بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | Lecture 12

Pharmacokinetics Pt.6

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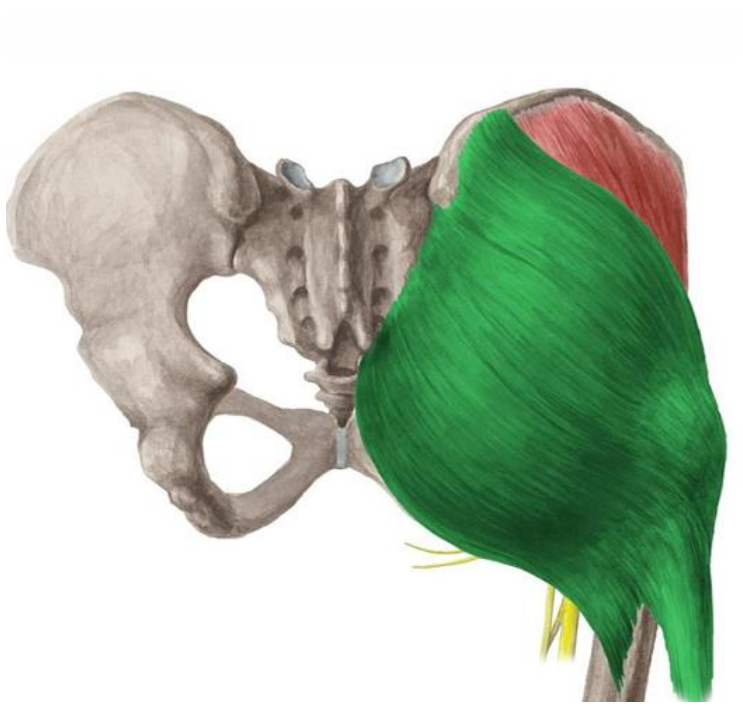
Parenteral Routes

2. Intramuscular route (IM):

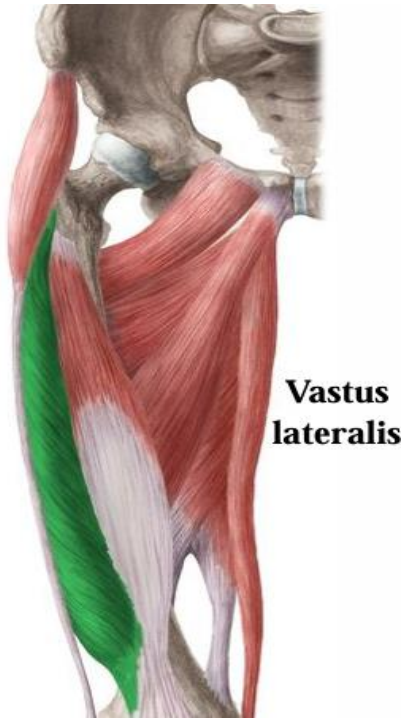
- The drug is injected within muscle fibers of deltoid, gluteus maximus or vastus lateralis.
- Absorption of drug depends on blood supply (slower for g.m).
- Absorption is reduced in circulatory failure or shock.
- To be injected IM, the drug must be non-irritating to tissues.

g.m.= gluteus maximus. Drug absorption is slower in the gluteus maximus because it has less blood supply compared to other sites

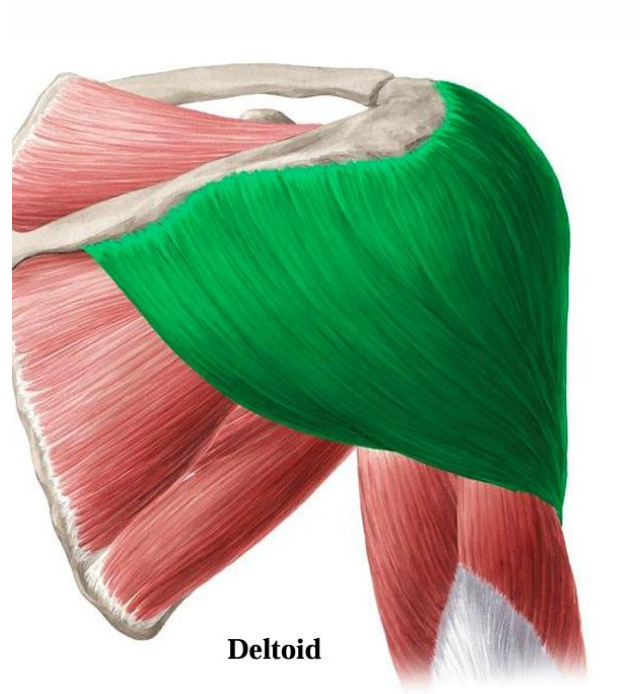
Sites of injection regarding the IM route:



