include decreased cardiac output and therefore slower distribution of drug molecules to their sites of action, metabolism, and excretion. In the liver, blood flow and metabolizing enzymes are decreased. Thus, many drugs are metabolized more slowly, have a longer action, and are more likely to accumulate with chronic administration. In the kidneys, there is decreased blood flow, decreased glomerular filtration rate, and decreased tubular secretion of drugs. All of these changes tend to slow excretion and promote accumulation of drugs in the body. *Impaired kidney and liver function greatly increase the risks of adverse drug effects.* In addition, older adults are more likely to have acute and chronic illnesses that require multiple drugs or long-term drug therapy. Thus, possibilities for interactions among drugs and between drugs and diseased organs are greatly multiplied.

Body Weight

Body weight affects drug action mainly in relation to dose. The ratio between the amount of drug given and body weight influences drug distribution and concentration at sites of action. In general, people heavier than average need larger doses, provided that their renal, hepatic, and cardiovascular functions are adequate. Recommended doses for many drugs are listed in terms of grams or milligrams per kilogram of body weight.

Genetic and Ethnic Characteristics

Drugs are given to elicit certain responses that are relatively predictable for most drug recipients. When given the same drug in the same dose, however, some people experience inadequate therapeutic effects, and others experience unusual or exaggerated effects, including increased toxicity. These interindividual variations in drug response are often attributed to genetic or ethnic differences in drug pharmacokinetics or pharmacodynamics. As a result, there is increased awareness that genetic and ethnic characteristics are important factors and that diverse groups must be included in clinical trials.

Genetics

A person's genetic characteristics may influence drug action in several ways. For example, genes determine the types and amounts of proteins produced in the body. When most drugs enter the body, they interact with proteins (eg, in plasma, tissues, cell membranes, and drug receptor sites) to reach their sites of action, and with other proteins (eg, drug-metabolizing enzymes in the liver and other organs) to be biotransformed and eliminated from the body. Genetic characteristics that alter any of these proteins can alter drug pharmacokinetics or pharmacodynamics.

One of the earliest genetic variations to be identified derived from the observation that some people taking usual doses of isoniazid (an antitubercular drug), hydralazine (an antihypertensive agent), or procainamide (an antidysrhythmic) showed no therapeutic effects, whereas toxicity developed in other people. Research established that these drugs are normally metabolized by acetylation, a chemical conjugation process in which the drug molecule combines with an acetyl group of acetyl coenzyme A. The reaction is catalyzed by a hepatic drug-metabolizing enzyme called acetyltransferase. It was further established that humans may acetylate the drug rapidly or slowly, depending largely on genetically controlled differences in acetyltransferase activity. Clinically, rapid acetylators may need larger-than-usual doses to achieve therapeutic effects, and slow acetylators may need smaller-than-usual doses to avoid toxic effects. In addition, several genetic variations of the cytochrome P450 drug-metabolizing system have been identified. Specific variations may influence any of the chemical processes by which drugs are metabolized.

As another example of genetic variation in drug metabolism, some people lack the plasma pseudocholinesterase enzyme that normally inactivates succinylcholine, a potent muscle relaxant used in some surgical procedures. These people may experience prolonged paralysis and apnea if given succinylcholine.

Other people are deficient in glucose-6-phosphate dehydrogenase, an enzyme normally found in red blood cells and