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# 17/MHS01/168

# MEDICINE AND SURGERY

# BIOCHEMISTRY

Assignment

Discuss in details factors affecting drug metabolism.

Answer

Factors Affecting Drug Metabolism

 Drug metabolism is the metabolic breakdown of drugs. It can also be said to be the chemical alteration of a drug by the body. Various factors can affect when a drug metabolizes, how fast and how long it will last in the body. The factors affecting it are from outside the body (external) and within the body (internal).

 The internal factors are species, genetics, age, sex, hormones, pregnancy and diseases. They are discussed below.

1) Species: Species difference have been observed in both phase-I and phase-II reactions. In phase-I reactions, both qualitative and quantitative variations 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 the livers of other species. For example, rat liver contains approximately 30 to 50nmol/g of cytochrome P-450, whereas human liver contains approximately 10 to 20 nmol/g. furthermore, human liver is approximately 2% of body weight, whereas rat liver is approximately 4%.

2) Genetics: Genetic difference is the main cause of rate of drug metabolism. It may be grouped into two:

* Pharmogenetics: It is a study of inter-subject variability in drug response. The inter-subject variations in metabolism may either be monogenetically or polygenetically controlled. A polygenetic control is observed in twins. In identical twins, very little or no difference in metabolism of halothane, phenylbutazone, dicoumarol and antipyrine was detected but large variations were observed in fraternal twins.
* Ethnic variations: Differences observed in the metabolism of drug among different races are called ethnic variations. Such variations may be monomorphic or polymorphic. The difference in the rate of acetylation is one example: Rapid acetylators have more hepatic acetyl N-transferase than the slow acetylators.90% of Asians and Eskimos are rapid acetylators. Egyptians and Mediterranean are slow acetylators. The rate of acetylation is clinically important in terms of therapeutic response and toxicity.

3) Age: Drugs are metabolized more slowly in fetal, neonatal and elderly humans and animals than in adults. The drug metabolic rate in different age groups differ mainly due to variations in the enzyme content, enzyme activity and hemodynamics. In neonates and infants, the microsomal enzyme system is not fully developed. So, many drugs are metabolized slowly. For example, caffeine has a half-life of 4 days in neonates compared 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 compared 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, clomethiazoles show a high bioavaibility within the elderly, therefore require a lower dose.

4) Sex: 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 benzodiazepines slower than men. Several studies have shown that women on contraceptive pill metabolize a number of drugs at a slow rate.

5) Hormones: 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 adrenocorticotropic hormone levels.

6) Pregnancy: It 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 hormone and prolactin. For example; in women, the metabolism of promazine and pethidine is reduced during pregnancy.

7) Diseases: There are many disease states that affect the metabolism of drugs. Some of them are cirrhosis of liver, alcoholic liver disease, malaria, acromegaly, jaundice, diabetes mellitus various infections and others. It can be seen that major effects are seen in the disease affecting the liver as 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
* Hypoalbuminemia

 The external factors are environment and diet. They are discussed below.

1. Environment: Several environmental agents influence the drug metabolizing ability of enzymes. For example:
* Halogenated pesticides such as polycyclic aromatic hydrocarbons and dichlorodiphenyltrichloroethane (DDT) 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 and so on.

2) Diet: Enzyme content and activity is altered by a number of dietary components. Generally, low protein decreases and high protein diet increases the drug metabolizing ability as enzyme syntheses is promoted by protein diet and also 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 iron (Fe), calcium (Ca), magnesium (Mg) and zinc (Zn) retard the metabolic activity of enzymes. Starvation results in decreased number of glucuronides formed than under normal conditions.