Gluteus maximus
The injection should be given in the upper lateral quarter to avoid accidently injuring the sciatic nerve and major vessels



Vastus lateralis
(the lateral muscle of the thigh)



Deltoid

Why is drug absorption reduced in circulatory failure or shock when using the intramuscular (IM) route?

Drug absorption from an intramuscular injection depends mainly on adequate blood flow to the muscle so the drug can enter the systemic circulation. In circulatory failure or shock, blood flow to peripheral muscles is significantly reduced, so the drug is absorbed much more slowly and becomes less effective. IM administration is also not as fast as IV, and the reduction in blood flow makes it even slower.

Additionally, because women generally have lower muscle blood flow than men, a woman with a critical illness or shock may experience even poorer absorption, making the IM route potentially inadequate in such situations.

Parenteral Routes

Can utilize:

a. **Aqueous solutions for fast absorption and rapid action.**
b. **Depot preparations and suspensions for slow or sustained absorption (oily vehicles or ethylene glycol).**

- **Can accommodate large volumes.**

IM route can utilize:

1. Aqueous (water-based) solutions
- These allow fast absorption and rapid onset of action, although not as fast as IV.

2. Depot preparations
- The drug precipitates or forms a depot inside the muscle, and from there it slowly diffuses into the systemic circulation, giving a sustained, long-lasting effect.
- If a drug is formulated in oil, it cannot be given IV, but it can be safely injected IM because IM does not require the solution to be fully transparent or free of precipitation. On the other hand, IV injections only utilize aqueous, transparent, and precipitation-free solutions.

IM injections can accommodate large volumes

- The muscle can hold a relatively large volume of injected fluid, which is why IM injections are suitable for drugs that require larger doses (0.5-5mL)
- patients who are on anticoagulants should not receive IM injections, because the injection can cause bleeding inside the muscle.
- A patient who is taking anticoagulants may lose up to 1 liter of blood inside the muscle before anyone realizes there is internal bleeding, because the bleeding spreads within the fascia surrounding the muscle and can move away from the injection site.
- This point does not mean we inject 1-2 liters of a drug.
  It means the muscle has the capacity to accommodate a large volume of fluid, so hidden bleeding can accumulate significantly before it becomes noticeable.
- Because the muscle can hold this much fluid, bleeding may be recognized late, and the patient may not immediately feel that something is wrong

Parenteral Routes

3. Subcutaneous injections (SC, or SQ):

- The drug is injected under the skin.
- Absorption is affected by blood flow.
- Drug should be non-irritating to tissues.
- Absorption is slow and sustained.
- Accommodate smaller volumes than IM.
- Solid pellets can be implanted under the skin to produce effects over weeks-months.

In areas like **Abdominal wall** and other areas with adequate subcutaneous fat

Absorption is affected by blood flow

- Absorption in oral, IM, and SC routes is affected by blood flow, but this does not apply to IV.

Drugs should be non-irritating to tissues

- Some SC/SQ injections may be painful after administration because certain drugs are irritating to tissues.
- Certain rare drugs, if given IV, can irritate the vein and cause pain at the injection site or even lead to thrombosis.

Absorption is slow and sustained

- SC injections are not used for immediate effect (unlike IV).

