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ASSIGNMENT

1. Discuss in details the factors affecting drug metabolism.

DRUG METABOLISM

Drug metabolism is the metabolic breakdown of drugs by living organisms, usually through specialized enzymatic systems. More generally, **xenobiotic metabolism** 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 any drug or poison. There are various factors which affect how drugs are metabolized in the body. They are divided into two main parts:

1. INTERNAL FACTORS

a. Gender or Sex

Sex differences in metabolism (phase I and II) are believed to be the major cause of differential pharmacokinetics between men and women. Many CYP450 enzymes (phase I metabolism) show a sex-dependent difference in activity. Most of the phase II enzymes have a higher activity in men than in women. Activities of these enzymes can also change during pregnancy and with the use of oral contraceptives.

b. Genetic (Strain)

Patient response to drugs varies widely and the reasons for this are diverse and complex. It is estimated that genetic factors account for 20 to 95 per cent of patient variability in response to individual drugs.

Genetic influences on drug metabolism interact with other factors, such as: age, gender, race/ethnicity, disease states, concomitant medicines and social factors, determining the outcome from treatment with any pharmacological agent.

The differences are observed between strains of same species, it may be studied under two headings;

- **Pharmacogenetics;** a study of inter-subject variability in drugs response is called pharmacogentics. 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 Ethnic Variations. Such variations may be monomorphic or polymorphic. Example; approximately equal percent of slow and rapid acetylators are found among whites and blacks whereas the slow acetylators dominate Japanese and Eskimo population.

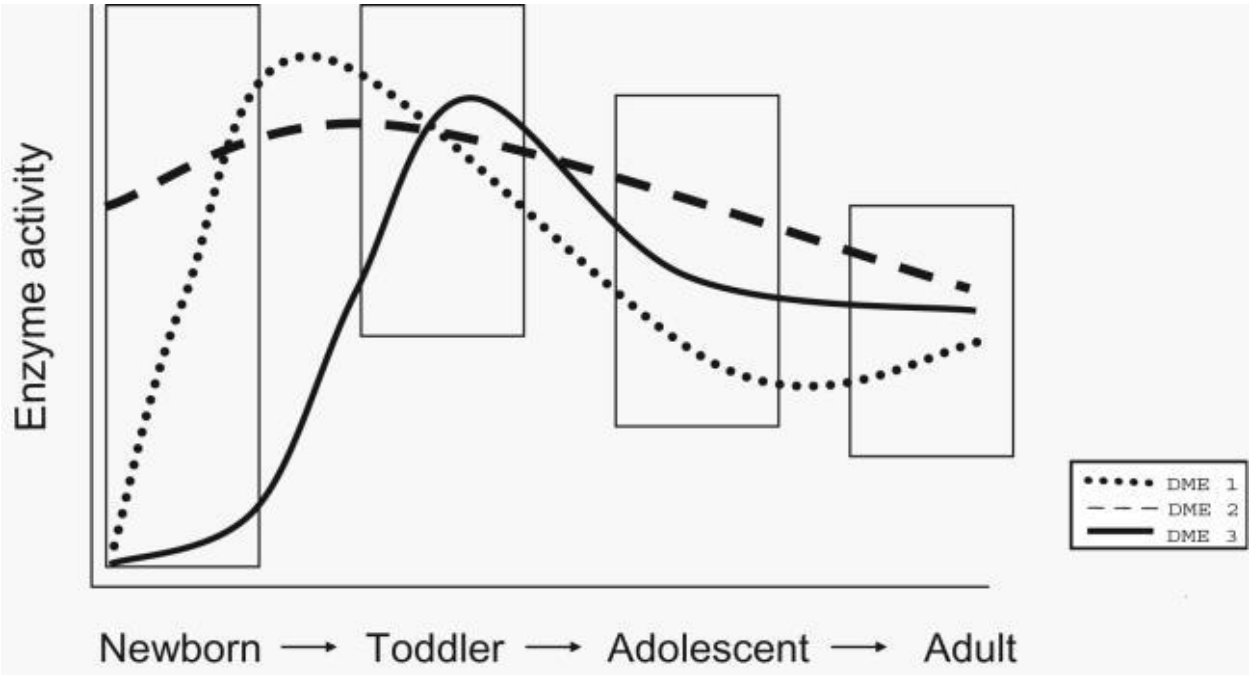
c. Age

Overall hepatic metabolism of many drugs through the cytochrome P-450 enzyme system decreases with age. For drugs with decreased hepatic metabolism, clearance typically decreases 30 to 40%. Theoretically, maintenance drug doses should be decreased by this percentage; however, rate of drug metabolism varies greatly from person to person, and dose adjustments should be individualized.

- In neonates (up to 2months) and infants (2months to 1yr), the microsomal enzyme system is not fully developed so many drugs metabolize slowly. For example, caffeine has a half life of 4days in neonates in comparison to 4hrs in adults.
- Children (1yr to 12yrs) metabolize several drugs much more rapidly than adults as the rate of metabolism reaches a maximum somewhere between 6months and 12yrs. As a result they require large mg/kg dose in comparison to adults.
- In elderly persons, the liver size is reduced, microsomal 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, chlomethiazole shows a high bioavailabity within the elderly, therefore they require a lower dose.

d. <u>Hormones</u>

Cytochrome P450 (CYP) is a group of enzymes that metabolize drugs to a more water-soluble form, rendering them available for renal excretion. The major site of CYP expression is the liver. Nearly 50% of all medications currently on the market are metabolized by the enzyme CYP3A4, while metabolism of another 35-40% occurs through enzymes CYP1A2, CYP2C19, CYP2D6, CYP3A5 CYP3A6, and CYP3A7. While the clinical significance of hormonal effects on the CYP system remains to be determined, we anticipate that such effects will be most pertinent to drugs with a narrow therapeutic range.



Developmental Profile for Drug Metabolic Enzymes

e. <u>Altered Physical Conditions</u>

- Pregnancy; affects hepatic drug metabolism and this may be due to the physiological changes during pregnancy. These include elevated concentration of various hormones such as estrogen, progesterone, placental growth hormones and prolactin.
- Disease State; some of these diseases are cirrhosis of liver, alcoholic liver disease, cholestatic jaundice. Other factors responsible for variation in drug metabolism are the endocrine disorders, such as

diabetes mellitus, hypo and hyperthyroidism, pituitary disorders and various types of infections (bacterial, viral, malaria).

2. EXTERNAL FACTORS

a. Environment

These are usually considered to be those influences in our surroundings that can affect drug metabolism. These environmental factors include a large number of environmental chemicals that potentially could affect drug biotransformation, usually grouped into heavy metals, industrial pollutants and pesticides.

The most important industrial pollutants are typically aromatic or aromatic polycyclic compound and poly chlorinated biphenyls and they have various effects like inductive enzyme effects, procarcinogenic effects, etc.

Pesticides are also of various types (insecticides, herbicides,) and are considered environmental contaminants in air, soil, water and food.

b. Diet

The enzyme content and activity is altered by a number of dietary components. Generally,

- Low protein diet decreases and high protein diet increases the drug metabolizing ability enzyme synthesis is promoted by protein diet and also raises the level of amino acids 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, B_2, B_3, C and E and minerals such as Fe, Ca, Mg, and Zn retard the metabolic activity of enzymes.

- Starvation results in decreased amount of glucoronides formed than normal conditions.