Onibalusi oluwatimilehin Victoria

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**Discuss in details the factors affecting drug metabolism**

Many factors affect the rate and pathway of metabolism of drugs, and the major influences can be sub-divided into internal (physiological and pathological) and external (exogenous) factors as indicated below:

-Internal:

Species

genetic (strain): it is clear that variability in drug response depends on the complex interplay between multiple factors (including age, organ function, concomitant therapy, drug interactions, and the nature of the disease) and genetic background.

sex: since variations between male and female are observed following puberty. So sex related differences may be due to sex hormones. Such sex differences are widely studied in rats where male rats have greater drug metabolizing capacity. In humans, women metabolize benzodiazepines slowly than men. Several studies have shown that women on contraceptive pills metabolize a number of drugs at slower rate.

Age: in neonates and in infants, the microsomal enzyme system is not fully developed, so many drugs are metabolized slowly

 Children between 1year and 12years metabolize several drugs much more rapidly than adults as the rate of metabolism reaches a maximum within this age range

 In elderly persons, the liver size is reduced, the microsomal enzyme activity is decreased and the hepatic blood flow also decreases as a result of reduced Cardiac output all of which contributes to decreased metabolism of drugs.

Hormones: higher level of one’s hormone may inhibit the activity of few enzymes while inducing that of others

Pregnancy: this is known to affect hepatic drug metabolism. Physiological changes during pregnancy are responsible for the alterations in drug metabolism

disease: there are many disease state that affects the metabolism of drugs such as cirrhosis of the liver, alcoholic liver disease, cholestatic jaundice e.t.c

-External:

Diet and

Environment

There are, however, factors from outside the body that can also have a profound influence on drug metabolism. The body can be exposed to these factors by design (e.g. alcohol, tobacco smoke, and substances taken as food) or by accident (air, water and food contaminants or pollutants). The first group will be referred to as dietary factors and the second group as environmental factors.

The duration and intensity of pharmacological action of most lipophilic drugs are determined by the rate they are metabolized to inactive products. The Cytochrome P450 monooxygenase system is the most important pathway in this regard. In general, anything that increases the rate of metabolism (e.g., enzyme induction) of a pharmacologically active metabolite will decrease the duration and intensity of the drug action. The opposite is also true (e.g., enzyme inhibition). However, in cases where an enzyme is responsible for metabolizing a pro-drug into a drug, enzyme induction can speed up this conversion and increase drug levels, potentially causing toxicity.

Various physiological and pathological factors can also affect drug metabolism. Physiological factors that can influence drug metabolism include age, individual variation (e.g., pharmacogenetics), enterohepatic circulation, nutrition, intestinal flora, or sex differences.

In general, drugs are metabolized more slowly in fetal, neonatal and elderly humans and animals than in adults.

Genetic variation (polymorphism) accounts for some of the variability in the effect of drugs. With N-acetyltransferases (involved in Phase II reactions), individual variation creates a group of people who acetylate slowly (slow acetylators) and those who acetylate quickly, split roughly 50:50 in the population of Canada. This variation may have dramatic consequences, as the slow acetylators are more prone to dose-dependent toxicity.

Cytochrome P450 monooxygenase system enzymes can also vary across individuals, with deficiencies occurring in 1 – 30% of people, depending on their ethnic background.

Dose, frequency, route of administration, tissue distribution and protein binding of the drug affect its metabolism.

Pathological factors can also influence drug metabolism, including liver, kidney, or heart diseases.

In silico modelling and simulation methods allow drug metabolism to be predicted in virtual patient populations prior to performing clinical studies in human subjects. This can be used to identify individuals most at risk from adverse reaction.