Solid pellets can be used

- Pellets can be implanted under the skin—similar to tablets—used for:
  - Some forms of contraception
  - Diseases requiring continuous, long-term treatment

Other Routes

1. **Inhalational or pulmonary route:**

- **Used for gaseous or volatile drugs, such as general anesthetics.**
- **Can also be used for solids that can be put in an aerosol, such as drugs for bronchial asthma.**
- **Drugs are absorbed across pulmonary epithelium and mucous membranes of respiratory tract.**
- **Absorption is rapid.**
- **Avoids first-pass effect.**
- **The lung acts as a route of elimination also.**

Aerosols are solutions of solids in air

بخاخات

Immediate response because most inhaled medications like asthma drugs are designed to act locally in the airways

Also applies to IM and SC injections

The drug is removed by exhalation

Other Routes

2. **Topical application:**

- **For a local effect on:**

  a. mucous membranes: conjunctiva, nose, mouth, nasopharynx, oropharynx, vagina, rectum, colon(by enema ,(حقنة شرجية)urethra, and urinary bladder.

  b. skin: highly lipid-soluble drugs can be absorbed systemically.

- **Systemic absorption also occurs from abraded, burned and inflamed skin.**

Abnormal skin (abraded, burned, or inflamed) allows increased systemic absorption from topical drugs, which may lead to adverse reactions. This is also true for mucous membranes if there was a problem in their integrity

Topical Application

(Local Action at the Site of Application)

- At the site (the drug works locally).
- If there is a skin lesion, the medication is applied directly on the skin.
- If the lesion is in the rectum, you give the patient a suppository (تحميلة) or an ointment to produce a local effect.
- Oral thrush: a fungal infection in the mouth treated with topical antifungals on the mucous membranes.
- Fungal infections on the skin are also treated with topical medications.

Other Routes

3. **Transdermal route (TD):**

- **The drug is applied to the skin for systemic effect, such as in angina.**
- **For a sustained effect.**
- **Avoids first-pass metabolism.**

  - Transdermal route is different from topical: the drug goes from the skin into the systemic circulation.
  - Sublingual and sometimes transdermal patches are used for angina (patch usually placed on the chest area).
  - Organic nitrates are used for treating angina (trans-dermally) because they undergo extensive first-pass metabolism if taken orally.
  - There are other specialized routes for administration
  - Angina is chest pain caused by reduced blood flow to the heart muscle

Read the table below the professor said he might ask about it

Enteral Routes			
Buccal or sublingual (SL)	Rapid absorption from lipid-soluble drugs.	No "first-pass" effects. Buccal route may be formulated for local prolonged action. Eg, adhere to the buccal mucosa with some antifungal. Buccal is different from sublingual which is usually placed "under tongue."	Some drugs may be swallowed. Not for most drugs or drugs with high doses.
Oral (PO)	Absorption may vary. Generally, slower absorption rate compared to IV bolus or IM injection.	Safest and easiest route of drug administration. May use immediate-release and modified-release drug products.	Some drugs may have erratic absorption, be unstable in the gastointestinal tract, or be metabolized by liver prior to systemic absorption.
Rectal (PR)	Absorption may vary from suppository. More reliable absorption from enema (solution).	Useful when patient cannot swallow medication. Used for local and systemic effects.	Absorption may be erratic. Suppository may migrate to different position. Some patient discomfort.
Other Routes			
Transdermal	Slow absorption, rate may vary. Increased absorption with occlusive dressing.	Transdermal delivery system (patch) is easy to use. Used for lipid-soluble drugs with low dose and low MW (molecular weight).	Some irritation by patch or drug. Permeability of skin variable with condition, anatomic site, age, and gender. Type of cream or ointment base affects drug release and absorption.
Inhalation and intranasal	Rapid absorption. Total dose absorbed is variable.	May be used for local or systemic effects.	Particle size of drug determines anatomic placement in respiratory tract. May stimulate cough reflex. Some drug may be swallowed.

