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**MEDICINE AND SURGERY**

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MEDICAL BIOCHEMISTRY ASSIGNMENT:

Discuss in details the factors affecting drug metabolism

DRUG METABOLISM

Drug metabolism is the metabolic breakdown of drugs by living organisms, usually through specialized enzymatic systems. It is the process by which the body breaks down and converts medication into active chemical substances.

More generally, **xenobiotic metabolism** (from the Greek [xenos](https://en.m.wikipedia.org/wiki/Xenos_%28Greek%29) "stranger" and biotic "related to living beings") is the set of [metabolic pathways](https://en.m.wikipedia.org/wiki/Metabolic_pathway) that modify the chemical structure of [xenobiotics](https://en.m.wikipedia.org/wiki/Xenobiotic)( which are compounds foreign to an organism's normal biochemistry such as any [drug](https://en.m.wikipedia.org/wiki/Drug) or [poison](https://en.m.wikipedia.org/wiki/Poison)). These pathways are a form of [biotransformation](https://en.m.wikipedia.org/wiki/Biotransformation) present in all major groups of organisms. These reactions often act to [detoxify](https://en.m.wikipedia.org/wiki/Detoxification) poisonous compounds (although in some cases the [intermediates](https://en.m.wikipedia.org/wiki/Reaction_intermediate) in xenobiotic metabolism can themselves cause toxic effects).

FACTORS THAT AFFECT DRUG METABOLISM

Drugs can be metabolized by many different pathways and many factors can determine which pathway is to be used by a drug and to what extent and rate at which a particular drug is bio transformed by a particular pathway. These factors range from the species of organism studied to the environment in which that organism lives.

In general, anything that increases the rate of metabolism (e.g., [enzyme induction](https://en.m.wikipedia.org/wiki/Enzyme_induction_and_inhibition)) of a pharmacologically active metabolite will decrease the duration and intensity of the drug action. The opposite is also true (e.g., [enzyme inhibition](https://en.m.wikipedia.org/wiki/Enzyme_induction_and_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.

 The factors affecting drug metabolism can be classified generally into two:

* **Internal factors (i.e. physiological and pathological)**

These factors include:

* 1. species
	2. genetic (strain)
	3. age
	4. sex (Gender)
	5. hormones
	6. disease

It's important to appreciate that none of the physiological factors affecting drug metabolism operate in isolation.

* **External factors**

These factors include:

* 1. diet
	2. environment



INTERNAL FACTORS

* + 1. **INFLUENCE OF SPECIES ON DRUG METABOLISM**

Different species metabolizes drug at different rate, mainly due to differences in enzymes involved due to different amino acids makeup.

A research was carried out aimed to investigate interspecies differences in drug metabolism. For this, in vitro model systems, combined with sensitive analytical techniques and with analysis of gene expression were developed and compared to the in vivo situation. Animal studies are commonly used to predict metabolism and toxicity of potential new human drugs.

However, it is important to realize that **humans differ from animals** in isoform composition, expression and catalytic activities of enzymes involved in drug metabolism. In fact, even small changes in the amino acid sequences of these enzymes can give rise to profound differences in substrate specificity and catalytic activity. Therefore, differences in expression between species of the most important family of drug metabolizing enzymes, the cytochrome P450s (CYPs) are a major cause of species differences in drug metabolism.

* + 1. **INFLUENCE OF GENETICS ON DRUG METABOLISM**



Genetic variation ([polymorphism](https://en.m.wikipedia.org/wiki/Polymorphism_%28biology%29)) accounts for some of the variability in the effect of drugs. Differences in genetic (inherited) makeup among individuals affect what the body does to a drug and what the drug does to the body. The study of genetic differences in the [response to drugs](https://www.msdmanuals.com/home/drugs/factors-affecting-response-to-drugs/overview-of-response-to-drugs) is called pharmacogenetics.

Some people [metabolize](https://www.msdmanuals.com/home/drugs/administration-and-kinetics-of-drugs/drug-metabolism) drugs slowly because of their genetic makeup. As a result, a drug may accumulate in the body, causing toxicity. Other people metabolize drugs so quickly that after they take a usual dose, drug levels in the blood never become high enough for the drug to be effective.

