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MATRIC NUMBER: 17/MHS01/290

COURSE: BCH 313 ASSIGNMENT

QUESTION: Discuss in details the factors affecting drug metabolism.

**FACTORS AFFECTING DRUG METABOLISM**

Drug metabolism is affected by two main factors:

1. Internal factors and
2. External factors

1. Internal factors affecting drug metabolism include:

* Age: The drug metabolism rate in different age groups differs 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. E.g caffeine has a half life of 4 days in neonates in comparison to 4hrs in adults.

In children between 1 year and 12 years of age, they metabolize several drugs much more rapidly than adults as the rate of metabolism reaches maximum somewhere between 6 months and 12 years. As a result they require large mg/kg dose in comparison to adults.

In adults, the liver size is reduced, microsomal enzyme activity is decreased and hepatic blood flow also declines as a result of reduced cardiac output, all of which contributes to the decreased metabolism of drugs. For example, chlomethiazole shows a high bioavailability within the elderly therefore they require a lower dose.

* Sex difference: Since variations between male and female are observed following puberty, sex related differences 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 benzodiadipines slowly than men. Several studies have shown that women on contraceptive pils metabolize a number of drugs at a slow rate.
* Species difference: This has been observed in phase I and phase II reactions. In phase I reactions, both quantitative and qualitative 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 amount 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. Foe example, rat liver contains approximately 30 to 50 nmol/g of cytochrome P-450, whereas human liver contains approximately 10 to 20nmol/g. Furthermore, the human liver is 2 percent of body weight, whereas rat liver is approximately 4 percent.

Similarly in men, amphetamine and ephedrine are predominantly metabolized by oxidative deamination, whereas in rats aromatic oxidation is the major rote in phase II reactions. Similarly in pigs, the phenol is excreted mainly as glucuronide whereas is sulphate conjugate dominates in cats.

* Genetics or strain difference: Just as the difference in drug metabolizing ability between species is attributed to genetics, the differences are also observed between strains of same species also. It may be studied under two headings:

1. Pharmacogenetics: A study of inter-subject variability in drug response is called Pharmacogenetics. The inter-subject variations in metabolism may be either monogenetically or polygenetically controlled. A polygenic control is observed in twins. In identical twins (monozygotic),vey little or no difference in metabolism of halothane, phenylbutazone, dicoumaral and antipyrine was detected but large variations were observed in fraternal twins(dizygotic).
2. Ethical 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.

* 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 as liver is quantitatively the important site for metabolism. The possible cause in the effect of metabolism due to diseases may be:

1. Decreased enzyme activity in the liver
2. Altered hepatic blood flow
3. Hypoalbuminaemia(leading to lower plasma binding of dugs).

For example: Glycine conjugation of salicylates, oxidation if vitamin D and hydrolysis of procaine are impaired in kidney diseases.

* Hormones: High level of one hormone may inhibit the activity of few enzymes while inducing that of others. Adrenolectomy, 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.

2. External factors affecting drug metabolism include:

* Diet: The enzyme content and activity is altered by a number of dietary components. Generally,
* Low protein diet deceases and high protein diet increases the drug metabolizing ability as enzyme synthesizes 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 Fe, Ca, Mg, Zn) retard the metabolic activity of enzymes.
* Starvation results in decreased amount of glucuronides formed than under normal conditions.
* Environment: Several environmental agents influence the drug metabolizing ability of enzymes. For example:
* Halogenated pesticides such as DDT and polycyclic aromatic hydrocarbons contained in cigarettes 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.