Table 13-1 Common Routes of Drug Administration

Route	Bioavailability	Advantages	Disadvantages
Parenteral Routes			
Intravenous bolus (IV)	Complete (100%) systemic drug absorption. Rate of bioavailability considered instantaneous.	Drug is given for immediate effect.	Increased chance for adverse reaction. Possible anaphylaxis.
Intravenous infusion (IV inf)	Complete (100%) systemic drug absorption. Rate of drug absorption controlled by infusion rate.	Plasma drug levels more precisely controlled. May inject large fluid volumes. May use drugs with poor lipid solubility and/or irritating drugs.	Requires skill in insertion of infusion set. Tissue damage at site of injection (infiltration, necrosis, or sterile abscess).
Subcutaneous injection (SC)	Prompt from aqueous solution. Slow absorption from repository formulations.	Generally, used for insulin injection.	Rate of drug absorption depends on blood flow and injection volume. Insulin formulaton can vary from short to intermediate and long acting.
Intradermal injection	Drug injected into surface area (dermal) of skin.	Often used for allergy and other diagnostic tests, such as tuberculosis.	Some discomfort at site of injection.
Intramuscular injection (IM)	Rapid from aqueous solution. Slow absorption from nonaqueous (oil) solutions.	Easier to inject than intravenous injection. Larger volumes may be used compared to subcutaneous solutions.	Irritating drugs may be very painful. Different rates of absorption depending on muscle group injected and blood flow.
Intra-arterial injection	100% of solution is absorbed.	Used in chemotherapy to target drug to organ.	Drug may also distribute to other tissues and organs in the body.
Intrathecal Injection	100% of solution is absorbed.	Drug is directly injected into cerebrospinal fluid (CSF) for uptake into brain.	
Intraperitoneal injection	In laboratory animals, (eg, rat) drug absorption resembles oral absorption.	Used more in small laboratory animals. Less common injection in humans. Used for renally impaired patients on peritoneal dialysis who develop peritonitis.	Drug absorption via mesenteric veins to liver, may have some hepatic clearance prior to systemic absorption.

Drug Biotransformation = Drug metabolism

The process of converting the drug from one form to the other by biological enzymes

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Drug Biotransformation

- **Humans are exposed always to foreign compounds called xenobiotics, through the GIT, skin, lung, etc.** In Latin Xeno means foreign
- **Xenobiotics include drugs, environmental toxins and industrial toxins.**
- **Xenobiotics excreted by the kidney are usually small polar molecules, or ionized at physiologic pH.**

Xenobiotics examples

1)Toxic plants like Toxic Mushrooms

- Some Mushrooms are considered toxic.
- There are 7-8 different types of mushroom poisons, caused by different toxic mushroom species.
- Some people die from mushroom poisoning, usually during winter.
- In general, the more colorful and pretty the mushroom looks, the more toxic it tends to be.

2)Polycyclic Aromatic Hydrocarbons

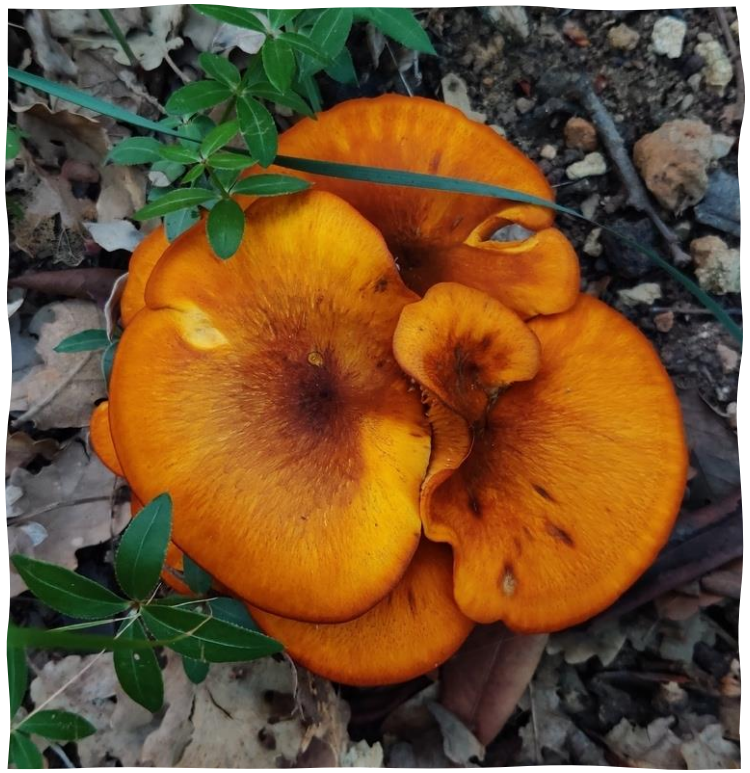
- Some drugs or toxins metabolized in the liver become activated and turn toxic.
- Polycyclic aromatic hydrocarbons (PAHs) are carcinogenic substances found in tobacco smoke and in smoke produced during barbecue grilling.
- These compounds are activated by liver enzymes into carcinogens.

