XENOBIOTICS ASSIGNMENT

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QUESTION

Discuss in details the factors affecting drug metabolism

Introduction

Most drugs undergo chemical alteration by various bodily systems as a way to create compounds that are more easily excreted from the body. These chemical alterations occur primarily in the liver and are known as biotransformations. Understanding these alterations in chemical activity is crucial in utilizing the optimal pharmacological intervention.

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.

These factors range from the species of organism and the environment in which such organisms live.

Factors affecting drug metabolism are split into internal factors (i.e physiological and pathological) and external factors (i.e diet and environment).

Internal Factors

Specie:

The metabolism of many drugs and foreign compounds is often species dependent.

Different animal species may biotransform a particular xenobiotic or drug by similar or markedly different metabolic pathways. Sometimes even, within same species, individual variations (strain differences) may result in significant differences in a specific metabolic pathway.

Species have qualitative differences generally as a result of either the presence or absence of specific enzymes or enzymes in those species.

Qualitative differences also result from variations in the amount and localization of enzymes, the amount of natural inhibitors, and the competition of enzymes for specific substrates.

Human liver contains less cytochrome P-450 per gram of tissue than do the livers of other species.

For example, rat liver contains approximately 30-50 mmol/g of cytochrome P-450, whereas human liver contains 10-20 mmol/g.

Furthermore, human liver is 2 percent of body weight, whereas rat liver is approximately 4 percent.

Similarly, in men, amphetamine and ephedrine are predominantly metabolized by oxidative deamination, whereas in rats aromatic oxidation is the major route in phase-II reactions. Also in pigs, phenol is excreted mainly as glucuronide whereas its sulphate conjugate dominates in cats.

Also, species variation has been observed in many oxidative biotransformation reactions. For example, metabolism of amphetamine occurs by two main pathways: oxidative deamination or aromatic hydroxylation. In humans (rabbits and guinea pigs also), oxidative deamination is said to be the predominant pathway; in the rat, aromatic hydroxylation is said to be the more important route.

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 influence the rate of oxidation of drugs, hence, the rate of oxidation of drugs varies widely among different individuals. However, the differences are not distributed bimodally, as in acetylation.

Generally, individuals who oxidize one drug rapidly are also likely to oxidize other drugs rapidly.

This difference in drug metabolism may either be monogenetically or polygenetically controlled (as observed in twins).

In identical twins (monozygotic), very little or no difference in metabolism of halothane, phenylbutazone, dicoumaral and antipyrine was detected but large variations were observed in fraternal (dizygotic) twins.

Differences could also be observed in the metabolism of drug among different races. This is referred to as ethnic variations. Such variations may be monomorphic or polymorphic. For example, approximately equal percent of slow and rapid acetylators are found among whites and blacks whereas the slow acetylators dominate Japanese and Eskimo population.

Hormone:

Higher level of one hormone may inhibit the activity of few enzymes while inducing that of others.

For example, adrenolectomy, thyroidectomy and alloxan-induced diabetis in animals usually show impairment in the enzyme activity with subsequent fall in the rate of metabolism.

A similar effect is also usually observed with regards to pituitary growth

hormone and stress related changes in adrenocorticotropic hormone (ACTH) levels.

Sex:

The rate of metabolism of drugs also varies according to gender in some animal species.

Variations between male and female are observed following puberty. This also applies to drug metabolism.

Sex related differences in the rate of metabolism may be due to sex hormones.

For example, male rats have greater drug metabolizing activity. Also in humans, women metabolize benzodiazepines slowly than men and also, women on contraceptive pills metabolize a number of drugs at a slow rate. Also, nicotine and aspirin are metabolized differently in women and men.

This sex difference also depends on the substrate, because some drugs are metabolized at the same rate in both male and female.

Differences in microsomal oxidation are under the control of sex hormones, particularly androgens. The anabolic action of androgens increases metabolism.

Pregnancy

Pregnancy, with increasing evidence, is said to alter the function of drug-metabolizing enzymes and drug transporters in a gestational-stage and tissue specific manner.

Pregnancy is associated with many physiologic changes that can influence drug absorption, distribution, metabolism, and excretion, such as increase in gastric pH and reduction in intestinal motility, increased cardiac output, increased glomerular filtration rate, and reduced plasma albumin concentrations, hence, activities of all key drug-metabolizing P450 enzymes change during pregnancy.

Also contributing to how pregnancy affects hepatic drug metabolism is elevated concentration of various hormones such as estrogen, progesterone, placental growth hormone and prolactin owing to complex inter-relationships between multiple regulators of drug metabolism and transport genes.

Age:

The drug metabolic rate in the different age groups differs mainly due to variations in the enzyme content, enzyme activity and haemodynamics.

Age-related differences in drug metabolism are generally quite apparent in the new born which is usually due to undeveloped or deficient oxidative and conjugative enzymes. 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 ault mice. 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 also, oxidative and conjugative (e.g. glucuronidation) capabilities ot newborns are low compared with those of adults.

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 hyperbilirubinaemia (kernicterus) results from the inability of newborn babies to glucuronidate bilirubin.

In neonates (up to 2 months), and in infants (2 months to 1 year), the microsomal enzyme system is not fully developed, therefore many drugs are metabolized slowly. For example, caffeine has a half-life of four (4) days in neonates in comparison to 4 hours in adults.

Children (between 1 year and 12 years) metabolize several drugs much

more rapidly than adults as the rate of metabolism reaches a maximum between 6 months and 12 years, hence, they require large mg/kg dose in comparison to adults.

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.

Disease:

There are many diseases that affect the metabolism of drug.

As liver is quantitatively the important site for drug metabolism, major effects are seen in diseases that affect the liver.

The effect on metabolism due to disease is due to:

i. Decreased enzyme activity in the liver

ii. Altered hepatic blood flow

iii. Hypoalbuminaemia (leading to lower plasma binding of drugs).

External Factors

Diet:

Enzyme content and activity is altered largely by a number of dietary components.

Generally:

i. Low protein diet decreases and high protein diet increases the drug metabolizing ability as enzyme synthesis is promoted by protein diet and also raise the level of amino acids for conjugation with drugs.

ii. Fat free diet depresses cytochrome P-450 levels since

phospholipids, which are important components of microsomes become deficient.

iii. Grapefruit inhibits metabolism of many drugs and improve their oral bioavailability

iv. 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.

v. Starvation results in decreased amount of glucuronides formed than under normal conditions.

Environmental Factor:

Various kinds of environmental factors alter drug metabolism by having direct effect on the activity of cytochrome P-450 enzymes in liver microsomes.

The effects will depend on the relative importance of excretory and metabolic machanisms in the elimination of the drug, the relative importance of various metabolic reactions in different tissues, extraction ratio of drug by the liver and the route of administration of the drug.

Environmental factors may not only alter relative activities of the cytochrome P-450 alone, but can also alter the activities of other drug metabolizing enzyme.

Also, the relative effect of environmental factors on enzymes involved in drug metabolism differ depending on the animal species or strain.

Several environmental agents influence the drug metabolizing ability of enzymes. Examples include:

i. Halogenated pesticides such as Dichlorodiphenyltrichloroethane (DDT) and polycyclic aromatic hydrocarbons contained in cigarette smoke have enzyme induction effect.

ii. Organophosphate insecticides and heavy metals such as mercury, nickel, cobalt and arsenic inhibit drug metabolizing ability of enzymes.

Other environmental factors that influence drug metabolism are temperature, altitude, pressure, atmosphere etc.