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**QUESTION**

Discuss in detail the factors affecting drug metabolism.

**SOLUTION**

Drug metabolism is the chemical alteration of a drug by the body. It is the metabolic breakdown of drugs by living organisms, usually through specialized enzymatic systems.

Drugs can be metabolized by oxidation, reduction, hydrolysis, hydration, conjugation, condensation, or isomerization; whatever the process, the goal is to make the drug easier to excrete. The enzymes involved in metabolism are present in many tissues but generally are more concentrated in the liver.

Many factors can determine which pathway is used by which drug and to what extent a particular drug is biotransformed by a particular pathway. These factors range from the species of organism studied to the environment in which that organism lives and can be grouped as follows:

•Internal (i.e. physiological and pathological) factors

•External factors (i.e. diet and environment)

**Internal**

•species

•genetic (strain)

•age

•sex

•hormones

•disease

**External**

•diet

•environment

The liver’s primary mechanism for metabolizing drugs is via a specific group of cytochrome P-450 enzymes. The level of these cytochrome P-450 enzymes controls the rate at which many drugs are metabolized. Many substances (such as drugs and foods) affect the cytochrome P-450 (CYP450) enzymes. If these substances decrease the ability of the enzymes to break down a drug, then that drug's effects (including side effects) are increased. If the substances increase the ability of the enzymes to break down a drug, then that drug's effects are decreased.

Below, some of these factors will be explained;

**INTERNAL FACTORS**

AGE:

Because metabolic enzyme systems are only partially developed at birth, newborns have difficulty metabolizing certain drugs. As people age, enzymatic activity decreases, so that older people, like newborns, cannot metabolize drugs as well as younger adults and children do. Consequently, newborns and older people often need smaller doses per pound of body weight than do young or middle-aged adults.

GENETIC:

Differences in genetic (inherited) makeup among individuals affect what the body does to a drug and what the drug does to the body. The study of genetic differences in the response to drugs is called pharmacogenetics. Because of their genetic makeup, some people process (metabolize) drugs slowly. As a result, a drug may accumulate in the body, causing toxicity. Other people metabolize drugs so quickly that after they take a usual dose, drug levels in the blood never become high enough for the drug to be effective. In individuals whereby N-acetyltransferase, a liver enzyme that metabolizes certain drugs, works slowly, such people are called slow acetylators. Drugs, such as isoniazid (which is used to treat tuberculosis), that are metabolized by this enzyme tend to reach higher blood levels and remain in the body longer in slow acetylators than they do in people in whom this enzyme metabolizes drugs rapidly (fast acetylators).

SEX:

In most clinical trials, women are underrepresented, and gender-specific analysis is uncommon. Sex differences in metabolism (phase I and II) are believed to be the major cause of differential pharmacokinetics between men and women. Many CYP450 enzymes (phase I metabolism) show a sex-dependent difference in activity. Most of the phase II enzymes have a higher activity in men than in women. Activities of these enzymes can also change during pregnancy and with the use of oral contraceptives. Sex differences are also found in other pharmacokinetic parameters such as drug absorption, drug distribution, and excretion. Despite these differences between men and women, sex-specific dosing recommendations are absent for most drugs. Therefore, when a woman consistently experiences less therapeutic effect or more adverse effects from a drug, a change in its dosing regimen may be necessary.

**EXTERNAL FACTORS**

DIET:

Nutrition can affect the body’s response to drugs; conversely, drugs can affect the body’s nutrition.

Foods can enhance, delay, or decrease drug absorption. Foods impair absorption of many antibiotics. They can alter metabolism of drugs; eg, high-protein diets can accelerate metabolism of certain drugs by stimulating cytochrome P-450. Eating grapefruit can inhibit cytochrome P-450 34A, slowing metabolism of some drugs (eg, amiodarone, carbamazepine, cyclosporine, certain Ca channel blockers). Diets that alter the bacterial flora may markedly affect the overall metabolism of certain drugs. Some foods affect the body’s response to drugs. For example, tyramine, a component of cheese and a potent vasoconstrictor, can cause hypertensive crisis in some patients who take monoamine oxidase inhibitors and eat cheese.

Nutritional deficiencies can affect drug absorption and metabolism. Severe energy and protein deficiencies reduce enzyme tissue concentrations and may impair the response to drugs by reducing absorption or protein binding and causing liver dysfunction. Changes in the GI tract can impair absorption and affect the response to a drug. Deficiency of Ca, Mg, or zinc may impair drug metabolism. Vitamin C deficiency decreases activity of drug-metabolizing enzymes, especially in the elderly.

ENVIRONMENT:

Although various kinds of environmental factors may alter the activity of cytochrome P-450 enzymes in liver micromes, their effects on the pharmacokinetics of drugs and other foreign compounds in living animals may not be as great as might be predicted from assays of these enzymes in vitro. Indeed, the effects will depend on the relative importance of excretory and metabolic mechanisms in the elimination of the drug, the relative importance of various metabolic reactions in different tissues, the extraction ratio of the drug by the liver, and in some instances on the route of administration of the drug. Moreover, the effect of the various environmental factors on the pharmacologic and the toxicologic actions of the drug will depend on whether these actions are caused by the parent foreign compounds or by one or more of their metabolites. It may also be important that the environmental factors may alter not only relative activiteis of the cytochrome P-450 in liver microsomes but also the activities of other drug-metabolizing enzymes and that the relative effects of the environmental factors of these enzymes may differ depending on the animal species or the animal strain. Indeed, a given factor may increase the pharmacologic effects of a drug metabolite in one animal species but decrease it in another. For these reasons, it frequently is not possible to predict the effects of environmental factors on drug action in living animals solely from in vitro rates of metabolism of model substrates.