Elimination of Xenobiotics

- Foreign substances are eliminated either by the kidney or the liver.
- Elimination can happen by metabolism or renal excretion.
- The process depends on the physicochemical properties of the poison/xenobiotic.

Drugs and xenobiotics

- What applies to drugs also applies to foreign substances because drugs themselves are foreign to the body.
- A toxin may be eliminated by metabolism, or metabolism may convert it into an even more toxic form – just like what happens with some drugs.



Toxic mushrooms!

Drug Biotransformation

- Many drugs are lipophilic at physiologic pH, and are readily reabsorbed from the glomerular filtrate in the nephron.
- Lipophilic drugs bound to plasma proteins are not readily filtered at the glomerulus.
- Such drugs are metabolized in the liver to more polar molecules that can be excreted in urine and/or bile.

Drug Biotransformation

- **Metabolic products are often less active than the parent drug and may be even inactive.**

Exception:

1. **Some drug metabolites have enhanced activity or even toxicity.** Sometimes metabolites are more active than the parent drug, example: the metabolites of morphine (CNS depressant, analgesic) are more active than morphine
2. **Some drugs are inactive and need activation by metabolism (prodrugs) like levodopa, codeine.**
3. **Some drugs are metabolized into toxins.** And cyclic aromatic hydrocarbons which need activation to become cancerogenic.

Drug Biotransformation

Examples:

a) Paracetamol may be converted to the hepatotoxin N-acetyl-p-benzoquinone imine.

b) Halothane is metabolized to free radicals that are hepatotoxic.

Paracetamol

- Paracetamol is not safe in high doses because it can cause liver damage and pulmonary damage.
- Severe toxicity may lead to the death of the patient or the need for a liver transplant.

Halothane

- Halothane is a general anesthetic.
- If a patient undergoes surgery and halothane is used for general anesthesia, and the patient later develops hepatic toxicity, then halothane becomes contraindicated (forbidden) for that patient for the rest of their life.
- Halothane should not be used again in future operations for that patient.

Drug Biotransformation

- Biotransformation reactions can be classified as phase I or phase II reactions.
- Phase I reactions usually convert the drug to more polar metabolites by introducing (or unmasking) a functional group (- OH, - NH_2, - SH), which makes them more polar and can be excreted by the kidney.
- These metabolites can be inactive, less active or more active than the parent compound.

Metabolism is a method of elimination but also a method of activation!

General Notes

- Phase I increases the polarity of the drug, but sometimes this is not enough for renal excretion.
- Phase II makes the drug even more polar, so it becomes more easily excreted in urine.
- In reality, Metabolism does not always follow the sequence "Phase I → Phase II."
  A drug can undergo:
  - Phase I only,
  - Phase II only,
  - Or Phase II followed by Phase I.
- So, the old idea "Phase I must happen before Phase II" is not valid anymore.

Classification of Reactions

Phase I Reactions

- Oxidation reactions, Reduction reactions, Hydrolysis reactions
  (These generally "destroy" or modify part of the drug molecule.)

Phase II Reactions

- Conjugation reactions
  (A new molecule binds to the drug – synthetic step.)

(1) Introducing
Adding a new OH or NH_2 that did NOT exist before
e.g., hydroxylation adds a brand-new OH
(2) Unmasking
Revealing an OH or NH that was ALREADY part of the molecule
$O-CH_3 \rightarrow O-H$

Drug Biotransformation

- Many phase I products may need a subsequent reaction to become polar enough to be readily excreted.
- The subsequent reactions are conjugation reactions with an endogenous substrate such as glucuronic acid, sulfuric acid, acetyl-CoA and glutathione or methyl group. .These conjugation reaction are phase II reactions.

Phase I Biotransformation reactions

1. Oxidation mainly but not only by the microsomal mixed function oxidase system or cytochromes P450 enzymes.
2. Reduction reactions may be cytochrome P450 dependent systems or by dehydrogenases and other reductases.

