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ASSIGNMENT : DISCUSS IN DETAILS THE FACTORS AFFECTING DRUG METABOLISM

**INTRODUCTION**

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

The following are the importance of drug metabolism

* Inactivation: most drugs get inactive due to metabolism eg ibruprofen.
* Active metabolite from the active drug eg codeine- morphine
* Activation of inactive drugs eg levodopa- dopamine.

Two main categories of enzymes are required for drug metabolism, they are;

* Microsomal enzymes: located in smooth endoplasmic reticulum in liver, kidney, lungs and intestinall mucosa eg cytochrome p450
* Non microsomal enzymes: located in the cytoplasm and mitochondria of hepatic cells and plasma eg esterase, flavoprotein oxidase.

**Factors affecting drug metabolism**

There are a number of factors that affect the metabolic rate. Some of them are;

1) **chemical factor**

a. Enzyme induction

b. Enzyme inhibition

c. Environment chemicals

2) **biological factor**

a. Age

b. Diet

c. Sex difference

d. Strain difference

f. Altered physiological factors

3) **physiochemical properties of the drug**

**Chemical factors**

a. **Enzyme induction**

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

Mechanism of enzyme induction

* Increase in both liver size and liver flow
* Increase in both total and microsomal protein content
* Increased stability of enzymes
* Increased stability 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 mechanism of endogenous compounds such as sex hormones.

Some examples drug induction are

Oral contraceptive steroids$→$inactive, excreted

b. **Enzymes inhibition**

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

1) direct inhibition: it may result from interaction at the enzymatic site, the net income being a change in enzyme activity. Direct enzyme inhibition can occur by one of the following mechanisms:

- competitive inhibition :occurs when structurally similar compounds compete for the same site on an enzyme

-non competitive inhibition: occur when a structurally unrelated agents interacts with the enzyme and prevent the metabolism of drugs.

- product inhibition: occurs when the metabolic product compete with the substrate for the same enzyme.

2) indirect inhibition: it is caused by one of the following mechanism:

- repression: it may be due to fall in the rate of enzymes synthesis or rise in the rate of enzyme degration

- altered physiology: it may be to nutritional deficiency or hormonal imbalance.

c. **environment chemical**

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

* Halogenated pesticides such as DDT and polycytics aromatic hydrocarbons contained in cigratte smoke have enzymes induction effect.
* Organophosphate insecticides and heavy metals succ as mercury, nickel, cobalt and arsenic inhibit drug metabolizing ability of enzymes.
* Other environment factors that may influence drug metabolism are temperature, altitude, pressure, atmosphere.

**Biological factors**

a.**Age**

The drug metabolic rate in the different age group differs mainly due to variations in the enzyme content, enzyme activity and haemodynamics

* In neonates (up to 2 month) andin infants (2month and 1 year), the microsomal enzyme system is not fully developed. So, many drugs are metabolized slowly. For example: caffeine has a half life of 4days in neonates in comparison to 4hrs in adult
* Children (beween I year and 12 years) metabolise several drugs much more rapidly than adults as the te 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 enzymes activity is decreased and hepatic blood flow also declines as a result of the reduced cardiac output all of which contribute to decreased metabolism of drugs. For example, chlomethiazole shows a high bioavailiability within the elderly therefore they require a lower dose.

b.**Diet**

The enzyme content and activity is altered by a number of dietary components. Generally,

* Low protein diet decrease and high protein diet increases the drug metablolizing ability as enzymes synthesis is promoted by protein diet and also raises the level of amino acid for conjugation.
* Grape fruit inhibits metabolism of many drugs and improve their oral bioavailability .
* Starvation results in decreased amount of glucuronides formed than under normal conditions.

c. **Sex difference**

Since variation 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 bezodiazeoines slowly than men.

d. **species differences**

Species differences have been observed in both phase I and phase II reactions. In phase I reactions, both qualitative and quatitative variations in the enzymes and their activity has been observed. Qualitative differences among species generally result from the presence or absence of specific enzymes in those species. Qualitative differences result from variation in the amount and localization of enzymes, the amount of natural inhitors, and the competition of enzymes for specific substrate.human liver contains cytochrome p-450 per gram of tissue than do the liver of other species.

e. **Strain difference**

Just as the difference in drug metabolizing ability between different species is attributed to genetics, the difference 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 mongentically or polygenetically controlled.

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

f. **Altered physiological factors**

Pregnancy

Pregnancy is known to affect hepatic drug metabolism. Physiological chages during pregnancy are probably responsible for the reported alteration in drug metabolism. These include elevated concentration of various hormones lie estrogen , progesterone, placental growth hormone and prolactin. For example in women the metabolism of promazine and pethidine is reduced during pregnancy.

Disease state

 There are many disease states that affect the metabolism of drugs. Some of them are cirerhosis of liver, alcoholic liver disease, cholestatic jaundice, diabetes mellitus. 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 disease may be;

* Decreased enzyme activity in liver
* Altered hepatic blood flow
* Hypoalbuminaemia .

**Physiological properties of the drug**

 Molecular size and shape, pKa , acidity/basicity and electronic characteristics of drugs influence in interaction with the active site of enzymes and the metabolism to which it is subjected. However such an interrelationship is not clearly understood.