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Assignment Question

1. Discuss in details the factors affecting drug metabolism

Answers

1. Introduction:

Metabolism is a biotransformation or chemical alteration of a drug to other molecular species usually called the metabolites, within the body via an enzymatic or non-enzymatic processes. The primary site for drug metabolism is liver and other sites are kidney, intestine, lungs and plasma.

Metabolism of a drug may lead to:

* Inactivation: most drugs get inactive due to metabolism e.g ibuprofen, paracetamol.
* Active metabolite from an active drug: eg codeine – morphine, primidone-phenobarbitone.
* Activation of inactive drug: eg levodopa- dopamine, prednisone- prednisolone

Metabolic Enzymes:

For a drug to be metabolized, it is requires various enzymes which can be broadly divided into two categories:

* Microsomal enzymes: this enzyme is located on smooth endoplasmic reticulum in liver, kidney, lungs and intestinal mucosa eg cytochrome p450, monooxygenase, glucurunyl transferase etc. This type of enzyme catalyse oxidative, reductive, hydrolytic and glucuronidation reactions.
* Nonmicrosomal enzymes: this enzyme is present in cytoplasm and mitochondria of hepatic cells and plasma. Eg flavoprotein oxidase, esterase, amidase and conjugase. This enzymes catalyzes all conjugations, many hydrolytic reactions, and some oxidation and reduction reaction.

Drugs

Highly lipophilic Lipophilic Polar Hydrophilic

Accumulation

(Storage in body tissues)

Phase-1 Metabolism

(Bioactivation or Inactivation)

Polar

Phase-II Metabolism

(Inactivation)

Excretion

(Renal or biliary)

Hydrophilic

Factors Affecting Drug Metabolism

Drugs and xenobiotics often are metabolized by several different phase I and phase II pathways to give several metabolites. The relative amount of any particular metabolite is determined by the concentration and activity of the enzyme(s) responsible for the biotransformation. 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. Many factors may affect drug metabolism, and they are discussed in the following sections. These include age, species and strain, genetic or hereditary factors, sex, enzyme induction, and enzyme inhibition.

* Age Differences

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 newborn and adult mice.489 When given a dose of 10 mg/kg of body weight, the newborn 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 newborns.490 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.

The effect of old age on drug metabolism has not 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., antipyrine, 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](https://www.pharmacologicalsciences.us/hepatitis.html), [cirrhosis](https://www.pharmacologicalsciences.us/cirrhosis.html), etc., plus decreased renal function, because much of the water-soluble conjugation products are excreted in the liver.

* 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 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.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.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](https://www.pharmacologicalsciences.us/cats.html) 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. For example, [glycine conjugation](https://www.pharmacologicalsciences.us/pharmaceutical-chemistry/info-xub.html) 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](https://www.pharmacologicalsciences.us/pharmaceutical-chemistry/info-xub.html) 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 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.501 Interindividual differences in drug metabolism in humans are considered in the section that follows.

* Hereditary or Genetic Factors

Marked individual differences in the metabolism of several drugs exist in humans. Many of these genetic or heredi tary factors are responsible for the large differences seen in the rate of metabolism of these drugs. The frequently cited example of the biotransformation of the antituberculosis agent isoniazid is discussed previously under acylation. 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.503

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.504 Genetic polymorphism with CYP isozymes is well documented as evidenced by the many examples in this chapter. There is limited evidence of polymorphism involving MAO-A and MAO-B.

* Sex Differences

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](https://www.pharmacologicalsciences.us/increase-metabolism.html).

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](https://www.pharmacologicalsciences.us/nicotine.html) 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](https://www.pharmacologicalsciences.us/drug-interactions.html) based on the drug's metabolism. For women, the focus is on drugs used for contraception. Note in Table 3.4 that the antibiotic rifampin, a CYP3A4 inducer, can shorten the half-life of oral contraceptives.

* 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. 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.

Conclusion

The therapeutic efficacy, toxicity and biological half-life of a drug greatly depends on the metabolism of the drug and a number of factors affect the metabolism of the drug. Hence various factors affecting drug metabolism must be considered during administration and also in proper dosing of any drug to the patients.