Examples on effect of genetics on drug metabolism include:

* In about half of the people in the United States, N-acetyltransferase, a liver enzyme that metabolizes certain drugs, works slowly. Such people are called slow acetylators. The people in whom this enzyme metabolizes drugs rapidly are called fast acetylators. Drugs, such as isoniazid (which is used to treat tuberculosis), that are metabolized by this enzyme tend to reach higher blood levels and remain in the body longer in slow acetylators than they do in fast acetylators.
* About 1 of 1,500 people have low levels of pseudocholinesterase, a blood enzyme that inactivates drugs such as succinylcholine, which is sometimes given to temporarily relax muscles during surgical procedures. If succinylcholine is not rapidly inactivated, muscle relaxation may be prolonged, and people may not be able to breathe on their own as soon after surgery as is usual. They may need a ventilator for an extended time.
* About 10% of black men and fewer black women have a deficiency of glucose-6-phosphate dehydrogenase (G6PD), an enzyme that protects red blood cells from certain toxic chemicals. For example, in people with G6PD deficiency, some drugs (such as chloroquine and primaquine, which are used to treat malaria) destroy red blood cells and cause [haemolytic anaemia](https://www.msdmanuals.com/home/blood-disorders/anemia/overview-of-anemia).
* About 1 of 20,000 people have a genetic defect that makes muscles overly sensitive to certain inhaled anaesthetics such as halothane, isoflurane, and sevoflurane. When such people are given one of these anaesthetics with a muscle relaxant (usually succinylcholine), a life-threatening disorder called [malignant hyperthermia](https://www.msdmanuals.com/home/injuries-and-poisoning/heat-disorders/malignant-hyperthermia) may develop. It causes a very high fever. Muscles stiffen, the heart races, and blood pressure falls.
	+ 1. **EFFECTS OF AGE ON DRUG METABOLISM**

In general, drugs are metabolized more slowly in [fetal](https://en.m.wikipedia.org/wiki/Fetal), [neonatal](https://en.m.wikipedia.org/wiki/Neonatal) and [elderly](https://en.m.wikipedia.org/wiki/Elderly) [humans](https://en.m.wikipedia.org/wiki/Human) and [animals](https://en.m.wikipedia.org/wiki/Animal) than in [adults](https://en.m.wikipedia.org/wiki/Adult).

The fetal, neonatal and young people are more susceptible to drug actions cause in newborn, drug metabolism capacity is not yet fully developed and, in the elderly, their drug metabolism capacity is reduced.

* + 1. **INFLUENCE OF SEX (GENDER) ON DRUG METABOLISM**

Sex differences in drugs metabolism are believed to be a major cause of differential pharmacokinetics between men and women. Many Cytochrome P450 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. Sex differences are also found in other pharmacokinetic parameters such as drug absorption, drug distribution, and excretion. For example, A systematic evaluation of 14 studies showed that women are more affected than men in driving after taking zolpidem (10 mg) the previous night. This gender-specific adverse effect is due to a slower clearance of zolpidem in women, who have shown a significantly higher serum concentration of zolpidem than men.

Despite these differences between men and women, sex-specific dosing recommendations are absent for most drugs. Therefore, when a woman consistently experiences less therapeutic effect or more adverse effects from a drug, a change in its dosing regimen may be necessary.

* Drug metabolism consists of phase I and phase II reactions.
* Phase I metabolism is mediated mainly by hepatic Cytochrome P450(CYP450). The CYP450 superfamily of enzymes is responsible for metabolizing 70% to 80% of all prescribed drugs. A total of 18 CYP gene families have been identified, and the majority of drug metabolism is mediated by CYP1, CYP2, and CYP3. These CYP enzymes and their known gender-specific activity, which can cause a difference in overall therapeutic effects between men and women.

The following are a few examples:

* 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. On the other hand, women show greater improvement of psychotic symptoms due to slower metabolism of these drugs, but suffer more ADEs (e.g., weight gain, metabolic syndrome) associated with the drugs.
* CYP2D6, which metabolizes >20% of prescribed drugs such as analgesics (e.g., codeine), antidepressants (e.g., selective serotonin reuptake inhibitors [SSRIs]), and haloperidol, exhibits extensive genetic poly-morphism. Among the extensive metabolisers, CYP2D6 activity is higher in women than in men, and increased activity is seen during pregnancy.
* Most phase II enzymes have a higher activity in men than in women UGTs (uridine diphosphate (UDP)-glucuronosyltransferases), the most predominant phase II enzymes in the liver, kidney, and intestine, are superfamily enzymes with two major subfamilies—UGT1 and UGT2.

