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**FACTORS THAT AFFECT DRUG METABOLISM**

The extent to wish a drug is metabolized by one individual can be dramatically different than that of another. Thus the effect a drug will have on one individual can be dramatically different from the effect it has on another, hence the need to discuss the factors that affect drug metabolism.

The factors affecting drugs metabolism can be grouped into;

1. Biological factors, which include;
* Age
* Diet
* Sex difference
* Species difference
* Strain difference
* Altered physiological factors
1. Chemical factors, which include;
* Enzyme induction
* Enzyme inhibition
* Environmental chemicals
1. Physicochemical properties of the drug

**BIOLOGICAL FACTORS**

1. AGE: the drug metabolic rate in the different age groups differs mainly due to variations in the enzyme content, enzyme activity and haemodynamics.
* In neonates (up to 2 months) and in infants (2 months to 2 years), the microsomal enzyme system is not fully developed. So, many drugs are metabolized slowly. For example, caffeine has a half-life of 4 days in neonates in comparison to 4 hours in adults.
* Children (between 1 year and 12 years) metabolize several drugs much more rapidly than adults as the rate of metabolism reaches a maximum somewhere between 6 months and 12 years. As a result they require large mg/kg dose in comparison to adults.
* In elderly persons, the liver size is reduced, the microsomal enzyme activity is decreased and hepatic blood flow also declines as a result of reduced cardiac output, all of which contributes to decreased metabolism of drugs. For example, chlomethazole shows a high bioavailability within the elderly, therefore they require a lower dose.
1. DIET: the enzyme content and activity is altered by a number of dietary components. Generally;
* Low protein diet decreases, and high protein diet increases the drug metabolizing ability as enzyme synthesis is promoted by protein diet and also raises the level of amino acids for conjugation with drugs.
* Fat free diet depresses cytochrome P-450 levels since phospholipids, which are important components of the microsomes become deficient.
* Grapefruit inhibits metabolism of many drugs and improve their oral bioavailability
* Dietary deficiency of vitamins (like vitamin A, B2, B3, C and E) and minerals (such as Fe, Ca, Mg, Zn) retard the metabolic activity of enzymes.
* Starvation results in decreased amount of glucuronides formed than under normal conditions.
1. SEX DIFFERENCE: since variation between male and female are observed following puberty. So, sex relayed differences in the rate of metabolism may be due to sex hormone. Such sex differences are widely studied in rats where male rats have greater drug metabolizing capacity. In humans, women metabolize benzodiazepines slowly than men. Several studies have shown that women on contraceptive pills metabolize a number of drugs at a slow rate.
2. SPECIES DIFFERENCE: species difference have been observed in both phase-1 and phase-2 reactions. In phase-1 reaction, both qualitative and quantitative variations in the enzyme and their activity have been observed. Qualitative differences among species generally result from the presence or absence of specific enzymes in those species. Quantitative differences result from variation in the amount and localization of enzymes, the amount of natural inhibitors, and the competition of enzymes for specific substrates.

Human liver contains less cytochrome P-450 per gram of tissue than do the livers of other species. For example, rat liver contains approximately 30 to 50nmol/g of cytochrome P-450, whereas human liver contains 10 to 20nmol/g. furthermore, human liver is 2 percent of body weight, whereas rat liver is approximately 4 percent.

Similarly, in man, amphetamine and ephedrine are predominantly metabolized by oxidative deamination, whereas in rats, aromatic oxidation is the major route in phase-2 reactions.

1. STRAIN DIFFERENCE

Just as the difference in drug metabolizing ability between different species is attributed to genetics, the differences are observed between strains of same species also. It may be studied under two headings:

* Pharmacogenetics: a study of inter-subject variations in metabolism may either be monogenetically or polygentically controlled. A polygenetic control is observed in twins. In identical twins (monozygotic), very little or no difference in metabolism of halothane, phenylbutazone, dicoumaral and antipyrine was detected but large variations were observed in a fraternal twins (dizygotic).
* Ethnic variations: differences in the metabolism of drug among different races are called ethnic variations. Such variations may be monomorphic or polymorphic. For example; approximately equal percent of slow and rapid acetylators are found among white and blacks whereas the slow acetylators dominate Japanese and Eskimo population.
1. ALTERED PHYSIOLOGICAL FACTORS
2. 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, placental growth hormones and prolactin. For example; the metabolism of promazine and pethidine is reduced during pregnancy.
3. Disease states: there are many disease states that affect the metabolism of drugs. Some of them are cirrhosis of liver, alcoholic liver disease, cholestatic jaundice, diabetes mellitus, acromegaly, malaria, various bacterial and viral infections etc. it can be seen that major effects are seen in the disease affecting liver as liver is quantitatively the important site for metabolism. The possible cause in the effect of metabolism due to diseases may be;
* Decreased enzyme activity in liver
* Altered hepatic blood flow
* Hypoalbuminaemia (leading to lower plasma binding of drugs).

For example; oxidation of vitamin D and hydrolysis of procaine are impaired in kidney diseases.

1. Hormonal imbalance: higher level of one hormone may inhibit the activity of few enzymes while inducing that of others. Adrenolectomy, thyroidectomy and alloxan-induced diabetes in animals showed impairment in the enzyme activity with subsequent fall in the rate of metabolism.

**CHEMICAL FACTORS**

1. ENZYME INDUCTION

The phenomenon of increased drug metabolizing ability of enzymes by several drugs and chemicals is known as enzyme induction and the agent which bring about such an effect are called enzyme inducers.

Mechanisms of enzyme induction;

* Increase in both liver size and liver blood flow
* Increase in both total and microsomal protein content
* Increased stability of enzymes
* Increased stability of cytochrome P-450
* Decreased degradation of cytochrome P-450
* Proliferation of smooth endoplasmic reticulum

Consequences of enzyme induction include;

* Decrease in pharmacological activity of drugs
* Increased activity where the metabolites are active
* Altered physiological status due to enhanced metabolism of endogenous compounds such as sex hormones.
1. ENZYME INHIBITION

A decrease in the drug metabolizing ability of an enzyme is called an enzyme inhibition. The process of inhibition may be direct or indirect.

* Direct inhibition: it may result from interaction at the enzymic site, the net outcome being a change in enzyme activity. Direct enzyme inhibition can occur by one of the following instruction;
* Competitive inhibition: occurs when structurally similar compounds compete for the same site on the enzyme.
* Non-competitive inhibition: occur when a structurally unrelated agent interacts with the enzyme and prevents the metabolism of drugs.
* Product inhibition: occurs when the metabolic product competes with the substrate for the same enzyme.
* Indirect inhibition: it is caused by one of the following mechanism;
* Repression: it may be due to fall in the rate of enzyme synthesis or rise in the rate of enzyme degradation.
* Altered physiology: it may be due to nutritional deficiency or hormonal imbalance.
1. ENVIRONMENTAL CHEMICALS

 Several environmental agents influence the drug metabolizing ability of enzymes. For example;

* halogenated pesticides such as DDT and polycyclic aromatic hydrocarbons contained in cigarette smoke have enzyme induction effect
* organophosphate insecticides and heavy metals such as mercury, nickel, cobalt and arsenic inhibit drug metabolizing ability of enzymes
* Other environmental factors that may influence drug metabolism are temperature, altitude, pressure, atmosphere etc.

**PHYSICOCHEMICAL PROPERTIES OF 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. However, such an interrelationship is not clearly understood.