FACTORS AFFECTING DRUG METABOLISM

In order to properly address this topic, the factors affecting drug metabolism will e split into internal and external factors.

Internal Factors include:

* Species
* Genetic
* Age
* Sex
* Hormones
* Disease

External Factors include:

* Diet
* Environment

INTERNAL FACTORS:

* SPECIES:

Species differences have been observed in both Phase 1 and Phase 2 reactions. In Phase 1 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 the 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 the livers of other species. For example, rat liver contains approximately 30 to 50 nmol/g of cytochrome P-450 whereas the human liver contains 10 to 20 nmol/g. Furthermore, human liver is 2percent of body weight, whereas rat liver is approximately 4 percent.

* GENETICS:

Just as the difference in drug metabolizing activity between different species is attributed to genetics, the differences are observed between strains of the 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 polygenetic ally controlled. A polygenetic control is observed in twins. In identical twins, very little or no difference in metabolism of halothane, phemylbutazone, dicomural 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 omonomorphic 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.

* AGE:

The drug metabolic rate in different age groups differs mainly due to variations in the enzyme content, enzyme activity and haemodynamics.

* In neonates and infants the microsomal enzyme system is not fully developed. So many drugs are metabolized slowly. 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 a large mg/kg dose in comparison to adults.
* In elderly persons, the liver size is reduced, the microsomal enzyme activity is reduced 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 bioavailability within the elderly, therefore they require a lower dose.
* SEX:

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 more slowly than men. Several studies have shown that women on contraceptive pills metabolize a number of drugs at a slow rate.

* HORMONES:

Higher level of thee hormone may inhibit the activity of a few enzymes while inducing that of others. Adrenolectomy, thyroidectomy and alloxan-induced diabtes in animals showed impairment in the enzyme activity with a 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.

* DISEASES:

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:

* Decreased enzyme activity in the liver
* Altered hepatic blood flow
* Hypoalbunimaemia

EXTERNAL FACTORS

* 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 as enzyme synthesis is promoted by protein diet and also raises the level of amino acids for conjugation with drugs.
* Fat free diet depresses cytochrome P-450 level since phospholipids, which are important components of microsomes become deficient.
* Grapefruit inhibits metabolism of many drugs and improve their oral bioavailability.
* Starvation results in decreased amount of glucoronides formed than under normal conditions.
* Dietary deficiency of vitamins like Vitamins A, B2, B3, C and E and minerals such as Fe, Ca, Mg, and Zn retard the metabolic activity of enzymes.
* ENVIROMENT:

Several environmental agents influence the drugs 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 include: temperature, altitude, pressure, atmosphere etc.