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Question

Discuss in details the factors affecting drug metabolism. Dr. (Mrs) Owolabi

Drug metabolism is the metabolic breakdown of drugs by living organisms, usually through specialized enzymatic systems. The study of drug metabolism is called pharmacokinetics.

Xenobiotic metabolism is the set of metabolic pathways that modify the chemical structure of xenobiotics, which are compounds foreign to an organism's normal biochemistry, such as any drug or poison.

The metabolism of pharmaceutical drugs is an important aspect of pharmacology and medicine. For example, the rate of metabolism determines the duration and intensity of a drug's pharmacologic action. Drug metabolism also affects multidrug resistance in infectious diseases and in chemotherapy for cancer, and the actions of some drugs as substrates or inhibitors of enzymes involved in xenobiotic metabolism are a common reason for hazardous drug interactions.

Quantitatively, the smooth endoplasmic reticulum of the liver cell is the principal organ of drug metabolism, although every biological tissue has some ability to metabolize drugs. Factors responsible for the liver's contribution to drug metabolism include that it is a large organ, that it is the first organ perfused by chemicals absorbed in the gut, and that there are very high concentrations of most drug-metabolizing enzyme systems relative to other organs.

Other sites of drug metabolism include epithelial cells of the gastrointestinal tract, lungs, kidneys, and the skin. These sites are usually responsible for localized toxicity reactions.

FACTORS THAT AFFECT DRUG METABOLISM

1. **AGE DIFFERENCES:** Age-related differences in drug metabolism are generally quite apparent in the newborn. In most fetal and newborn animals, undeveloped or deficient oxidative and conjugative enzymes are chiefly responsible for the reduced metabolic capability seen. In general, the ability to carry out metabolic reactions increases rapidly after birth and approaches adult levels as the child develops. In humans, oxidative and conjugative (e.g., glucuronida-tion) capabilities of newborns are also low compared with those of adults. Drug metabolism also diminishes with old age.

2. **SPECIES AND STRAIN DIFFERENCES:** The metabolism of many drugs and foreign compounds is often species dependent. Different animal species may biotransform a particular xenobiotic by similar or markedly different metabolic pathways. Even within the same species, individual variations (strain differences) may result in significant differences in a specific metabolic pathway. This is a problem when a new drug is under development. A new drug application requires the developer to account for the product as it moves from the site of administration to final elimination from the body. It is difficult enough to find appropriate animal models for a disease. It is even harder to find animal models that mimic human

drug metabolism.

Species variation has been observed in many oxidative biotransformation and conjugation reactions. Often, these differences are caused by the presence or absence of transferase enzymes involved in the conjugative process.

Strain differences in drug metabolism exist, particularly in inbred mice and rabbits. These differences apparently are caused by genetic variations in the amount of metabolizing enzyme present among the different strains. For example, in vitro studies indicate that cottontail rabbit liver microsomes metabolize hexobarbital about 10 times faster than New Zealand rabbit liver microsomes.

3. HEREDITARY OR GENETIC FACTORS: Marked individual differences in the metabolism of several drugs exist in humans. Many of these genetic or hereditary factors are responsible for the large differences seen in the rate of metabolism of these drugs. Inter-individual variations might occur, as drugs behave differently in different individuals due to genetic variations resulting from absent or malformed enzymes. Mostly non microsomal enzyme show genetic variations. Genetic factors also appear to influence the rate of oxidation of drugs such as phenytoin, phenylbutazone, dicumarol, and nortriptyline. Numerous studies in twins (identical and fraternal) and in families indicate that oxidation of these drugs is under genetic control.

