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300l, BCH Assignment

Discuss in details the factors affecting drug metabolism

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

Drug metabolismis the metabolic breakdown of drugs by living organism usually through specialized enzymatic system The primary site for drug metabolismis the liver and other sites are kidney, intestine, lungs and plasma.

Drug metabolismis divided into three phases.

In phase 1, enzymes such as cytochromeP450 oxidases introduce reactive or polar groups into Xenobiotics

In phase 2, these modified compounds are then conjugated to polar compound. These reactions are catalysed by transferase enzyme such as glutathioneS-transferases

In phases3, the conjugated Xenobiotices may be further processed before being recognized by efflux transporters and pumped out of the cells

Factors affecting Metabolism

A number of factors may influence the metabolic rate of drug. Some of them are;

1. **Chemical factors**

a) **Enzyme induction**

b) **Enzyme inhibition**

c) **Environmental chemicals**

2. **Biological factors**

a) **Age**

b) **Diet**

c) **Sex difference**

d) **Species difference**

e) **Strain difference**

f) **Altered physiological factors**

3. **Pysiochemical properties of drug**

Chemical factors

a) **Enzyme induction :** this phenomenon of increased drug metabolizing ability of enzyme by several drugs and chemical is called as enzyme induction and the agents which bring about such an effect are called enzyme inducers

Mechanismof enzyme induction

- Increase in both liver size and liver blood flow
- Increase in both total and microsomal protein content
- Increased stability of enzymes
- Increase stability of cytochrome P-450
- Decreased degradation of cytochrome P-450

b. Enzyme inhibition

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

i. Direct inhibition: it may result frominteraction at the enzymatic site,the netoutcome being a change in enzymatic activity. Direct enzyme inhibition can occur by one of the following mechanism

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

   ii. Non-competitive inhibition: occurs when a structurally unrelated agent interact with the enzyme and prevents the metabolismof drugs

   iii. Product inhibition: occurs when the metabolic product

competes with the substrate for the same enzyme

ii. Indirect inhibition: it is caused by one of the following mechanism

i. Repession: it may be due to fall in the rate of enzyme synthesis or rise in the ratte of enzyme degradation

ii. Altered Physiology: it may be due to nutritional deficiency or hormonal imbalance

c. Environmental chemicals

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

- ✓ Halogenated pesticide such as DDT and polycyclic aromatic hydrocarbons contained in cigarrete soke 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 metabolismare temperature,altitude, pressure, atmosphere etc

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 systemis not fully developed. So, many drugs are metabolized slowly. For 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 rapildly than adults as the rate of metabolismreaches a maximu somewhere between 6months 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

deciline as a result of reduced cardiac output, all of which contributes to decreased metabolismof drug. E.g. Chlomethiazole shows a high bioavailability with 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 increase the drug matabolizing ability as enzyme synthesis is promoted by protein diet and also raisis the level of aminoacid for conjugation of drugs
   - Fat free diet depresses cytochromeP-450 level since phospjolipids, which are important components of microsomes become deficient
   - Grapefruit inhibits metabolismof many drugs and improve their oral bioavailability
   - Dietary defiency of vitamin like Vitamin A,B_2, B_3, C and E, minerals such as Fe, Ca, Mg, Zn reatrd the metabolic activity of enzymes
   - Starvation results in decreased amount of glucuronides formed thsn under normal conditions

c. **Sex difference:** Since variation between male and female are observed following puberty. So, sex related difference in the rate of metablolismmay be due to sex hormones. In humans, women metabolize benzodiazepines slowly than men. Women on contraceptive pills metabolize a number of drugs at a slow rate

d. **Species difference:**Species difference have been observed in both Phase 1 and Phase 2 reactions.

   In phase1 reactions, both qualitative and quantitative variations in the enzyme and their activity have been observed. Qualitative differences among species generally result fromthe presence or absence of specific enzymes in those species. Quantitative difference result fromvariation in that amount and localization of enzyme the amount of natural inhibitors and the competition of enzymes for specific substrate

e. **Altered Physiological factors**

i. **Pregnancy:** Pregnancy is known to affect hepatic metabolism Ohysiological changes during pregnancy are probably responsible for the reported alteration of drug metabolism These include elevated concentration of various hormones such as estrogen, progesterone. For example in women, the metabolismof promazine and pethidine is reduced during pregnancy

ii. **Disease state**: There are many disease that affect the metabolismof drugs. Some of themare; cirrhosis of the liver, alcoholic liver disease, cholestatic jaundice, diabetic mellitus, acromegaly, malaria, various bacterial and viral infections etc. Most of these disease affect the liver as liver is quantitatively the major site for metabolism The possible cause in the effect of metabolismdue to disease may be

- Decreased enzyme activity in liver
- Altered hepatic blood flow
- Hypoalbuminaemia(leading to low blood binding of drugs)

iii. **Hormonal imbalance:** Higher level of one hormone may inhibit the activity of few enzymes while inducing that of others. Adrenoloectomy, thyroidectomy and alloxan-induced diabetes rate of metabolismreduces.

Physicochemical properties of the drug

Molecular size and shape, pKa, acidity/basicity, lipophilicity and steric and electronic characteristic of a drug influence in interaction with the active site of enzyme and the metabolismto which it is subjected to