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BCH 30

Assignment

1). Discuss the factors that affect drug metabolism.

Definition:

Drug metabolism is the metabolic breakdown of drugs by living organisms usually through specialized enzymatic systems. It is the set of metabolic pathways that modify the chemical structure of xenobiotics; which are compounds foreign to an organism's normal biochemistry, such as a drug or poison.

These factors that affect the biotransformation pathways for the metabolism of xenobiotics can be grouped into 2;

a). Chemical factors.

b). Biological factors.

1. Chemical Factors

- Enzyme induction
- Enzyme inhibition
- Environmental chemicals

2. Biological Factors

- Age
- Sex difference
- Strain difference
- Altered physiological factors.

3. Physiochemical properties of the drug

1. Chemical Factors

a. **Enzyme induction**

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

Mechanism 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 states due to enhanced metabolism of endogenous compounds such as sex hormones

b. Enzyme inhibition

A decrease in drug metabolizing activity of an enzyme is known as enzyme inhibition. The process of inhibition may be direct or indirect.

Direct inhibition: it may result from interaction at the enzyme site, the net outcomebeing 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: occurs when a structurally unrelated agent interacts with the enzyme and prevent metabolism of drugs.

Product inhibition: when the metabolic product compete 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.

Note: Enzyme inhibition is more important clinically than enzyme induction especially for drugs with narrow therapeutic index. e.g anticoagulants, antiepileptics, hypoglycemias e.t.c

c. Environmental chemicals

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

Halogenated pesticides such as DDT and polypeptide aromatic hydrocarbons contained in cigarette smoke have enzyme induction effect.

Organophosphate insecticide 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.

2. Biological Factors

a. 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 (upto 2 months) and in infants (2 months to 1 year), the microsomal enzyme system is not fully developed. So, many drugs are metabolized slowly. For e.g caffeine has a half-life of 4 days in neonates in comparism to 4hrs 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 reduced, the microsomal enzyme activity is decreased and hepatic blood flow also declines as a result of reduced cardiac output, all which contributes to decreased metabolism of drugs. For example, chlomethiazoleshows a high bioavailability within the elderly, therefore they require a lower dosage

b.Sex difference

Since variations between male and female are observed following puberty. So, sex related difference in the rate of metabolism may be due to sex hormones. Such sex diffrence are widely studied in where male rats have greater drug metabolizing capacity. In humans, women on contraceptive pills metabolize a number of drugs at a slow rate.

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c.Strain difference

Just as the difference in drug metabolising 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 polygenetically 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 fraternal twins (dizygotic).

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

d.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.

Diseases states: There are many diseases states that affect the metabolism of drugs. Some of them are liver cirrhosis, alcoholic liver disease, chloestatic jaundice, diabetes mellitus acromegaly, malaria, various bacterial and viral infections e.t.c.the possible cause in the effect of metabolism due to diseases may be: decreased enzyme activity in the liver, altered hepatic flow, hypoalbuminaemia (leading to lower plasma binding of drugs.

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

3. Physicochemical properties of the drug

Molecular size and shape pKa, acidity/basicity, lipophilicity and steric and electronic characteristics of a drug influence the interaction with the active sites of enzyme activity and the metabolism to which it is subjected.