MATRIC NO: 17/MHS01/302

DEPT.: MBBS

COURSE TITTLE: BIOCHEMISTRY 3

QUESTION

Discuss in details the factors affecting drug metabolism.

ANSWER

INTERNAL FACTORS

1. **SEX DIFFERENCE:** cytochrome P450 (CYP) 3A4 activity is higher in women than in men, whereas the activity of many other systems involved in drug metabolism may be higher in men than in women. Women and men also show different pharmacodynamic responses to a variety of drugs. While the clinical significance of these sex differences remains to be determined, we anticipate that they will be most important in the administration of drugs that have a narrow therapeutic range. In addition, sex differences in drug metabolism may be involved in the higher incidence of adverse reactions to drugs in women compared with men. Further research is needed to determine the scope and significance of these sex differences. Female-specific issues such as pregnancy, menopause, oral contraceptive use and menstruation may also have profound effects on drug metabolism. These effects can often be clinically important. Pregnancy may increase the elimination of antiepileptic agents, reducing their efficacy. Oral contraceptive use can interfere with the metabolism of many drugs and, conversely, certain drugs can impair contraceptive efficacy.

2. **SPECIES:** difference in species has been observed in both phase 1 and phase 2 reactions. In phase 1 reactions, both qualitative and quantitative variations in enzyme and their activity has been observed. Qualitative differences among species generally results from the presence of absence of specific enzymes in those species. Quantitative differences results from variation 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 P450 per gram of tissue than do the liver of other species. For example, rat liver contains approximately 30 – 50 nmol/g of cytochrome P450, whereas human liver contains 10 – 20 nmol/g. Furthermore, human liver is 2% of the body's weight, whereas rat liver is approximately 4%. Similarly in men, amphetamine and ephedrine are predominantly metabolized by oxidative deamination, whereas in rat, aromatic oxidation, is the major route in phase 2 reactions.

3. **AGE:**

   Aging involves progressive impairments in the functional reserve of multiple organs, which might also affect drug metabolism.

- **In elderly:** In the elderly, hepatic drug clearance of some drugs can be reduced by up to 30% and CYP-mediated phase I reactions are more likely to be impaired than phase II metabolism, which is relatively preserved in the elderly. Concerning the most important Cytochrome P3A4 studies with human liver microsomes and clinical studies with the validated probe, midazolam, it is indicated that there are no significant differences in CYP3A4 activity between young and old populations. Finally, renal excretion is decreased (up to 50%) in about two thirds of elderly subjects, but confounding factors such as hypertension and coronary heart disease account also for a decline in kidney function. In conclusion, age-related physiological and pharmacokinetic changes as well as the presence of comorbidity and polypharmacy will complicate drug therapy in the elderly.
- **In children, infants and neonates:** Drug metabolism and elimination vary with age and depend on the substrate or drug, but most drugs, and most notably phenytoin, barbiturates, analgesics, and cardiac glycosides, have plasma half-lives 2 to 3 times longer in neonates than in adults. Drug metabolites are eliminated primarily through bile or the kidneys. Renal elimination depends on
- Plasma protein binding
- Renal blood flow
- GFR
- Tubular secretion

All of these factors are altered in the first 2 year of life. Renal plasma flow is low at birth (12 mL/min) and reaches adult levels of 140 mL/min by age 1 yr. Similarly, GFR is 2 to 4 mL/min at birth, increases to 8 to 20 mL/min by 2 to 3 days, and reaches adult levels of 120 mL/min by 3 to 5 mo.

Infants are at higher risk of toxicity via skin absorption due to a larger surface area to volume ratio and they also absorb more of a drug across skin due to their thinner stratum corneum. This explains why infants have an increased risk of methaemoglobinaemia with topical anaesthetics.

Metabolic processes are often immature at birth, which can lead to a reduced clearance and a prolonged half-life for those drugs for which metabolism is a significant mechanism for elimination. Renal excretion is also reduced in neonates due to immature glomerular filtration, tubular secretion, and reabsorption. Reduced protein binding in neonates will increase the clearance of drugs by these renal processes due to higher concentrations of unbound drug available. The capacity for drug metabolism by the neonatal liver is affected by the ontogeny of many drug-metabolizing enzymes.

4. DISEASES:

- **Diabetes:** For most drugs which cross the gastrointestinal wall by passive diffusion, oral absorption is unlikely to be affected by diabetes, although a delay in the absorption of tolazamide and a decrease in the extent of absorption of ampicillin have been reported. Subcutaneous absorption of insulin is more rapid in diabetic patients, whereas the intramuscular absorption of several drugs is slower. The binding of a number of drugs in the blood is reduced in diabetes, which may be due to glycosylation of plasma proteins or displacement by plasma free fatty acids, the level of which is increased in diabetic patients. Plasma concentrations of albumin and alpha 1-acid glycoprotein do not appear to be changed by the disease. The distribution of drugs with little or no binding in the blood is generally not altered, although the volume of distribution of phenazone (antipyrine) is reduced by 20% in insulin-dependent diabetes mellitus (IDDM). The presence of fatty liver in non-insulin-dependent diabetes mellitus (NIDDM) may contribute to a reduced hepatic clearance, whereas decreased binding in the blood may cause an increase in clearance. The effect of diabetes on hepatic blood flow in humans appears to be unknown. Diabetes affects kidney function in a significant number of diabetic patients. During the first 10 years after the onset of the disease, glomerular filtration is elevated in these patients. Thus, the renal clearance of a number of antibiotics has been shown to be increased in diabetic children. As the disease progresses, renal function is impaired and glomerular function declines from the initial elevated state. In diabetic adults the renal clearance of drugs either is comparable with that found in nondiabetic individuals or is reduced. diabetes may affect the pharmacokinetics of various drugs by affecting
  (i) absorption, due to changes in subcutaneous adipose blood flow, muscle blood flow and gastric emptying;
  (ii) distribution, due to non-enzymatic glycation of albumin;
  (iii) biotransformation, due to regulation of enzymes/transporters involved in drug biotransformation; and
  (iv) Excretion, due to nephropathy.