4. SEX DIFFERENCES: The rate of metabolism of xenobiotics also varies according to gender in some animal species. A marked difference is observed between female and male rats. Adult male rats metabolize several foreign compounds at a much faster rate than female rats. Apparently, this sex difference also depends on the substrate, because some xenobiotics are metabolized at the same rate in both female and male rats. Differences in microsomal oxidation are under

the control of sex hormones, particularly androgens; the anabolic action of androgens seems to increase metabolism.Females, during pregnancy, have an increased rate of metabolism. Thus, the drug dose has to be increased. After the pregnancy is over, the dosage is decreased back to normal levels

Sex differences in drug metabolism appear to be species dependent. Rabbits and mice, for example, do not show a significant sex difference in drug metabolism. In humans, there have been a few reports of sex differences in metabolism. For instance, nicotine and aspirin seem to be metabolized differently in women and men. On the other hand, gender differences can become significant in terms of drug-drug interactions based on the drug's metabolism.

5. **ENZYME INDUCTION:** The activity of hepatic microsomal enzymes, such as the CYP mixed-function oxidase system, can be increased markedly by exposure to diverse drugs, pesticides, polycyclic aromatic hydrocarbons, and environmental xenobiotics. The process by which the activity of these drug-metabolizing enzymes is increased is termed enzyme induction. The increased activity is apparently caused by an increased amount of newly synthesized enzyme. Enzyme induction often increases the rate of drug metabolism and decreases the duration of drug action.Inducing agents may increase the rate of their own metabolism as well as those of other unrelated drugs or foreign compounds. Concomitant administration of two or more drugs often may lead to serious drug interactions as a result of enzyme induction. For instance, a clinically critical drug interaction occurs with phenobarbital and warfarin. Induction of microsomal enzymes by phenobarbital increases the metabolism of warfarin and, consequently, markedly decreases the anticoagulant effect. Therefore, if a patient is receiving warfarin anticoagulant therapy and begins taking phenobarbital, careful attention must be paid to readjustment of the warfarin dose

6. **ENZYME INHIBITION:** The process in which drug metabolizing capacity of cytochrome is decreased is known as enzyme inhibition. The rate of metabolism is decreased. Drugs bringing about these changes are known as enzyme inhibitors. Examples include ketoconazole- antifungal drug, cimetidine and verapamil- calcium channel blocker.

   Enzyme inhibition is a rapidly occurring process, most critical for the drugs having a large therapeutic index. Competition for the active sites takes place between the enzymes and the given drugs. When enzyme inhibitor attaches, less metabolism occurs. As rate of metabolism is decreased, plasma levels of parent drug are increased while that of metabolites are low. Serious drug-drug interactions might occur, as the plasma half life is also increased.

7. **EXPOSURE TO POLLUTANTS FROM ENVIRONMENT OR INDUSTRY:** Cigarette smokers might act as enzyme inducers. Chronic alcoholism might lead to enzyme induction as well. Similarly, pesticides or insecticides may act as enzyme inducers.

   In hot and humid climate drug metabolism is decreased and vice versa. At high altitude, decreased drug metabolism occurs due to decreased oxygen leading to decreased oxidation of drugs.

8. **NUTRITION:** Malnutrition may also affect drug metabolism. Depletion of amino acids and glycine may affect drug metabolizing capacity, especially during the phase II, which depends on the food stores. Synthesis of microsomal enzymes depend on nutritional status.

9. **PATHOLOGICAL CONDITIONS:** Most of the drugs are metabolized in the liver, any disease of which (cirrhosis, viral hepatitis, drugs induced hepatitis, hepatocarcinoma) may affect and slow down the metabolizing capacity. Jaundice depresses glucuronic acid conjugation and oxidative function of liver microsomes.

   Cardiovascular diseases, although have no direct effect,

decrease the blood flow, which may slow down biotransformation of drugs like isoniazid, morphine and propanolol. Similarly pulmonary conditions may decrease drug metabolism. Procaine and procainamide hydrolysis is impaired.

Hypothyroidism increases drug metabolizing capacity (increased half life of antipyrine, digoxin, methimazole, practolol) while hyperthyroidism decreases it.

10. **Circadian rhythm:** The rate of hepatic metabolism of certain drugs follow diurnal rhythm in rats and mice. This may be true in humans as well.