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BCH 313

QUESTION: DISCUSS IN DETAILS THE FACTORS AFFECTING DRUG METABOLISM.

Drugs can be metabolised by many different pathways and many factors can determine which pathway is used by which drug and to what extent a particular drug is biotransformed 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 is split into internal (i.e. physiological and pathological) factors and external factors (i.e. diet and environment)

The internal factors include:

- Disease
- Age
- Sex
- Specie
- Hormones
- Genetics

Disease

diseases of the liver and kidney affect the metabolism of some drugs for example, cirrhosis of the liver, hepatic carcinoma, alcohol liver disease other diseases include diabetes mellitus, malaria, acromegaly. The diseases affecting the liver cause major effects because it is the organ for metabolism, some of the possible causes in the effect may be:

- altered hepatic blood flow
- decreased enzyme activity in the liver
- Hypoalbuminaemia

Age

Drug metabolism rate in different age groups differ due to variations in the enzyme content, enzyme activity and haemodynamics.

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. 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 people there is a reduction in liver size, 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.

Sex

The rate of metabolism of xenobiotic 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, and glucuronidation of o-aminophenol). Apparently, this sex difference also depends on the substrate, because some xenobiotic 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.

Species

The capability to bio transform specific chemicals varies by species. These differences are termed selective toxicity, which refers to differences in toxicity between species similarly exposed. Research uses what is known about selective toxicity to develop chemicals that are effective but relatively safe in humans. For example, the pesticide Malathion in mammals is biotransformed by hydrolysis to relatively safe metabolites, but in insects, it is oxidized to malaoxon, which is lethal to insects.

Hormones

The presence of some hormones either increase or decrease the rate of metabolism that is to say higher level of some hormones may inhibit the activity of enzymes as well as inducing the activity of others. Its typical example is seen in the pituitary growth hormone and stress related changes in ACTH levels (adrenocorticotropic hormone). For example, during pregnancy, the metabolism of promazine and pethidine is reduced this is because In pregnancy physiological changes like increase in hormones like oestrogen, Progesterone, prolactin and placental growth hormone cause change in drug metabolism.

Genetics

Due to the different genetic makeup of every human being, there is a rapidly expanding list of genetic variants that affect the function of drug metabolizing enzymes and lead to altered drug responses. With this, it is possible to see why on identical exposure; certain individuals tend to fall sick while others do not.

Genetic factors can account for 20-95% of patient variability and because of their genetic makeup, some people metabolize drugs slowly and as a result a drug may accumulate in the body, causing toxicity whereas other people metabolize drugs so quickly that after they take a usual dose, drug levels in the blood never become high enough for the drug to be effective.

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

The external factors include

- Diet
- Environment

Diet

Poor nutrition can have a detrimental effect on biotransforming ability. Poor nutrition relates to inadequate levels of protein, vitamins, and essential minerals. These deficiencies can decrease a person's ability to synthesize biotransforming enzymes. Many diseases can impair an individual's capacity to biotransforming enzymes. For example, hepatitis (a liver disease) is well known to reduce hepatic biotransformation to less than half of its normal capacity.

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.

Mechanisms of drug induction are:

- 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 p450
- 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

- Competitive inhibition: Occurs when structurally similar compounds compete for the same site on an enzyme.
- Non-competitive inhibition: Occurs when a structurally unrelated agent interacts with the enzyme and prevents metabolism of drugs.
- 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:

- Repression: It may be due to fall in the rate of enzyme synthesis or rise in the rate of enzyme degradation.
- Altered physiology: it may be due to nutritional deficiency or hormonal imbalance.