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QUESTION: FACTORS AFFECTING DRUG METABOLISM.

ANSWER

Introduction:

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

Metabolism of a drug may lead to:

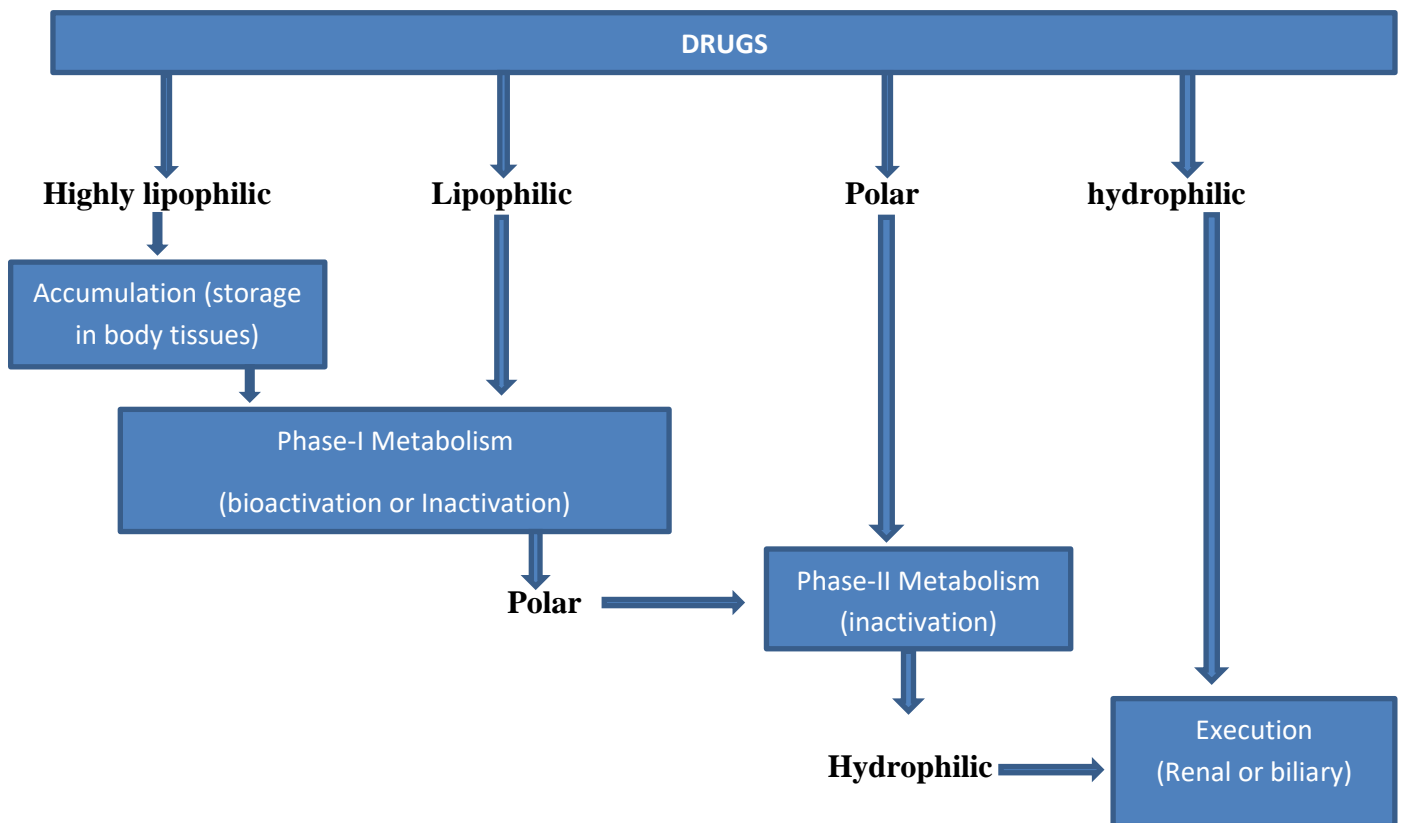
- Inactivation: most drugs get inactive due to metabolism e.g. paracetamol, ibuprofen.
- Active metabolite from an active drug: e.g. codeine – morphine, primidone – phenobarbitone.
- Activation of inactive drug: e.g. levodopa –dopamine.

Metabolic enzymes

For a drug to be metabolized, it requires various enzymes which can be broadly divided into two categories:

1. **Microsomal Enzymes:** this enzyme is located on smooth endoplasmic reticulum in liver, kidney, lungs and intestinal mucosa e.g. cytochrome p450, glucuronyl transferase, monooxygenase, etc. This type of enzyme catalyses oxidative, reductive, hydrolytic, and glucuronidation reactions.
2. **Nonmicrosomal Enzymes:** this enzyme is present in cytoplasm and mitochondria of hepatic cells and plasma e.g. esterase, amidase and conjugase. This enzyme catalyzes all conjugation, many hydrolytic reactions and some oxidation and reduction reactions.

Mechanism of metabolism



Factors Affecting Metabolism

Several factors may influence the metabolic rate of a drug. Some of them are:

1. Chemical factors

- Enzyme induction.
- Enzyme inhibition.
- Environmental chemicals.