Men show a faster clearance of drugs that are primarily eliminated by glucuronidation. Thus, oxazepam, metabolized mainly by UGT2B15, has a longer half-life in women than in men.



* Sex differences are also found in other pharmacokinetic parameters such as:
	+ - 1. **Drug Absorption**: The gastrointestinal (GI) transit rate can affect the plasma concentration and absorption of orally taken drugs. Since women have slower gastric motility and intestinal transit than men, they may need to wait longer between food consumption and medication if a drug is to be taken on an empty stomach. Captopril, felodipine, ampicillin, demeclocycline, and loratadine are some example drugs.

A well-known example is the faster alcohol absorption in women than in men.Alcohol dehydrogenase, the gastric mucosal enzyme responsible for alcohol oxidation, is less active in women than in men. Therefore, women have higher peak blood concentration and subsequently faster absorption of alcohol after its consumption. They are also more susceptible to both acute and chronic effects of alcohol when compared to men.

* + - 1. **Drug Distribution**: Compared to men, women have a higher percentage of body fat but lower body water content, which can affect the volume of distribution (Vd) of certain drugs.

For lipophilic drugs such as opioids and benzodiazepines, the Vd is usually higher in women. Upon accumulation in the body fat, which acts as a reservoir, the half-life of these lipophilic drugs is extended in women. Chronic dosage can further increase the load in the fatty tissues, with the potential consequence of toxic effects. Thus, it is logical to administer lower dosages of benzodiazepines to women than to men. Since body fat can increase disproportionately with age among women, the sex-dependent disparities in lipophilic drug distribution may also increase with age.

Conversely, Vd for water-soluble drugs such as muscle relaxants is lower in women, leading to a higher initial plasma concentration. Women also show a 20% to 30% greater sensitivity for the muscle-relaxing effects of vecuronium, rocuronium, and pancuronium. Therefore, a dosage reduction of muscle relaxant is necessary for women if shorter drug duration is the goal (i.e., during anaesthesia).

* + - 1. **Excretion**: Both renal blood flow and glomerular filtration rate (GFR) are higher in men than in women. Therefore, women show a slower clearance of drugs that are actively eliminated via the kidney. Examples of these drugs include digoxin, methotrexate, gabapentin, and pregabalin.
			2. Other Factors: Differences in body weight, cardiac output, plasma volume, and regional blood flow between men and women can also lead to sex differences in drug disposition. For example, the plasma concentration of aliskiren, an antihypertensive renin inhibitor, is usually lower in men than in women, but a previous study showed the gender difference could be eliminated when plasma concentration was adjusted for overall body weight. Therefore, clinical dosages of certain drugs may require an adjustment for body weight.
		1. **EFFECTS OF DISEASES ON DRUG METABOLISM**

Pathological factors can also influence drug metabolism, including [liver](https://en.m.wikipedia.org/wiki/Liver), [kidney](https://en.m.wikipedia.org/wiki/Kidney), or [heart](https://en.m.wikipedia.org/wiki/Heart) diseases. Diseases affecting these organs, especially the liver, would lead to a reduction in production of enzymes necessary for drugs metabolism.

* + 1. **HORMONAL EFFECTS ON DRUG METABOLISM**

Historically, women were less enrolled in clinical trials because both pharmacokinetics and pharmacodynamics of a drug can be influenced by menstrual cycle phases, hormonal fluctuations, use of oral contraceptives and hormonal therapy, and life events such as pregnancy and lactation.

Most phase II enzymes have a higher activity in men than in women UGTs (uridine diphosphate (UDP)-glucuronosyltransferases), the most predominant phase II enzymes in the liver, kidney, and intestine, are superfamily enzymes with two major subfamilies—UGT1 and UGT2.Both estrogens and androgens regulate the expression of the UGT2B subfamily of enzymes, and the activity of UGTs is increased during pregnancy. As an example, pregnant women taking lamotrigine for epilepsy have shown increased seizuresbecause the increased metabolism by UGT and subsequent faster clearance of lamotrigine during pregnancy have resulted in subtherapeutic drug concentrations.

