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**17/MHS01/201**

**MBBS**

**BCH assignment.**

**DRUG METABOLISM.**

**Drug metabolism** is the metabolic breakdown of drugs by living organisms, usually through specialized enzymic systems. More generally, **xenobiotic metabolism** (from the Greek “xenos” means stranger" and biotic "related to living beings") is the set of metabolic pathways that modify the chemical structure of xenobiotics which are compounds foreign to an organism's normal biochemistry, such as any drug or poison.

Drug metabolism is divided into three phases. In phase I, enzymes such as cytochrome P450 oxidases  introduce reactive or polar groups into xenobiotics. These modified compounds are then conjugated to polar compounds in phase II reactions. These reactions are catalysed by  transferase enzymes such as glutathione S-transferases. Finally, in phase III, the conjugated xenobiotics may be further processed, before being recognised by efflux transporters and pumped out of cells. Drug metabolism often converts lipophilic compounds into hydrophilic products that are more readily excreted. These metabolic process however can be affected by some factors.

FACTORS AFFECTING DRUG METABOLISM

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 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 induction). 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 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.