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**FACTORS AFFECTING DRUG METABOLISM**

 Metabolism of a drug is the biotransformation or chemical alteration of the drug to other molecular species usually called metabolites, within the body via an enzymatic or non-enzymatic process.

There are various factors that affect drug metabolism in an individual, they include:

1. Chemical factors
2. Enzyme induction
3. Enzyme inhibition
4. Environmental chemical
5. Biological factors
6. Age
7. Diet
8. Sex difference
9. Strain difference
10. Species difference
11. Altered physiological factors
12. Physiochemical properties of the drug
13. **Chemical factors**
14. **Enzyme induction**:

This is the phenomenon of increased drug metabolizing ability of enzymes by several drugs and chemicals. The agents that bring about such effects 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:

* Decreased pharmacological activity of drugs
* Increased activity where the metabolites are active
* Altered physiological statues due to enhanced metabolism of endogenous compounds such as sex hormones.
1. **Enzyme inhibition**:

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

* Direct inhibition may result from interaction at the enzyme site which will result in change in enzyme activity, it may be by:
* Competitive inhibition
* Non-competitive inhibition
* Product inhibition
* Indirect inhibition is caused by one of the following mechanisms:
* Repression: fall in the rate of enzyme synthesis or rise in 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 such as:

* Halogenated pesticides and polycyclic aromatic hydrocarbons contained in cigarettes.
* Organophosphate insecticides and heavy metals such as mercury.
* Other environmental factors such as temperature, altitude, pressure atmosphere, etc.
1. **Biological factors**
2. **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 1 year), the microsomal enzyme system is not fully developed. So, many drugs are metabolized slowly, 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, chlomethiazole 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 or dietary

components. Generally low protein diet decreases and high protein

diet increases the drug metabolizing ability as enzyme synthesis

promoted by protein diet and also raises the level of amino acids for

conjugation with drugs.

1. **Sex difference**

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.

1. **Species difference**

 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 or absence 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.

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 variability in drug response is called pharmacogenetics. The inter-subject variations in metabolism may either be monogenetically or poly genetically controlled.
* **Ethnic variations**: Differences observed in the metabolism of drug among different races are called ethnic variations. Such variations may be monomorphic or polymorphic. Example: Approximately equal percent of slow and rapid acetylators are found among whites and blacks whereas the slow acetylators dominate Japanese and Eskimo population.
1. **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, placental growth hormones and prolactin. For example: in women, the metabolism of promazine and pethidine is reduced during pregnancy.
* **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.
* Hypo albuminaemia ( leading to lower plasma binding of drugs). For example: glycine conjugation of salicylates, oxidation of Vitamin D and hydrolysis of procaine are impaired in kidney diseases.
* Hormonal imbalance: higher level of one hormone may inhibit the activity of few enzymes while inducing that of others
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 an interrelationship is not clearly understood .

**Conclusion**

The therapeutic efficacy, toxicity and biological half-life of a drug greatly depend on the metabolism of the drug and a number of factors affect the metabolism of the drug. Hence various factors affecting drug metabolism must be considered during administration and also in proper dosing of any drug to the patients.