Remember: oxidation reduction are reversible reactions

Alcohol is converted to an aldehyde by alcohol dehydrogenase, and then the aldehyde is converted to acetic acid by aldehyde dehydrogenase...Alcohol→aldehyde→carboxylic acid
e.g.Methanol→formaldehyde→Formic acid

Click here

For more explanation about dehydrogenases and whether they do oxidation reactions or reduction reactions

3. Hydrolysis of esters and amides by esterases and amidases, respectively.

Oxidation mainly by the microsomal mixed function oxidase system or cytochromes P450 enzymes.

Microsomal refers to structures found in the ER, as part of the ER membrane. The membrane contains not only lipids but also proteins, some of which are cytochrome P450. They are called “microsomal ”because of research reasons. Scientists used to isolate the ER from cells through homogenization and centrifugation to study drug metabolism. Under the microscope, these structures appear as small circular bodies, so they named them “microsomes” (small bodies). This happens because if the ER is cut, its membrane naturally curls and forms tube-like structures.

Phase I Biotransformation reactions

- **Cytochrome P450 enzymes are located in the endoplasmic reticulum.**
- **They can metabolize a wide range of structurally different and lipid soluble drugs.**

Human Liver Cytochrome P450 Enzymes

CYP1A –2 the gene of the enzyme 1A2

Function :
Drug metabolism
Prostaglandin synthesis
Steroid synthesis

- There are numerous P450 isoenzymes.
- The most important are CYP1A2,

  CYP1A2 metabolizes drugs and activates toxins, such as polycyclic aromatic hydrocarbons (PAHs). These toxins require activation, which is carried out by CYP1A.2

- CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. The most important

You have to memorize those in green color

- CYP3A4 alone is responsible for the metabolism of > 50% of prescription drugs metabolized in the liver.

CYP3A4 and Drug-Drug Interactions:

1)Most drugs are metabolized by CYP3A4 → important for drug-drug interactions

2)substrates compete for metabolism → can inhibit each other

3)If metabolism is reduced → duration in the body increases→ effect increases

4)If the substance is a toxin → toxicity increases
This process is called substrate inhibition so that means substrate of an enzymes are competitive inhibitors of each other

5)The strongest inhibitor → the one with higher concentration and affinity → inhibits the others

Phase II Biotransformation reactions

- The drug is conjugated with endogenous substrates to yield drug conjugates.
- In general, conjugates are polar molecules readily excreted and inactive. The explanation is in the slide below.
- Conjugations are synthetic reactions, involve high-energy intermediates and specific transfer enzymes called transferases.

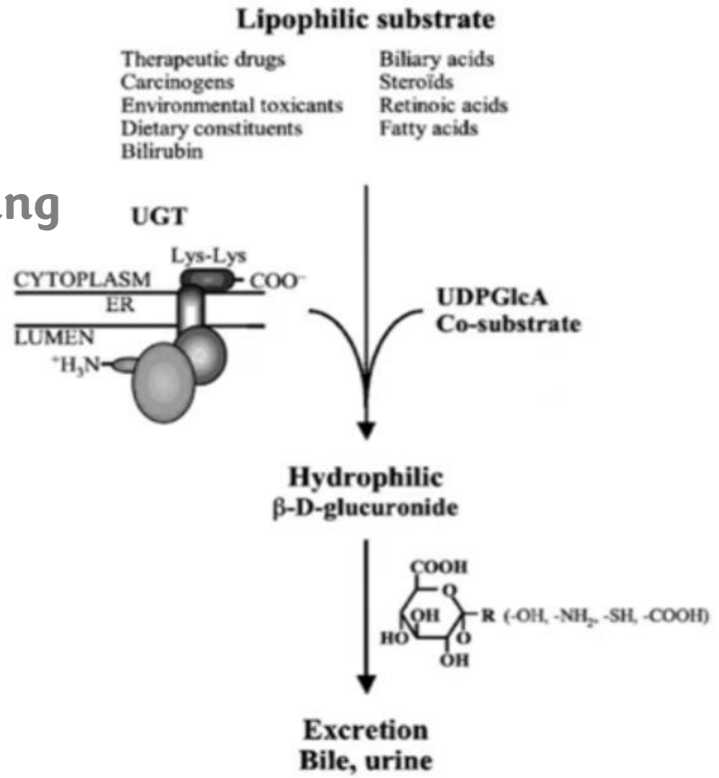
These enzymes are called transferases because they transfer a group from one molecule to another molecule

