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**QUESTION 1**

**Explain in details the factors affecting drug metabolism**

**Internal Factors:**

* **species**
* **genetic (strain)**
* **age**
* **sex**
* **hormones**
* **disease**

**External Factors:**

* **diet**
* **environment**

**AGE**

As age increases, the functions of tissues and organs in the body gradually decline. Due to this decline in organ function, drug absorption, distribution, metabolism and excretion (ADME processes) in elderly people are worse than those of young people. Furthermore, drug sensitivity is different in the elderly, who are prone to have adverse reactions to drugs. Thus, it is very important to design drugs according to the characteristics of the elderly.

**Drug absorption**

Drug dissolution is effected by the aging of the gastrointestinal mucosa in the elderly and the decrease of gastric acid secretion (25% - 20% reduction). However, due to the weakening of gastrointestinal movement in the elderly and slow gastric emptying rate, drugs stay longer in the gastrointestinal tract, which is conducive to greater drug absorption. The combination of these negative and positive factors usually results in normal drug absorption rate.

**Drug distribution**

Due to a decrease in the amount of plasma proteins, an increase of fat percentage and decrease of lean tissues (skeletal muscle, liver, brain, kidney, etc.), when the same dose of drug is used in elderly and young people, it has a high level of free state and greater functionality in the elderly. The elderly are therefore more prone to toxic reactions.

**Drug metabolism**

There were no abnormal changes in liver function indexes in the elderly, but the activity of drug metabolism enzyme in the liver is decreased so that the half-life of the drug is prolonged. Also, the age associated reduction of parenchymal cells in the liver and a reduction of liver blood flow affects the ability of the liver to metabolise drugs.  These factors further compound the drug scavenging capacity of the elderly, causing drug effect enhancement and more adverse reactions.

**Drug excretion**

The kidney is the main organ involved in drug excretion; therefore the pharmacokinetics of aging induced change mainly results from reduced kidney functionality. It is the most important factor in producing toxic drug reactions in the elderly.

**SPECIES**

The metabolism of many drugs and foreign compounds is often species dependent. Different animal species may biotransform a particular xenobiotic by similar or markedly different metabolic pathways. Even within the same species, individual variations (strain differences) may result in significant differences in a specific metabolic pathway. This is a problem when a new drug is under development. A new drug application requires the developer to account for the product as it moves from the site of administration to final elimination from the body. It is difficult enough to find appropriate animal models for a disease. It is even harder to find animal models that mimic human drug metabolism.

Species variation has been observed in many oxidative biotransformation reactions. For example, metabolism of amphetamine occurs by two main pathways: oxidative deamination or aromatic hydroxylation. In human, rabbit, and guinea pig, oxidative deamination appears to be the predominant pathway; in the rat, aromatic hydroxylation appears to be the more important route.495 Phenytoin is another drug that shows marked species differences in metabolism. In the human, phenytoin undergoes aromatic oxidation to yield primarily GS)(-)-p-hydroxyphenytoin; in the dog, oxidation occurs to give mainly (R)(+)-m-hydroxyphenytoin.There is a dramatic difference not only in the position (i.e., meta or para) of aromatic hydroxylation but also in which of the two phenyl rings (at C-5 of phenytoin) undergoes aromatic oxidation.

Species differences in many conjugation reactions also have been observed. Often, these differences are caused by the presence or absence of transferase enzymes involved in the conjugative process. For example, cats lack glu-curonyltransferase enzymes and, therefore, tend to conjugate phenolic xenobiotics by sulfation instead. In pigs, the situation is reversed: pigs are not able to conjugate phenols with sulfate (because of lack of sulfotransferase enzymes) but appear to have good glucuronidation capability. The conjugation of aromatic acids with amino acids (e.g., glycine, glutamine) depends on the animal species as well as on the substrate.

**GENETICS**

Just as the difference in drug metabolising 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-suject 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)[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.

**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 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 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.

**DISEASE**

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 liver • Altered hepatic blood flow • Hypoalbuminaemia (leading to lower plasma binding of drugs). [2] For example: glycine conjugation of salicylates, oxidation of Vitamin D and hydrolysis of procaine are impaired in kidney diseases.

**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 raise 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 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.