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Metabolism is a biotransformation or chemical alteration of a drug to other molecular species usually called metabolites, within the body via an enzyme or non-enzymatic process. The primary site of drug metabolism is the liver and the secondary sites are the kidney, intestine, lungs and plasma.

Drug-metabolizing enzymes in liver microsomes can be influenced markedly by the administration of various foreign compounds and hormones and by the age, sex, strain, and nutritional status of the animal. These factors may contribute to the observed individual variations in drug metabolism in man. Individual differences in the metabolism of drugs may be under genetic control. Localization of drugs in fat, other tissues, and plasma protein can also markedly influence the degree of drug metabolism.

Factors that may influence the metabolic rate of a drug are majorly categorised into two;

1. Chemical factors

a) Enzyme induction

b) Enzyme inhibition

c) Environmental chemicals

2) Biological factors.

a) Age

b) Diet

c) Gender

d) Specie difference

e) Strain difference

f) altered physiological factors

g) Genetics

a) Enzyme induction: Enzyme induction occurs when chemicals cause an increase in synthesis and activity of enzymes, thereby increasing the metabolism of drugs that are catalysed by those enzymes.

When one drug causes an increased rate of metabolism of another drug by inducing the CYP enzyme involved in the biotransformation of that drug, there is a resultant effect on the drug’s efficacy. The parent drug is metabolized at an accelerated rate, leading to low potency and reduced effect. In cases where a CYP enzyme catalyzes the conversion of a less active parent (prodrug) to a more active metabolite, induction could be responsible for increasing active metabolite levels to potentially toxic levels.

b) Enzyme inhibition: Inhibitors are molecules that reduce enzyme activity by binding to the enzyme. In a normally functioning cell, enzymes are regulated by a variety of inhibitors. Drugs and other toxins can also inhibit enzymes. Some inhibitors bind to the enzyme’s active site, while others inhibit enzymatic activity by binding to other sites on the protein structure.

Competitive inhibitors occupy the active site of enzymes, making them unable to accommodate the substrate. However, sufficiently high concentrations of the substrate can outcompete the inhibitor; as a result, competitive inhibitors slow an enzymes initial reaction rate but do not impact the enzyme’s maximum rate. One example of a competitive inhibitor is the drug disulfiram, used to treat chronic alcoholism. When alcohol is ingested, it is normally converted to acetaldehyde, which is then converted to acetyl coenzyme A by acetaldehyde dehydrogenase. Disulfiram binds to and occupies the active site of acetaldehyde dehydrogenase, making the enzyme unable to perform this conversion. As a result, a patient taking disulfiram immediately begins to experience hangover-like symptoms, such as headache, thereby decreasing alcohol consumption.

Noncompetitive inhibitors bind to distinct sites on the enzyme, away from the active site. These are called allosteric sites and when molecules bind to them, the shape of the active site is changed such that the enzyme has a lower affinity for the substrate. Because noncompetitive inhibitors do not occupy the active site, the presence of additional substrate is unable to overcome noncompetitive inhibition and the enzyme is unable to achieve its maximum reaction rate.

Age: As age increases, the functions of tissues and organs in the body gradually decline. Due to this decline in organ function, drug absorption, distribution, metabolism and excretion (ADME processes) in elderly people are worse than those of young people. Furthermore, drug sensitivity is different in the elderly, who are prone to have adverse reactions to drugs. Thus, it is very important to design drugs according to the characteristics of the elderly. 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 in about 1 to 2 months. An illustration of the influence of age on drug metabolism is seen in the duration of action (sleep time) of hexobarbital in newborn and adult mice.When given a dose of 10 mg/kg of body weight, the newborn mouse sleeps more than 6 hours. In contrast, the adult mouse sleeps for fewer than 5 minutes when given the same dose.

Sex: 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.

Diet: Metabolic food-drug interactions occur when the consumption of a particular food modulates the activity of a drug-metabolising enzyme system, resulting in an alteration of the pharmacokinetics of drugs metabolised by that system. Foods that contain complex mixtures of phytochemicals, such as fruits, vegetables, herbs, spices and teas, have the greatest potential to induce or inhibit the activity of drug-metabolising enzymes, although dietary macroconstituents (i.e. total protein, fat and carbohydrate ratios, and total energy intake) can also have effects. high-protein diets can accelerate metabolism of certain drugs by stimulating cytochrome P-450.

Specie difference: qualitative differences among species generally result from the presence or absence of specific enzymes in those species. Quantitative differences result from variations in the amount and localisation of enzymes, the amount of natural inhibitors, and the competition of enzymes for specific substrates.

Strain difference: 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.

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. Genetic factors also appear to influence the rate of oxidation of drugs such as phenytoin, phenylbutazone, dicumarol, and nortriptyline. The rate of oxidation of these drugs varies widely among different individuals; however, these differences do not appear to be distributed bimodally, as in acetylation. In general, individuals who tend to oxidize one drug rapidly are also likely to oxidize other drugs rapidly. Numerous studies in twins (identical and fraternal) and in families indicate that oxidation of these drugs is under genetic control.

Altered physiological factors:

Pregnancy: pregnancy is known to affect hepatic drug metabolism.

Physiological changes during pregnancy are probably responsible for the reported alteration in drug metabolism. These include elevated concentrations of various hormones such as estrogen, progesterone, prolactin and placental growth hormones.

Disease states are also known to affect the metabolic rate of drugs. The possible cause in the effect of metabolism due to diseases may be:

a) Decreased enzyme activity in the liver

b) Altered hepatic blood flow

c) Hypoalbunaemia (leading to lower plasma binding of drugs)

3. Physicochemical properties if the drug

Molecular size and shape, pKa, acidity/basicity, lipophilicity and steric and electronic characteristics of a drug influence in interaction with the active sites of enzyme and the metabolism to which it is subjected.