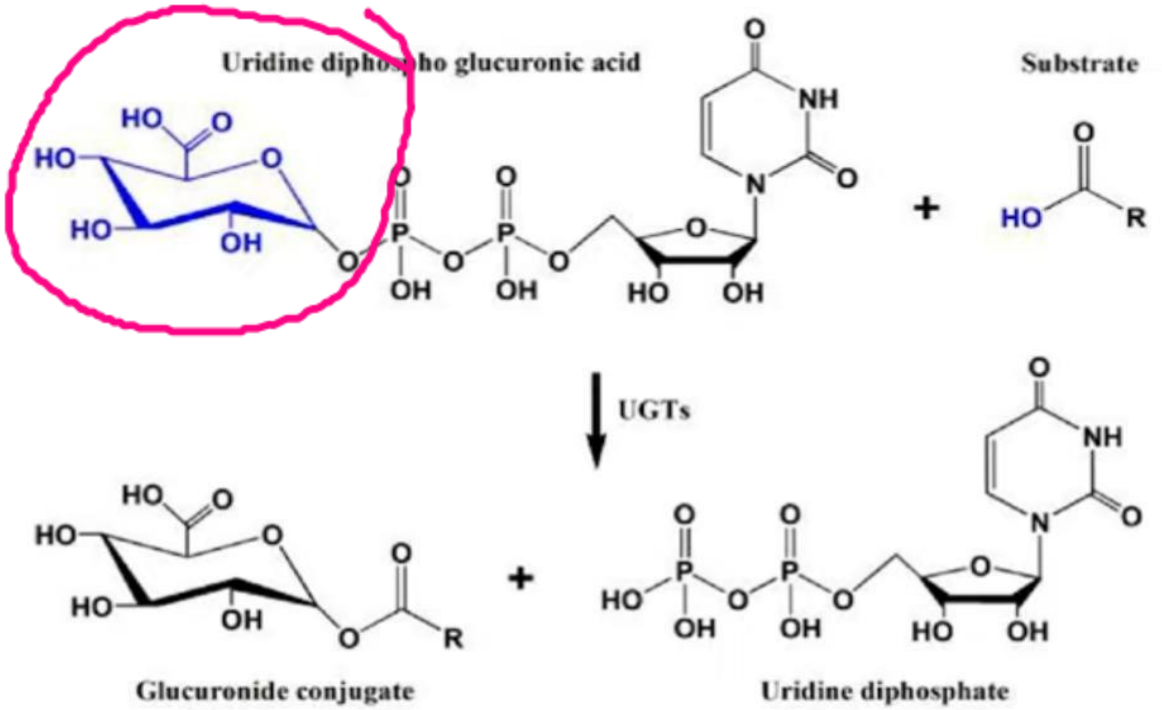
If a drug conjugates with glucuronic acid, it means adding 6 hydroxyl groups to the drug (5 hydroxyl groups, 1 carboxyl)

This makes the drug very polar →easily excreted in urine.

If the molecule is large, it can be excreted in bile.

For better understanding





need ATP

Phase II Biotransformation reactions

1. **Uridine 5'-diphosphate , [UDP]-glucuronosyl transferases (UGTs) are the most dominant conjugating enzymes. Groups glucuronidated are –OH, -NH, -SH, -COOH, -NHOH.**

We usually don't focus on chemical structures in pharmacology, but if you're doing specific research and examine a drug's structure, you can often predict its metabolic pathway based on the functional groups it contains. This helps you determine whether the drug is more likely to undergo conjugation, oxidation, reduction, or another metabolic reaction.

