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**AFFECTING DRUG METABOLISM**

Introduction

Drug metabolism is the metabolic breakdown of drugs by living organisms, usually through specialized enzymatic systems. It is the set of metabolic pathways that modify the chemical structure of xenobiotic, which are compounds foreign to an organism's normal biochemistry, such as any drug or poison. These pathways are a form of biotransformation present in all major groups of organisms. There are many factors that can affect these pathways for the metabolism of xenobiotic in the body. Mainly they are divided into two forms which are;

Physiological factors

Pathological factors

**Physiological factors**

They include normal functions of the body that affect the metabolism of drugs

* Age: The age of an organism can determine how the drugs are metabolized in the body.

For instance, neonates are more likely to have a poorer metabolism of drugs, this is because their metabolic enzyme system is not well developed to undertake the task of metabolizing certain xenobiotic. Same can be said for older people as metabolism is on average slower than in the average adult. This is because as people age, enzymatic activity decreases, so older people, like newborns, cannot metabolize drugs as well as younger adults do.

Genetics: Genetics influence how a drug interacts with the body. This is a branch of medicine mainly known as pharmacogenomics. Pharmacogenomics is the study of the effect of single-gene genetic factors on the response of individuals or population subgroups to certain drugs.  
Pharmacogenomics evaluates genetic differences within a population that explain certain observed responses to a drug or susceptibility to a health problem, and involves a larger genome approach that considers not only single-gene effects but also multi-gene interactions and pathways. The most common of example is the Cytochrome P450 super family of enzymes. Many medicines are metabolised by the cytochrome P450 super-family of enzymes. The term ‘cytochrome P450’ is a generic term for the entire family of enzymes. Under this system, the P450 enzymes are divided into families and subfamilies. The activity of metabolising enzymes such as the cytochrome P450 is influenced by a variety of factors, including genetic differences between people, enzyme inhibition and induction, diet, health status, gender and age.

The effect of genetic polymorphisms (differences) on catalytic activity is most prominent for three isoforms: CYP2C9, CYP2C19, and CYP2D6, 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) metabolisers have markedly reduced or no enzyme activity.
* Intermediate metabolisers have reduced enzyme activity.
* Extensive metabolisers have normal enzyme activity (the bulk of the population).
* Ultrarapid metabolisers have high enzyme activity.

The distribution of CYP2D6 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 CYP2C9 and CYP2C19 enzymes.

* Gender: Another factor that can affect the individual is the gender of the individual. Many CYP450 enzymes (phase I metabolism) show a sex-dependent difference in activity. Most of the phase II enzymes have a higher activity in men than in women. Activities of these enzymes can also change during pregnancy and with the use of oral contraceptives. *CYP1A2*, the primary enzyme for metabolizing the antipsychotic drugs olanzapine and clozapine, shows a higher activity in men. Therefore, clearance of these antipsychotic drugs is faster in men than in women. As a result women tend to experience less therapeutic effect when given the same dosage with men.

**Pathological factors:**  the liver and kidney are two organs by which most of the drugs are metabolized. The factors that can alter their functions in drug metabolism are listed below

* **Kidney impairments**: Renal disease will perturb the disposition of drugs that primarily depend upon renal excretory function for elimination. Renal failure has been shown to alter the hepatic microsomal mixed-function oxidase system of drug metabolizing enzymes. Therefore, in end-stage renal failure, the potential exists for the modification of the disposition of drugs whose elimination is primarily hepatic. The kidneys themselves contain many of the enzymes important in hepatic drug metabolism. Drugs such as morphine, paracetamol, and p-aminobenzoic acid are metabolized in the kidney and experimental renal disease has been shown to reduce drug metabolism in the diseased kidney compared with the contralateral normal kidney. Renal disease, then, has the potential to alter not only the renal clearance of unchanged drug but also may substantially modify the metabolic transformation of drugs in both the liver and the kidneys.
* **Liver Impairments**: The liver is the most important site of drug metabolism and patients with liver disease might be expected to have a reduced capacity to metabolize drugs. The rates of elimination of extensively metabolized drugs have been measured. The results of the studies are conflicting, however, and it seems that many patients with chronic liver disease can metabolize drugs at normal rates. On the other hand, drug metabolizing enzyme activity was reduced in liver biopsies from patients with serious liver conditions such as primary and secondary hepatic tumours.