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ASSIGNMENT

Discuss in details the factors having drug metabolism.

ANSWER

FACTORS AFFECTING DRUG METABOLISM

The factors affecting drug metabolism are divided into:

1) Internal Factors
2) External Factors

INTERNAL FACTORS

The internal factors are species difference, genetic (strain) difference, genetic variation, sex, age, pregnancy, disease.

- **Specie Differences:**

Species differences occur in both phase I and phase II metabolism and can be either quantitative (same metabolic route but differing rates) or qualitative (differing metabolic routes). Qualitative differences among specie generally results from the presence or absence of specific enzymes in those species. Quantitative differences result from variation in the amount and localization of enzymes, the number of natural inhibitors and the competition of enzymes for specific substrates.

Species variation has been observed in many oxidative biotransformation reactions. For example.

a) 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.
b) Phenytoin is another drug that shows marked species differences in metabolism. In the human, phenytoin undergoes aromatic oxidation to yield primarily GS)(-)-p-hydroxy phenytoin; in the dog, oxidation occurs to give mainly (R)(+)-m-hydroxy phenytoin. 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.
c) 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 glucuronyltransferase 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 sulphate (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. For example, glycine conjugation is a common conjugation pathway for benzoic acid in many animals. In certain birds (e.g., duck, goose, turkey), however, glycine is replaced by the amino acid ornithine. Phenylacetic acid is a substrate for both glycine and glutamine conjugation in humans and other primates. However, nonprimates such as rabbit and rat, excrete phenylacetic acid only as the glycine conjugate. The metabolism of the urinary antiseptic, phenazopyridine (Pyridium) depends strongly on the animal. The diazo linkage remains intact in over half of the metabolites in humans, whereas 40% of the metabolites in the guinea pig result from its cleavage. The metabolic product pattern in human or guinea pig does not correlate with that of either rat or mouse.

- **Strain Difference:**

There are differences observed between the strains of the same species. These differences apparently are caused by genetic variations in the amount of metabolizing enzyme present among the different strains. Strain differences in drug metabolism exist, particularly in inbred mice and rabbits. For example, in vitro studies indicate that cottontail rabbit liver microsomes metabolize hexobarbital about 10 times faster than New Zealand rabbit liver microsomes.

- **Genetic Variability:**

Genetic variability in bio transforming capability accounts for most of the large variation among humans. Marked individual differences in the metabolism of several drugs exist in humans. For example, human genetic differences influence the Phase II acetylation reaction. Some persons have rapid acetylation ("rapid acetylator") while others have a slow ability to carry out this reaction ("slow acetylator"). The most serious drug-related toxicity occurs in those who have slow acetylators, often referred to as "slow metabolizers." With slow acetylators, acetylation is so slow that blood or tissue levels of certain drugs (or Phase I metabolites) exceed their toxic threshold. Genetic factors also appear to influence the rate of oxidation of drugs such as phenytoin, phenylbutazone, dicumarol, and nortriptyline.

- **Sex Difference:**

The rate of metabolism of xenobiotics also varies according to gender in some animal species. This is usually limited to hormone-related differences in the oxidizing cytochrome P-450 enzymes.

In humans, variations between male and female are usually observed after puberty so sex related differences in the rate of metabolism may be due to sex hormones. Also, women on contraceptive pills metabolize a lot of drugs slower. Nicotine and aspirin also seem to be metabolized differently in women and men.

A marked difference is observed between female and male rats. Adult male rats metabolize several foreign compounds at a much faster rate than female rats (e.g., N-demethylation of aminopyrine, hexobarbital oxidation, glucuronidation of o-aminophenol). Apparently, this sex difference also depends on the substrate, because some xenobiotics are metabolized at the same rate in both female and male rats. Differences in microsomal oxidation are under the control of sex hormones, particularly androgens; the anabolic action of androgens seems to increase metabolism.

- **Age:**

The metabolic rate in different age groups differ mainly due to variations in the enzyme content, enzyme activity and haemodynamic.

