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Xenobiotics

Factors Affecting Drug Metabolism

Drugs can be metabolized by many different pathways and many factors can determine which pathway is used by which drug and to what extent a particular drug is bio transformed by a particular pathway. These factors range from the species of organism studied to the environment in which that organism lives.

The factors affecting drug metabolism will be split into internal (i.e. physiological and pathological) factors and external factors (i.e. diet and environment) . These are, of course, purely arbitrary divisions and much interaction exists between the various factors (cf. hormonal, sex and age influences).

- **internal**
    - species
    - genetic (strain)
    - age
    - sex
    - hormones
    - disease
- **external**
    - diet
    - environment

Internal Factors

1. 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 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 P450, whereas human liver contains 10 to 20 nmol/g. Furthermore, 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 route in Phase-II reactions. Similarly in pigs, the phenol is excreted mainly as glucuronide whereas its sulphate conjugate dominates in cats.

2. Strain difference

Just as the difference in drug metabolizing 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)[8] 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.

3. Age

The drug metabolic rate in the different age groups differs mainly due to variations in the enzyme content, enzyme activity and hemodynamics. In neonates (up to 2 months) and in infants (2 months to 1 year), the microsomal enzyme system is not fully developed. So, many drugs are metabolized slowly. For e.g. caffeine has a half-life of 4 days in neonates in comparison to 4 hrs. 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. Thus, the increased sensitivity of neonates may be related to their very low, undeveloped metabolizing capacity, until adult levels of enzyme activity are achieved. On the other hand, in the elderly, the decrease in drug-metabolizing capacity also appears to be dependent on these factors, important changes in the overall metabolism occurring with ageing.

4. 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 a number of drugs at a slow rate.

5. Hormones

known to play a major role in the general metabolism, have similarly been proven to control the biotransformation of drugs, in direct connection with other factors such as age, sex, or in particular physiological states, such as pregnancy. An example is the apparent connection between certain sex-specific drug- and steroid-metabolizing enzyme activities in rats and the sex dependent expression

of those specific enzymes, under gonadal steroid and growth hormone control. 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.

6. 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. In cirrhosis for example, replacement of parts of the liver by fibrous tissue leads to a reduction in the number of functional hepatocytes. In this situation, it seems absolutely reasonable that drug metabolism should be impaired. It is known for example that human cytochromes P450, particularly the CYP2A6 isoform, catalyze the bioactivation of various drugs and even carcinogens. The possible cause in the effect of metabolism due to diseases may be:

- Decreased enzyme activity in liver
- Altered hepatic blood flow
- Hypoalbuminemia (leading to lower plasma binding of drugs).

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 level

External Factors

1. 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 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.

2. Environmental Factors

These are usually considered to be those influences in our surroundings that can affect (sometimes markedly) drug metabolism. Of course, there are a large number of environmental chemicals that potentially could affect drug bio transformations, usually grouped into heavy metals, industrial pollutants and pesticides

Others include

i. 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.

ii. Chemical factors

a) Enzyme induction
b) Enzyme inhibition
c) Environmental chemicals

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: Oral Contraceptive Steroids CYP3A4 Inactive, Excreted Induction 3 Rifampin etc.

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 enzymic 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 mechanism: i. Repression: it may be due to fall in the rate of enzyme synthesis or rise in the rate of enzyme degradation. ii. Altered physiology: it may be due to nutritional deficiency or hormonal imbalance. Some examples of enzyme inhibition are: CYP3A4 Active Antihistamine Terfenadine Inhibition Erythromycin Ketoconazole etc. Enzyme inhibition is more important

clinically than enzyme induction esp. for drugs with narrow therapeutic index. E.g. anticoagulants, antiepileptics, hypoglycemia, etc.

c. Environmental chemicals: Several environmental agents 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.