Okoye Nwabufo Chukwuekezie

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Medicine and Surgery

BCH 313: Medical Biochemistry

Assignment

**Discuss in detail the 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 biotransformed by a particular pathway. The relative amount of any particular metabolite is determined by the concentration and activity of the enzymes responsible for the biotransformation as well as dose, frequency, route of administration, tissue distribution and protein binding of the drug. The rate of metabolism of a drug is particularly important for its pharmacological action as well as its toxicity. For example, if the rate of metabolism of a drug is decreased, this generally increases the intensity and duration of the drug action. In addition, decreased metabolic elimination may lead to accumulation of toxic levels of the drug. Conversely, an increased rate of metabolism decreases the intensity and duration of action as well as the drug's efficacy. These factors range from the species of organism studied to the environment in which that organism lives. Factors affecting drug metabolism can be split into internal (i.e. physiological and pathological) factors and external factors. These are, of course, purely arbitrary divisions and much interaction exists between the various factors (cf. hormonal, sex and age influences)

**Age**

Newborns and infants metabolize drugs relatively efficiently but at a rate generally slower than adults. Age-related differences in drug metabolism are generally quite apparent in the newborn. In most fetal and newborn animals, undeveloped 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. An illustration of the influence of age on drug metabolism is seen in the duration of action (sleep time) of hexobarbital in new-born and adult mice. When given a dose of 10 mg/kg of body weight, the new-born mouse sleeps more than 6 hours. In contrast, the adult mouse sleeps for fewer than 5 minutes when given the same dose.

In humans, oxidative and conjugative (e.g., glucuronida-tion) capabilities of newborns are also low compared with those of 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. As discussed previously, infants possess poor glucuronidating 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 hyperbilirubin-emia (or kernicterus) results from the inability of newborn babies to glucuronidate bilirubin.

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, chlomethiazole shows a high bioavailability within the elderly, therefore they require a lower dose. There is some evidence in animals and humans that drug metabolism diminish 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., antipyrine, phenobarbital, 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. There is a strong correlation between age and renal clearance: for example, the renal excretion rate of an 80-year-old is about 50% of that of a 30-year-old. This is why patient age is an important factor to consider when prescribing drugs.

**Gender**

Responsiveness to certain drugs is different for men and women. 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, 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.

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 drug's metabolism. For women, the focus is on drugs used for contraception. Note that the antibiotic rifampin, a CYP3A4 inducer, can shorten the half-life of oral contraceptives. In humans, women metabolize benzodiazepines slowly than men.

**Genetic predisposition**

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 do not 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 and 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 now is 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. (Genetic polymorphism with CYP isozymes) There is limited evidence of polymorphism involving MAO-A and MAO-B. The chemical imbalances seen with some mental diseases may be the cause.

Prior administration of the drug or co administration of other drugs also affect the bio transformation of drugs

**Diet**

The enzyme content and activity is altered by a number of dietary components. Low protein diet decreases and high protein diet increases the drug metabolizing ability as enzyme synthesis is promoted by protein diet and also raiss 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.

**Hormonal Effects**

The CYP system is a constellation of enzymes responsible for most of the phase I reactions in drug metabolism. These enzymes are expressed mainly in the liver; however, they can be found in other tissues, including the kidneys, skin, intestine, lung, and brain. By definition, all proteins that contain CYP domains are enzymes. Theoretically, assorted endocrine or inflammatory conditions resulting in the oversecretion or under-secretion of a particular hormone/neuropeptide/cytokine could have potent effects on drug metabolism. Heretofore, such effects have been attributed to hormonal influences on: a) gastrointestinal drug absorption rates, b) drug binding protein systems, c) drug distribution volume, d) blood flow dynamics in drug target organs, e) renal or hepatic drugexcretion systems, or f) drug effector systems per se (e.g., the expression of receptor systems in which a drug interferes with ligand binding). The effects of endocrine or inflammatory conditions on pharmacokinetics are significant and complex, yet they remain rather poorly studied.

CYP3A4 is the predominant constitutive CYP system in the human liver. Substrates for the enzymes are both endogenous (e.g. steroids, fatty acids, eicosanoids, and retinoids) and exogenous (e.g. drugs, chemicals, and plant products). The CYP1, CYP2, and CYP3 families, particularly their members CYP1A2, CYP2C8, CYP2C18, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, CYP3A6, and CYP3A7 are responsible for the metabolism of more than 80% of the most commonly prescribed drugs. Disease or state of health; liver disease- cirrhosis, alcoholic liver disease, jaundice, carcinoma. The liver is the major location of drug metabolizing enzymes. Dysfunction can lead to impaired drug metabolism-decreased enzyme activity. Cardiac failure causes decreased blood now to the liver.

**Species variation**

How fast or how slow a certain species metabolizes will vary amongst organisms of different species, because the fetid make up will not be the same. One species may contain high levels of the enzyme that can metabolize a particular drug whereby another may not contain the required enzyme at all. The metabolism of many drugs and foreign compounds is often species dependent. 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. 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 deamina-tion 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. 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.496 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 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 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. 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.498 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.

**Enzyme induction**

This is the process by which exposure to certain substrates (drugs, environmental pollutants) results in accelerated bio transformation with a corresponding reduction in unmetabolized drug. 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. 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 estrogens (e.g., 17a-ethinylestradiol) caused by phenobarbital513 and rifampin514 induction.

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

**Strain differences**

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

**Pregnancy**

Pregnancy is known to affect hepatic drug metabolism. Physiological changes during pregnancy are probably responsible for the reported alteration in drug metabolism. These include elevated concentrations of various hormones such as estrogen, progesterone, placental growth hormones and prolactin. 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. Despite the generally inhibitory actions of estrogenic compounds on the CYP systems discussed above, several human studies have shown that pregnancy has minimal effects on CYP2C19 and CYP3A4 but does induce an increase in CYP2D6 levels. CYP3A1 is the major component of the CYP system in the rat placenta. Women with intrahepatic cholestasis during pregnancy exhibited significantly decreased placental P450-dependent oxygenases and P450-aromatase; these decreases might be associated with risks to the well-being of the fetus.