In Fetal metabolism, placenta transfer of xenobiotics is possible. However, both phase I and particularly phase II pathways are poorly developed in fetus. Thus, toxicity of phase I metabolites may be in several folds.

In neonates and infants, the drug metabolizing system is not fully developed so many drugs are metabolized slowly. This can lead to accumulation of drug/toxic intermediates and operation of an alternate pathway due to lack of major metabolizing enzyme operating in adults. For example, the oxidative (CYP) metabolism of tolbutamide appears to be markedly lower in new-borns. Compared with the half-life of 8 hours in adults, the plasma half-life of tolbutamide in infants is more than 40 hours. Infants possess poor glucuronidation ability because of a deficiency in glucuronyltransferase activity. The inability of infants to conjugate chloramphenicol with glucuronic acid appears to be responsible for the accumulation of toxic levels of this antibiotic, resulting in the so-called gray baby syndrome. Similarly, neonatal hyperbilirubinemia (or kernicterus) results from the inability of new-born babies to glucuronidate bilirubin.

Children metabolize several drugs more rapidly than adults as the rate of metabolism reaches a maximum between 6 months and 12 years. As a result, they require larger mg/kg doses in comparison to adults. By early adulthood the enzyme activities have essentially stabilized.

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 reduced drug metabolism.

- **Pregnancy:**

Pregnancy is known to affect drug metabolism. Physiological changes occurring during pregnancy are responsible for the reported alteration in drug metabolism. This include elevation concentration of some hormones such as oestrogen, progesterone, placental grown hormone and prolactin. There is also reduced GI motility and gastric emptying. For example, during pregnancy, the metabolism of promazine and pethidine is reduced.

- **Disease:**

Disease of the liver and kidney affect the metabolism and excretion of some drugs. Some of this disease include cirrhosis of the liver, alcoholic liver disease, hepatic carcinoma. Other diseases include diabetes mellitus, acromegaly, malaria. Major effects are seen in the diseases affecting the liver because the liver is the organ for metabolism. The possible cause in the effect may be:

a) Decreased enzyme activity in liver.
b) Altered hepatic blood flow.
c) Hypalbuminaemia.

For example, glycine conjugates of salicylates, oxidation of vitamin D and hydrolysis of procaine are impaired in kidney diseases.

EXTERNAL FACTORS

The external factors are diet and environment.

- **Diet(nutrition):**

Nutrition can affect the body's response to drugs; conversely, drugs can affect the body's nutrition. Foods can enhance, delay, or decrease drug absorption. Foods impair absorption of many antibiotics. They can alter metabolism of drugs. For example, high-protein diets can accelerate metabolism of certain drugs by stimulating cytochrome P-450. Eating grapefruit can inhibit cytochrome P-450 34A, slowing metabolism of some drugs (eg, amiodarone, carbamazepine, cyclosporine, certain Ca channel blockers). Diets that alter the bacterial flora may markedly affect the overall metabolism of certain drugs. Some foods affect the body's response to drugs. For example, tyramine, a component of cheese and a potent vasoconstrictor, can cause hypertensive crisis in some patients who take monoamine oxidase inhibitors and eat cheese.

Nutritional deficiencies can affect drug absorption and metabolism. Severe energy and protein deficiencies reduce enzyme tissue concentrations and may impair the response to drugs by reducing absorption or protein binding and causing liver dysfunction. Changes in the GI tract can impair absorption and affect the response to a drug. Deficiency of Ca, Mg, or zinc may impair drug metabolism. Vitamin C deficiency decreases activity of drug-metabolizing enzymes, especially in the elderly.

- **Environment:**

Prior or simultaneous exposure to xenobiotics can cause enzyme inhibition and enzyme induction.

a) Enzyme induction:

Enzyme induction is a situation where prior exposure to certain environmental chemicals and drugs result in an enhance capability for bio transforming a xenobiotic. The prior exposure stimulates the body to increase the production of some enzymes. The increased level of enzyme activity results in increased biotransformation of a chemical that is

subsequently absorbed and decreases the duration of drug action. The chemicals which bring about such an effect are called enzyme inducers.

