17/MHS06/049

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Bch 313: Medical biochemistry IV

MBBS 300 level.

**Assignment**

1.Discuss in details the factors affecting drug metabolism

Factors affecting drug metabolism include both the internal factors and the external factors which could also be pathological or psychological.

 The internal factors include:

1. Disease
2. Age
3. Sex
4. Specie difference
5. Hormones
6. Genetics (genetic variability).

a. *Disease*- there are many diseases that affect the metabolism of drugs. Some of which include alcohol liver disease, cirrhosis of the liver , jaundice, diabetes mellitus, malaria, acromegaly and various bacterial and viral diseases. It is sen that the major disease effects are seen in the liver and the liver is qualitatively the most important site for metabolism. Some of the possible causes in the effect Of metabolism due to diseases may be:

-altered hepatic flow

-decrease in some activity in the liver

-Hypoalbuminaemia (leading to lower plasma binding of the drugs).

b. *Age*- drug metabolism rate in different age groups are mainly due to variations in the enzyme content, enzyme activity, development of the enzyme system , haemodynamics and the development of systems in general.

 - In elderly persons there is a reduction in liver size, the microtonal 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.

 - Between the ages 6-12- metabolism of drugs occurs more rapidly as the rates of metabolism which is a maximum between six months and 12 years of age. They require large doses of drugs.

 - In infants: there development of systems especially the enzyme system drug metabolism is really slow.

 c. *Sex*- this is largely due to the difference of sex hormones present in both males and females. Such is observed in rats where it is seen that male rats metabolize drugs faster than female rats. In humans, it is said that women metabolize benzodiazepines slower than men. On average, men are larger than women. Body size differences results in larger distribution volumes and faster total clearance of most medications in men compared to women. Greater body fat in women (until older ages) may increase distribution volumes for lipophilic drugs in women. Total drug absorption does not appear to be significantly affected by sex although absorption rates may be slightly slower in women.

 d. *Specie difference*- both qualitative and quantitative variations in the enzyme and the activity contributes to the difference in drug metabolism in different species. Qualitative differences generally results from the presence or absence or specific enzymes in those species. Quantitative differences result from variations in the months and localization of enzymes in the amount of natural inhibitors is a competition of enzymes for substrates ( for specific substrates). The human liver contains less cytochrome p-450 per gram of tissue then do the liver of some other species.

 e. *Hormones*- The presence of some hormones either increase or decrease the rate of metabolism, that is to say, higher level of some hormones may inhibit the activity of some enzymes were inducing the activity of others. It’s typical example is seen in the pituitary growth hormone and stress related changes in ACTH levels ( adrenocorticotropin hormone)

F. *Genetics*- Due to the different genetic makeup of every human being, there is a rapidly expanding list of genetic variants that affect the function of drug metabolizing enzymes and lead to altered drug responses. With this, it is possible to see why on identical exposure, certain individuals tend to fall sick while some others do not. Genetic factors can account for 20 to 95 percent of patient variability and because of their genetic makeup, some people metabolize) drugs slowly. As a result, a drug may accumulate in the body, causing toxicity. Other people metabolize drugs so quickly that after they take a usual dose, drug levels in the blood never become high enough for the drug to be effective.

 **External factors**

1. Diet
2. Environment

*Diet-*Food could either increase or decrease the rate at which drug metabolism occurs. In humans, they can alter metabolism of drugs; the enzyme content, site and activity is altered by a number of dietary components. Generally

* Low protein diet decreases the drug metabolism while high protein diets increases drug metabolizing activity as enzyme synthesis is promoted by protein diet and also in addition, raises the amount of amino acids for conjugation with drugs.
* Dietary deficiencies of vitamins such as vitamin A, B2, B3, C, E and of minerals such as Fe, Ca, Mg, Zn retards the metabolic activity of enzymes.
* Fat free diet depresses cytochrome P-450 levels since phospholipids which are important components of microsomes become more deficient.
* Starvation results in decreased amount of glucuronides formed under normal conditions. .

*Environment*- Prior or simultaneous exposure to xenobiotics can cause enzyme inhibition and enzyme induction.

1. **Enzyme induction:**

Enzyme induction is a situation where prior exposure to certain environmental chemicals and drugs result in an enhance capability for bio transforming a xenobiotic. The prior exposure stimulates the body to increase the production of some enzymes. The increased level of enzyme activity results in increased biotransformation of a chemical that is subsequently absorbed and decreases the duration of drug action. The chemicals which bring about such an effect are called enzyme inducers.

Mechanism of drug induction are:

a) Increase in both liver size and liver blood flow.

b) Increase in both total and microsomal protein content.

c) Increased stability of enzymes

d) Increased stability of cytochrome p450

e) Decreased degradation of cytochrome p450.

Examples of enzyme inducers include: Alcohol, Isoniazid, Polycyclic halogenated aromatic hydrocarbons (for example, dioxin), Phenobarbital, Cigarette smoke

The most induced enzyme reactions involve the cytochrome P450 enzymes.

Inducing agents may increase the rate of their own metabolism as well as those of other unrelated drugs or foreign compounds. Concomitant administration of two or more drugs often may lead to serious drug interactions as a result of enzyme induction. For instance, a clinically critical drug interaction occurs with phenobarbital and warfarin. Induction of microsomal enzymes by phenobarbital increases the metabolism of warfarin and, consequently, markedly decreases the anticoagulant effect. Therefore, if a patient is receiving warfarin anticoagulant therapy and begins taking phenobarbital, careful attention must be paid to readjustment of the warfarin dose. Dosage readjustment is also needed if a patient receiving both warfarin and phenobarbital therapy suddenly stops taking the barbiturate.

1. **Enzyme Inhibition:**

Enzyme inhibition is a decrease in the drug metabolizing activity of an enzyme. In some situations, exposure to a substance will inhibit the biotransformation capacity for another chemical due to inhibition of specific enzymes. A major mechanism for the inhibition is competition between the two substances for the available oxidizing or conjugating enzymes. The presence of one substance uses up the enzyme needed to metabolize the second substance. Enzyme inhibition may be direct or indirect

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

1. Non-competitive inhibition: this situation when a structurally unrelated agent interacts

 with the enzyme and prevents metabolism of drugs.

Ii. Product inhibition: this situation occurs when the metabolic product competes with the substrate for the same enzyme.

Iii. Indirect inhibition: It is caused by one of the following mechanisms:

a.Repression: It may be due to fall in the rate of enzyme synthesis or rise in the rate of enzyme degradation.

b. Altered physiology: it may be due to nutritional deficiency or hormonal imbalance.

Iv. Competitive inhibition: Occurs when structurally similar compounds compete for the same site on an enzyme.