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MEDICINE AND SURGERY

FACTORS AFFECTING DRUG METABOLISM

Factors affecting drug metabolism range from the species of organism to the environment in which that organism lives. The factors are split into internal/Biological (physiological and pathological) factors, Physicochemical properties of the drug and Chemical factors.

1. **INTERNAL (BIOLOGICAL FACTORS)**
* **SPECIES**: Species difference have been observed in both Phase-I and Phase-II reactions. In phase-I reactions, both qualitative and quantitative variations in the enzyme and their activity have been observed. Qualitative differences among species generally result from the presence of specific enzymes in those species. Quantitative differences result from variations 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 amphetamine and ephredrine are predominantly metabolized by oxidative deamination, whereas in rats, aromatic oxidation is the major route in Phase II reactions.

Similarly in pigs, the phenol is excreted mainly as glucoronide whereas its sulphate conjugate dominates in cells.

* **GENETIC(STRAIN):** this may be studied under two headings:
1. **Pharmacogenetics**: A study of inter-subject variability in drug response is called pharmacogenetics. The inter-subject variations in metabolism may either be monogenetically or polygenetically controlled. A polygenic 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 fraternal twins (dizygotic).

1. **Ethnic** **variations**: differences observed in the metabolism of drug among different races are called ethnic variations. Such variations may be monomorphic or polymorphic.

E.g approximately equal percent of slow and rapid acetylators are found among whites and blacks whereas the slow acetylators dominate Japanese and Eskimo population.

* **AGE**: The drug metabolic rate in the different age groups differs mainly due to variations in the enzyme content, enzyme activity and hemodynamics. In neonates (upto 2 months) and infants (2 months to 1 year), the microsomal enzyme system is not fully developed. So, many drugs are metabolized slowly.

E.g caffeine has a half-life of 4 days in neonate in comparison to 4hrs in adults.

Children (between 1 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.

* **SEX**: Since variations between male and female are observed following puberty. So, sex related differences in the rate of metabolism may be due to sex hormones. 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.
* **ALTERED PHYSIOLOGICAL FACTORS**
1. **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.

E.g In women, the metabolism of promazine and pethidine is reduced during pregnancy.

1. **Hormones**: 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 rate of metabolism. A similar effect was also observed in the pituitary growth hormone and stress related changes in ACTH levels.
2. **Disease**: There are many disease states that affect the metabolism of drugs. Some of them are cirrhosis of liver, alcoholic liver disease, cholestatic jaundice, acromegaly, Diabetes Miletus etc. It can be seen that major effects are seen in the disease affecting liver as liver is quantitatively the important site for metabolism.
* **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 an enzyme synthesis is promoted by protein diet and also raise the level of amino acids for conjugation with drugs.

Fat free diet depresses cytochrome P-450 levels since phospholipids, which are important components of microsomes become deficient.

Starvation results in decreased amount of glucoronides formed than under normal conditions.

1. **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 interrelationship is not clearly understood.

1. **CHEMICAL FACTORS**
* **ENZYME INDUCTION**: The phenomenon of increased drug metabolizing ability of enzymes by several drugs is called enzyme induction and the agents which bring such an effect is called enzyme inducers.

Mechanisms of enzyme induction:

1. Increase in both liver size and liver blood flow
2. Increase in both total and microsomal protein content
3. Increased stability of enzymes
4. Increased stability of cytochrome P-450
5. Decreased degradation of cytochrome P-450
6. Proliferation of smooth endoplasmic reticulum

Consequences of enzyme induction include:

1. Decrease in pharmacological activity of drugs
2. Increased activity where the metabolites are active
3. Altered physiological status due to enhanced metabolism of endogenous compounds such as sex hormones.
* **ENZYME INHIBITION**: A decrease in the drug metabolizing ability of an enzyme inhibition. The process of the inhibition may be direct or indirect

**Direct inhibition**: It may result from interaction at the enzyme site, the net outcome being a change in enzyme activity. Direct enzyme inhibition can occur by one of the following mechanisms:

1. **Competitive inhibition**- occurs when structurally similar compounds compete for the same site on an enzyme.
2. **Non-competitive inhibition**- this occurs when a structurally unrelated agent interacts with the enzyme and prevents the metabolism of drugs.
3. **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 mechanisms:

1. **Repression**- it may be due to a fall in the rate of enzyme synthesis or rise in the rate of enzyme degradation.
2. **Altered** **physiology**- it may be due to nutritional deficiency or hormonal inbalance
* **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.