Mechanism of drug induction are:

a) Increase in both liver size and liver blood flow.

b) Increase in both total and microsomal protein content.

c) Increased stability of enzymes

d) Increased stability of cytochrome p450

e) Decreased degradation of cytochrome p450.

Examples of enzyme inducers include: Alcohol, Isoniazid, Polycyclic halogenated aromatic hydrocarbons (for example, dioxin), Phenobarbital, Cigarette smoke

The most induced enzyme reactions involve the cytochrome P450 enzymes.

Inducing agents may increase the rate of their own metabolism as well as those of other unrelated drugs or foreign compounds. Concomitant administration of two or more drugs often may lead to serious drug interactions as a result of enzyme induction. For instance, a clinically critical drug interaction occurs with phenobarbital and warfarin. Induction of microsomal enzymes by phenobarbital increases the metabolism of warfarin and, consequently, markedly decreases the anticoagulant effect. Therefore, if a patient is receiving warfarin anticoagulant therapy and begins taking phenobarbital, careful attention must be paid to readjustment of the warfarin dose. Dosage readjustment is also needed if a patient receiving both warfarin and phenobarbital therapy suddenly stops taking the barbiturate. The ineffectiveness of oral contraceptives in women on concurrent phenobarbital or rifampin therapy has been attributed to the enhanced metabolism of oestrogens (e.g., 17a-ethinylestradiol) caused by phenobarbital513 and rifampin514 induction.

b) Enzyme Inhibition:

Enzyme inhibition is a decrease in the drug metabolizing activity of an enzyme. In some situations, exposure to a substance will inhibit the biotransformation capacity for another chemical due to inhibition of specific enzymes. A major mechanism for the inhibition is competition between the two substances for the available oxidizing or conjugating enzymes. The presence of one substance uses up the enzyme needed to metabolize the second substance. Enzyme inhibition may be direct or indirect

Direct Inhibition: It may result from interaction at the enzymatic site, the net outcome being a change in enzyme activity. Direct enzyme inhibition can occur by one of the following mechanisms:

a) Competitive inhibition: Occurs when structurally similar compounds compete for the same site on an enzyme.

b) Non-competitive inhibition: Occurs when a structurally unrelated agent interacts with the enzyme and prevents metabolism of drugs.

c) Product inhibition: Occurs when the metabolic product competes with the substrate for the same enzyme.

Indirect inhibition: It is caused by one of the following mechanisms:

a) Repression: It may be due to fall in the rate of enzyme synthesis or rise in the rate of enzyme degradation.

b) Altered physiology: it may be due to nutritional deficiency or hormonal imbalance.

Dose level: Dose level can affect the nature of the biotransformation. In certain situations, the biotransformation may be quite different at high doses compared to low dose levels. This difference in biotransformation contributes to a dose threshold for toxicity. The existence of different biotransformation pathways can usually explain what causes this dose-related difference in biotransformation. At low doses, a xenobiotic may follow a biotransformation pathway that detoxifies the substance. However, if the amount of xenobiotic exceeds the specific enzyme capacity, the biotransformation pathway is saturated. In that case, it is possible that the level of parent toxin builds up. In other cases, the xenobiotic may enter a different biotransformation pathway that may end up producing a toxic metabolite.

An example of a dose-related difference in biotransformation occurs with acetaminophen (Tylenol®). At normal doses:

-About 96% of acetaminophen is bio transformed to non-toxic metabolites by sulphate and glucuronide conjugation.

-About 4% of the acetaminophen oxidizes to a toxic metabolite. That toxic metabolite is conjugated with glutathione and excreted.

At 7-10 times the recommended therapeutic level:

-The sulphate and glucuronide conjugation pathways become saturated and more of the toxic metabolite is formed.

-The glutathione in the liver may also be depleted so that the toxic metabolite is not detoxified and eliminated. It can react with liver proteins and cause fatal liver damage.