2. Biological factors

- Age.
- Diet.
- Sex difference.
- Species 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 called as enzyme induction and the agents which bring about such an effect are called enzyme inducers

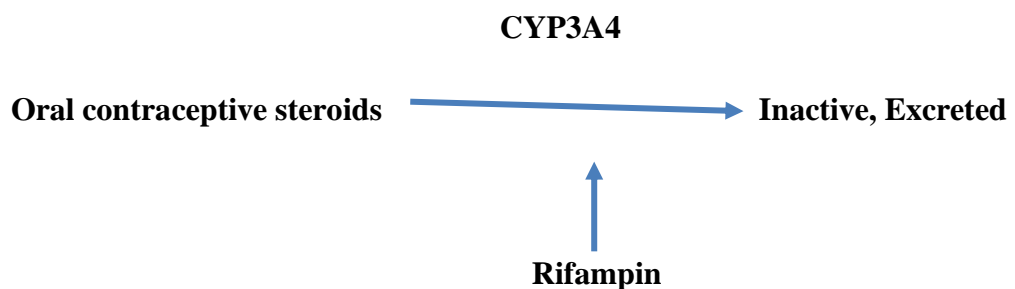
Mechanisms of enzyme induction:

- 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:

- Decrease in pharmacological activity of drugs.
- Increased activity where the metabolites are active.
- Altered physiological status due to enhanced metabolism of endogenous compounds such as sex hormones.

Some examples of drug induction are:

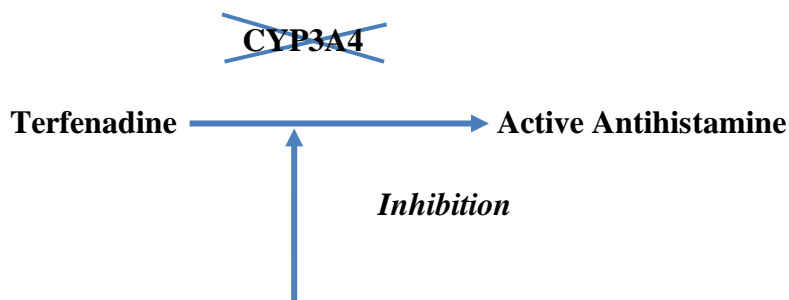


b) Enzyme inhibition

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

- 1) Direct inhibition: It may result from interaction at the enzyme site, the net outcome being a change in enzyme activity. Direct enzyme inhibition can occur by one of the following mechanisms:
 - i. Competitive inhibition: occurs when structurally similar compounds compete for the same site on an enzyme.
 - ii. Non-competitive inhibition: occur when a structurally unrelated agent interacts with the enzyme and prevents the metabolism of drugs.
 - iii. Product inhibition: occurs when the metabolic product competes with the substrate for the same enzyme.
- 2) Indirect inhibition: it is caused by one of the following mechanisms:
 - i. Repression: it may be due to fall in the rate of enzymes synthesis or rise in the rate of enzyme degradation.
 - ii. Altered physiology: it may be due to nutritional deficiency or hormonal imbalance.

Samples of enzyme inhibition are:



Erythromycin

Ketoconazole

Enzyme inhibition is more important clinically than enzyme induction especially for drugs with narrow therapeutic index.

E.g. anticoagulants, antiepileptics, hypoglycaemias, etc

c) Environmental chemicals

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

- Halogenated pesticides such as DDT and polycyclic aromatic hydrocarbons contained in cigarette smoke 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 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 (up to 2 months) and in infants (2 months to 1 year), the microsomal enzyme system is not yet 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 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, chlormethiazole shows a high bioavailability within the elderly, therefore they require a lower dose.

b. Diet

The enzyme content and activity are altered by several dietary components. Generally:

- Low protein diet decreases, and high protein diet increases the drug metabolizing ability as enzyme synthesis is promoted by protein diet and raises the level of amino acids for conjugation with drugs.

- Fat free diet depresses cytochrome P-450 levels since phospholipids, which are important components of microsomes become deficient.
- Grapefruit inhibits metabolism of many drugs and improve their oral bioavailability.
- Dietary deficiency of vitamins (like vitamin A, B2, B3, C and E) and minerals such as Fe, Ca, Mg, Zn retard the metabolic activity of enzymes.
- Starvation results in decreased number of glucuronides formed than under normal conditions.

c. 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 several drugs at a slow rate.

d. 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 number of natural inhibitors, and the competition of enzymes for specific substrates.

Human liver contains less cytochrome P-450 per gram of tissue than do livers of other species. For example, rat liver contains approximately 30 to 50 nmol/g of cytochrome P-450, whereas human liver contains 10 to 20 nmol/g. Furthermore, human liver is 2 percent body weight, whereas rat liver is approximately 4 percent.

Similarly, in men amphetamine and ephedrine are predominantly metabolized by oxidative deamination, whereas in rat's aromatic oxidation is the major route inn Phase-II reactions.

Similarly, in pigs, the phenol is excreted mainly as glucuronide whereas its sulphate conjugate dominates in cats.

e. 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, dicoumarol 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 ethnic variations. Such variations may be monomorphic or polymorphic. For example: Approximately equal percent of slow and rapid acetylators are found among whites and blacks whereas the slow acetylators dominate Japanese and Eskimo population.

f. 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. It was also confirmed by the study in animals. In pregnant Sprague-Dawley rats, hexobarbital biotransformation indicated unchanged or slightly elevated microsomal enzyme activity compared to normal rats.

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 has

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
- Hypalbuminaemia (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 disease.

Hormonal imbalance

Higher level of one hormone may inhibit the activity of few enzymes while inducing that of others. Adrenalectomy, thyroidectomy and alloxan-induced diabetes in animals showed impairment in the enzyme activity with subsequent fall in the rate of metabolism. A similar effect was also observed in the pituitary growth hormone and stress related changes in ACTH levels.

3. 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 depends 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.