- **Obesity:** The influence of obesity on drug metabolism and elimination greatly differs per specific metabolic or elimination pathway. Clearance of cytochrome P450 (CYP) 3A4 substrates is lower in obese as compared with non-obese patients. In contrast, clearance of drugs primarily metabolized by uridine-diphosphate glucuronosyltransferase (UGT), glomerular filtration and/or tubular-mediated mechanisms, xanthine oxidase, N-acetyltransferase or Cytochrome P2E1 appears higher in obese versus non-obese patients.

5. **GENETICS:**

   Patient response to drugs varies widely and the reasons for this are diverse and complex. It is estimated that genetic factors account for 20 to 95 per cent of patient variability in response to individual drugs.

   Genetic influences on drug metabolism interact with other factors, such as: age, gender, race/ethnicity, disease states, concomitant medicines and social factors, determining the outcome from treatment with any pharmacological agent. The effect of genetic polymorphisms (differences) on catalytic activity is most prominent for three isoforms: Cytochrome P2C9, Cytochrome P2C19, and Cytochrome P2D6, which collectively account for about 40 per cent of drug metabolism mediated by cytochrome P450. Patients who have some enzyme activity are classified into four subgroups:

   - Slow (poor) metabolizers have markedly reduced or no enzyme activity.
   - Intermediate metabolizers have reduced enzyme activity.
   - Extensive metabolizers have normal enzyme activity (the bulk of the population).
   - Ultra rapid metabolizers have high enzyme activity.

   The distribution of Cytochrome P2D6 phenotypes varies with race. For example, the frequency of the phenotype associated with poor metabolism is 5 to 10 per cent in white populations but only about 1 per cent in Chinese and Japanese populations. There are also further differences between other racial groups. Similarly, there are variations in activities of Cytochrome P2C9 and Cytochrome P2C19 enzymes.

6. **HORMONES:** The term "hormone" is used in its broad sense and includes products of the major endocrine glands (i.e., thyroid, adrenals, gonads, and pancreas) and compounds that are not classically considered hormones, such as neurogenic amines, cytokines, interleukins, and eicosanoids. In addition, we comment on the effects on CYP expression of states associated with profound hormonal changes, such as pregnancy, malnutrition, obesity, diabetes mellitus, systemic inflammation, and conditions of altered extracellular fluid volume or osmolality.

EXTERNAL FACTORS

1. **Environmental factors:** Studies in animals have shown that many environmental pollutants induce the synthesis or inhibit the activity of microsomal mixed-function oxygenases that metabolize drugs, carcinogens and normal body constituents such as steroid hormones. These effects on microsomal enzyme activity alter the duration and intensity of action of foreign and endogenous chemicals in animals, and such effects on metabolism may influence the carcinogenicity of some pollutants in man. Studies on the effects of environmental chemicals on drug metabolism in man are sparse. Exposure of

humans to DDT or lindane in a pesticide factory results in an enhanced rate of metabolism of antipyrine and phenylbutazone and an increased urinary excretion of 6-beta-hydroxycortisol. Polycyclic aromatic hydrocarbons present in cigarette smoke, in charcoal-broiled meats, and in polluted city air are potent inducers of drug-metabolizing enzymes in animals. In humans, cigarette smoking stimulates the activity of placental enzymes that metabolize several drugs and carcinogens. In addition, cigarette smokers metabolize phenacetin, theophylline, and other drugs more rapidly in vivo than nonsmokers. The pervasiveness of tobacco use in our society and the frequency of altered disposition of many common therapeutic and recreational drugs in smokers makes it apparent that the smoking habit should be considered as one of the primary sources of drug interactions in man.

2. **DIET:** Dietary factors are important in the regulation of drug metabolism in animals and man. Feeding rats brussels sprouts or cabbage stimulates the intestinal and hepatic metabolism of drugs in animals. This effect is caused, at least in part, by certain indoles normally present in these vegetables. The feeding of a charcoal-broiled beef diet to rats stimulates the metabolism of phenacetin in vitro, and a similar diet stimulates the in vivo metabolism of phenacetin in man. It is likely that polycyclic aromatic hydrocarbons are the major inducers in charcoal-broiled beef. 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 the pharmacokinetics of drugs metabolized by that system. 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 macroconstituents (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 (CYP) 3A4 appears to be especially sensitive to dietary effects. For example, interactions of grapefruit juice with cyclosporin and felodipine, St John’s wort with cyclosporin 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.