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MATRIC NUMBER: 17/MHS01/244

DEPARTMENT: MEDICINE & SURGERY

COURSE CODE: BCH 313(MEDICAL BIOCHEMISTRY IV)

ASSIGNMENT TITLE: XENOBIOTICS

Discuss in details the factors affecting drug metabolism.

Answers

Drugs and xenobiotics often are metabolized by many different pathways and many factors can determine which pathway is used by which drugs & to what extent a particular drug is biotransformed by a particular pathway. These factors range from the specie of organism studied to the environment in which the organism lives.

The factors affecting drug metabolism are divided into *internal factors* and *external factors*.

Internal factors:

- **Age Differences:** Age-related differences in drug metabolism are generally quite apparent in the newborn. In most fetal & newborn animals, underdeveloped or deficient oxidative and conjugative enzymes are chiefly responsible for the reduced metabolic capability seen. In general, the ability to carry out metabolic reactions increases rapidly after birth and approaches adult levels in about 1 to 2 months. The effect of old age on drug metabolism hasn't been as well studied. There is some evidence in animals and humans that drug metabolism diminishes with old age. Much of the evidence, however is based on prolonged plasma half-lives of drugs that are metabolized totally or mainly by hepatic microsomal enzymes(e.g. phenobarbital and acetaminophen). In evaluating the effect of age on drug metabolism, one must differentiate between "normal" loss of enzymatic activity with aging and the effect of a diseased liver from hepatitis, cirrhosis,etc., plus decreased renal function, because much of the water-soluble conjugation products are excreted in the liver.

An illustration of the influence of age on drug metabolism is seen in the duration of action (sleep time) of hexobarbital in newborn and adult mice. When given a dose of 10mg/kg of body weight, the newborn mouse sleeps for mor than 6 hours. In the adult mouse however, it sleeps for fewer than 5 minutes when given the same dose.

- **Species and Strain differences:** 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 with the same species, individual variations (strain differences) may result in significant differences in a specific metabolic pathway. Species variation has been observed in many oxidative biotransformation reactions. For example, metabolism of amphetamine occurs in 2 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 most important route. 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 aren't able to conjugate phenols with sulfate (because of lack of sulfotransferase enzymes) but appear to have good glucuronidation capability.
- **Genetics:** Marked individual differences in the metabolism of several drugs exist in humans. Many of these genetic or hereditary factors are responsible for the large differences seen in the rate of metabolism of these drugs. Genetic factors also appear to influence the rate of oxidation of drugs such as phenytoin, phenylbutazone, dicumarol and nortriptyline. The rate of oxidation of these drugs varies widely among different individuals; however, these differences don't appear to be distributed bimodally, as in acetylation. In general, individuals who tend to oxidize one drug rapidly are also likely to oxidize other drugs rapidly. Numerous studies in twins (identical & fraternal) and in families indicate that oxidation of these drugs is under genetic control.

Many patients state that they do not respond to codeine and codeine analogs. It is now realized that their CYP2D6 isozyme does not readily O-demethylate codeine to form morphine. This genetic polymorphism is seen in about 8% of Caucasians, 4% of African Americans, and less than 1% of Asians.

- **Sex:** The rate of metabolism of xenobiotics also varies according to gender in some animal species. 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). 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. Sex differences in drug metabolism appear to be species dependent. Rabbits and mice, for example, do not show a significant sex difference in drug metabolism. In humans, there have been a few reports of sex

differences in metabolism. For instance, nicotine and aspirin seem to be metabolized differently in women and men. On the other hand, gender differences can become significant in terms of drug-drug interactions based on the drugs' metabolism. For women, the focus is on drugs used for contraception.

- **Enzyme Induction:** The activity of hepatic microsomal enzymes, such as the CYP mixed function oxidase system, can be increased markedly by exposure to diverse drugs, pesticides, polycyclic aromatic hydrocarbons, and environmental xenobiotics. The process by which the activity of these drug-metabolizing enzymes is increased is termed **enzyme induction**. The increased activity is apparently caused by an increased amount of newly synthesized enzyme. Enzyme induction often increases the rate of drug metabolism and decreases the duration of drug action.

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.

External Factors

1. **Diet:** Metabolic food-drug interactions occur when the consumption of a particular food modulates the activity of a drug-metabolizing enzyme system, resulting in an alteration of pharmacokinetics of drugs metabolized by that system. A number of these interactions have been reported. Foods that contain complex mixtures of phytochemicals, such as fruits, vegetables, herbs, spices and teas, have the greatest potential to induce or inhibit the activity of drug-metabolizing enzymes, although dietary macro constituents (i.e. total protein, fat and carbohydrate ratios, and total energy intake) can also have effects. Particularly large interactions may result from the consumption of herbal dietary supplements. Cytochrome P450 appears to be especially sensitive to dietary effects, as demonstrated by reports of potentially clinically important interactions involving orally administered drugs that are substrates of this enzyme. For example, interactions of grapefruit juice with cyclosporine and felodipine, St John's wort with cyclosporine and indinavir, and red wine with cyclosporin, have the potential to require dosage adjustment to maintain drug concentrations within their therapeutic windows. The susceptibility of CYP3A4 to modulation by food constituents may be related to its high level of expression in

the intestine, as well as its broad substrate specificity. Reported ethnic differences in the activity of this enzyme may be partly due to dietary factors. Food-drug interactions involving CYP1A2, CYP2E1, glucuronosyltransferases and glutathione S-transferases have also been documented, although most of these interactions are modest in magnitude and clinically relevant only for drugs that have a narrow therapeutic range. Recently, interactions involving drug transporters, including P-glycoprotein and the organic anion transporting polypeptide, have also been identified.

2. **Environment:**

- **Smoking:** Cigarette smoking induces the activity of cytochrome P450 (CYP) 1A2 (via chemicals in cigarette smoke such as polycyclic aromatic hydrocarbons) and also CYP2B6. These enzymes metabolize several clinically important drugs (such as antidepressants and antipsychotics) and a number of procarcinogens (such as those in cigarettes). CYP1A2 activity is significantly higher in heavy smokers (more than 20 cigarettes per day) than in nonsmokers. This is likely to be clinically relevant for some drugs which have a narrow therapeutic index and are metabolized by CYP1A2, such as clozapine. The induction varies depending on the bioavailability of the components of cigarette smoke and the extent of inhalation. It is not known how the number of cigarettes smoked daily or inter-individual variation affects CYP1A2 induction, but heavier smokers appear to have a greater increase in the clearance of drugs. This enzyme induction is rapidly reversed when patients abruptly stop smoking, with a new steady state of CYP1A2 activity reached after approximately 1 week. This reduction in enzyme activity reduces clearance and increases the risk of adverse drug reactions for patients taking drugs metabolized by CYP1A2.
- **Alcohol:** Acute intake of ethanol inhibits the metabolism of many drugs but long term intake of ethanol at a high level (greater than 200g of pure ethanol per day) can induce liver enzymes to metabolize drugs more efficiently. At the present time there are no accurate means, with the possible exception of liver biopsy, to clinically predict the capacity of an alcoholic to metabolize drugs. Several drugs can inhibit the metabolism of ethanol at the level of alcohol dehydrogenase. Individual predisposition determines the severity of this drug-ethanol interaction.