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Tamunowari Valere

FACTORS AFFECTING DRUG METABOLISM

Many factors affect the rate and pathway of metabolism of drugs and the major influences can be sub-divided into ;

1.Biological factors

2.Chemical factors

BIOLOGICAL FACTORS

* Sex

Qualitative and quantitative differences in both phases of drug metabolism are related to sex well. Initial observations of this feature were made in the early 1930s, when researchers noticed that female rats required only half the dose of a barbiturate compared to male rats to induce sleep. Later investigations indicated that this was due to the reduced capacity of the female to metabolize barbiturates.

Sex differences have been intensively studied, not only in relation to sex-dependent metabolism of various xenobiotics, but also with the aim of correlating sex-dependent pharmacokinetics, pharmacodynamics, efficacy, and the possible occurrence of adverse reactions.Sex differences, sometimes related to species or age, are now being observed for a wide range of substrates, including commonly prescribed drugs or even endogenous compounds, including steroid sex compounds like other factors that influence drug metabolism, sex differences are considered to determine also biotransformation variations.

* Species

Examples of species differences in drug biotransformation are numerous continuously investigated, and encountered in both phases of biotransformation. An interesting observation is that they may involve the same route, but differ in the rate along that particular pathway (i.e.quantitatively different) or they may adopt different pathways (i.e. differing qualitatively) It should be noted as well that there is not always a direct relationship between metabolism, half-life and action of a drug an example of an interesting quantitative species difference in phase I metabolism is known for caffeine, both in terms of total metabolism and metabolite production. Thus the total metabolism is highest in humans, decreasing in the order - monkey, rat and rabbit. While there are no significant differences in the formation of theobromine, marked differences have been recorded for the other two metabolites, paraxanthine and theophylline, with paraxanthine formation highest in humans and lowest in monkey, whereas the reverse obtains for theophylline .

* Age

It has long been recognized that the newborn, young and elderly display marked differences in drug biotransformation and are more susceptible to drug action. These differences are chiefly due to the enzyme content, enzyme activity and enzyme hemodynamic involved in drug biotransformation and the development of their metabolizing capacity. Thus, the increased sensitivity of neonates may be related to their very low, undeveloped metabolizing capacity, until adult levels of enzyme activity are achieved, example in neonates coffee has a half life of 4days while in adult its 4hours.

In the elderly, the decrease in drug-metabolizing capacity is due to the liver size reduced and so reduced microsomal activities due to reduced hepatic flow as a result of the decline in cardiac output.

* Disease

The way in which the body clears drugs is affected by many disease states. Among them, those of primary concern are considered to be diseases affecting the liver: cirrhosis, alcoholic liver disease, cholestatic jaundice, and liver carcinoma.Other factors responsible for variation in drug metabolism are the endocrine disorders,such as diabetes mellitus hypo-and hyperthyroidism pituitary disorders and various types of infections (bacterial, viral,malaria).In cirrhosis for example, replacement of parts of

the liver by fibrous tissue leads to a reduction in the number of functional hepatocytes. In this situation, it seems absolutely reasonable that drug metabolism should be impaired.

* Hormonal control of drug metabolism

Hormones, known to play a major role in the general metabolism, have similarly been proven to control the biotransformation of drugs, in direct connection with other factors such as age, sex, or in particular physiological states, such as pregnancy. An example is the apparent connection between certain sex-specific drug- and steroid-metabolising enzyme activities in rats and the sex dependent expression of those specific enzymes, under gonadal steroid and growth hormone control. Another sex and age connection with the control of the growth hormone (GH) was the focus of interesting cDNA cloning investigations.The study examined especially cytochrome P450, it being established that GH is involved in the control of rat hepatic drug- and steroid-metabolism, particularly through the action of this enzymatic system. The results showed low levels of CYTP450 in neonates, and an increase after one month, both in male and female rats. At adult stage, important sex differences were recorded, in female rats the content being about three times higher than in male rats.

CHEMICAL FACTORS

* Enzyme induction

Enzyme induction is a process in which a molecule example a drug or chemical induces (i.e. initiates or enhances) the expression of an enzyme. The agents which bring about such an effect are called enzyme inducers

Increase in the enzyme activity or amount of cytochrome P450 increases the drug metabolism but decreases its effect.

* Enzyme inhibition

It’s the inhibition of the expression of an enzyme by another molecule. It refers to a decrease in enzyme after a stimulus. While common in bacterial enzyme regulation, they are observed less often in animal metabolism.

Decrease in the enzyme activity or amount of cytochrome P450 decreases drug metabolism but increases its effect.