Use of combined estrogen‑progesterone oral contraceptives can have profound effects on pharmacokinetics by reducing the plasma albumin level, increasing or inhibiting the activity of CYP enzymes and increasing the activity of UGTs. Therefore, it is important for clinicians to understand the pharmacokinetic changes of drugs during pregnancy or the use of oral contraceptives and properly readjust the dosage when necessary to avoid over- or underdosing female patients.

Likewise, significant hormonal changes and hormonal replacement therapy in menopausal and postmenopausal women can also lead to altered drug disposition in women. Therefore, dosage optimization may also be needed to maintain drug efficacy and safety in these subgroups. In contrast, the steady plasma level of androgens in adult men has minimal effects on drug pharmacokinetics.

Examples of hormonal influence on drug metabolism include:

* 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. On the other hand, women show greater improvement of psychotic symptoms due to slower metabolism of these drugs, but suffer more ADEs (e.g., weight gain, metabolic syndrome) associated with the drugs.

Sex hormones decrease CYP1A2 activity during pregnancy and with oral contraceptive use. Therefore, dosage adjustment may be necessary when olanzapine or clozapine is prescribed during concomitant use of oral contraceptives or at pregnancy, depending on the specific drug and the patient’s conditions.

* Both glucuronidation and sulphate conjugation are the main pathways for eliminating acetaminophen. Women have slower clearance of acetaminophen than men, but the sex difference appears to be offset with the use of combined estrogen-progesterone oral contraceptives, which increase the activity of UGTs. (uridine diphosphate (UDP)-glucuronosyltransferases).
* Testosterone can stimulate the activity of CYP3A in metabolizing certain drugs and has been postulated to enhance zolpidem metabolism in men. In contrast, the lower testosterone level in women may cause a slower CYP3A4-mediated metabolism of zolpidem, resulting in a slower clearance and an increased risk of morning-after activity impairment.
* Estrogen can influence pain pathways, alter pain perception, and affect response to certain drug classes. Because estrogen is present in substantially higher levels in women than in men, women tend to exhibit lower pain thresholds, increased pain ratings to standardized stimuli, and lower tolerance to pain. Women also demonstrate a greater analgesic response to opioids. To achieve equivalent pain relief, men require a 30 to 40 percent greater dosage of morphine. Sex differences have been attributed to dimorphism in central opioid metabolism or in opioid action at the cellular level. Women also are more likely to experience greater sedative properties and respiratory depression from opioids.

EXTERNAL FACTORS

1. **INFLUENCE OF DIETS ON DRUG METABOLISM**

Food changes one’s metabolism. Dietary factors may also play a significant role in the regulation of drug metabolism. Charcoal broiling which introduces polycyclic hydrocarbons into foods has been shown to enhance the metabolism of the test drug, antipyrine, and of such commonly used drugs as phenacetin and theophylline.

1. **INFLUENCE OF ENVIRONMENT ON DRUG METABOLISM**

Environmental factors may play a significant role in explaining the variation observed in the rates of drug metabolism between different individuals.

Intentional or unintentional exposure to environmental chemicals could enhance or inhibit the activity of hepatic mixed function oxidases (Cytochrome P450) that metabolise drugs and other foreign chemicals, as well as endogenous substrates such as steroid hormones. A major source of such exposure may be occupational. Exposure to the heavy metal, lead, has been shown to inhibit drug metabolism; whereas intensive exposure to chlorinated insecticides, and other halogenated hydrocarbons such as poly chlorinated biphenyls, has been shown to enhance the metabolism of test drugs such as antipyrine and phenylbutazone.

An intentional source of exposure to foreign chemicals is cigarette smoke. Cigarette smoke contains polycyclic hydrocarbons, which are known inducers of hepatic mixed function oxidases. A number of studies have shown that cigarette smoking can alter the pharmacological action and/or the metabolism of some drugs. Pharmacokinetic studies have shown that cigarette smoking decreases the bio-availability of phenacetin and increases dosage requirements of theophylline by enhancing their rate of metabolism. Data, which are not very conclusive, indicate that heavy marijuana use may have an inhibitory effect on metabolism of some drugs and an inducing effect on others such as theophylline.

These intentional or unintentional exposures to environmental chemicals which may alter the rates of drug metabolism in man indicates the importance of individualisation of drug therapy.