Explanation: UDP-glucuronosyl transferase (UGT) attaches glucuronic acid to a drug only if the drug contains one of these functional groups:-OH, -NH, -SH, -COOH, -NHOH

2. **Sulfotransferases (SULTs) use 3'-phosphoadenosine 5'-phosphosulfate (PAPS). Inorganic sulfate is a limiting factor for sulfation. Its sources are food and sulfur-containing amino acids.**

Sulfotransferases (SULTs) transfer a sulfate from PAPS (3′-phosphoadenosine-5′-phosphosulfate) to the drug

Note: Groups that can be conjugated with glucuronide acid and be conjugated with sulfate

Sulfotransferases (SULTs)

Sulfotransferases add a sulfate group (SO4)to drug molecule.
This process is called sulfation, and it converts the drug into a more water-soluble form that can be easily excreted.

What is the activated sulfate donor(the activated intermediate)?

PAPS (Phosphoadenosine-(etaflusohpsohp-5′

This molecule is considered very expensive for the body to produce

Why is it considered expensive?

Because the body needs to attach a sulfate group, and sulfate is not abundantly available inside the body.

So the body must obtain sulfate from two main sources:

Sources of Sulfate in the Body

.1Dietary sulfate from food, such as: garlic, onion, cabbage, cauliflower, turnip, and radish.

.2Breakdown of sulfur-containing amino acids:

Methionine
Cysteine

In other words: sulfates are easily depletable because their sources are limited.

Development

SULTs develop earlier than glucuronosyl-transferases.
Therefore, SULTs are more important in newborns and young children.

UGTs and SULTs –Development Sequence

Both UGTs and SULTs are Phase II enzymes, and just like organs develop gradually, enzymes also develop gradually.
SULTs: present immediately after birth.
UGTs: appear later, usually after a few months
This why the importance of SULTs later will decrease.

Clinical Example:Chloramphenicol

The drug Chloramphenicol was historically used, but it caused toxicity in newborns, known as Gray Baby Syndrome.
The newborns develop this toxicity because of UGT deficiency, and their skin becomes gray.
It could also cause aplastic anemia (serious bone marrow failure).
For this reason, the drug was withdrawn from the market for newborn use.

Phase II Biotransformation reactions

- **Almost all chemical groups that are glucuronidated are also sulfated.**
- **Infants are more capable of sulfation than glucuronidation, but in adults glucuronidation predominates.**

3. **N-acetyltransferases (NATs) utilize acetyl CoA as the endogenous cofactor for conjugation.**

Few drugs are metabolized by SULTs, and most of them are sulfonamide antibiotics.

Few drugs (like NTTP drugs) are metabolized by acetylation as well. E.g.Isoniazid

Phase II Biotransformation reactions

4. **Glutathione (GSH) transferases (GSTs).**

- **The donor is glutathione (GSH), which is Glu-Cys-Gly (tripeptide).**
- **GSH is a nucleophile that reacts with and detoxifies electrophiles.**
- **Cause halogen replacement (R-Cl → R-SG).**
- **Conjugates epoxides.**

Free radical

Highly reactive compounds

PAHs(poly cyclic aromatic hydrocarbons) → metabolically activated to epoxides,,,then these epoxides bind DNA and RNA

Can cause mutations and cancer

Glutathione (GSH) in Detoxification

GSH is important in detoxification because it protects cells from toxins.

It is a tripeptide composed of glutamate, cysteine, and glycine.

Its detoxifying action comes from the sulfhydryl (–SH) group in cysteine, which reacts with toxins,,,,and the conjugation happens on it.

Glutathione itself can withdraw toxin because it have sulfhydryl group and also it can withdraw the toxin through the activity of glutathione transferases(conjugating enzyme that utilizs glutathione as high energy intermediate).

Through this reaction, toxins are conjugated to GSH and can be safely removed from the body.

Phase II Biotransformation reactions

- **Glutathione conjugates do not appear in urine(because it is large), but may appear in bile.**
- **They are metabolized further to cysteine conjugates and then to mercaptouric acid conjugates (N-acetylated cysteine conjugates), that appear in urine by an active transport process.**

GSH is depletable because it depends on cysteine

Glutathione Conjugates and Toxicity

The body forms glutathion(GHS) Conjugates to detoxify certain drugs

GSH itself is not detectable in urine, but we can measure mercaptopuric acid conjugates.

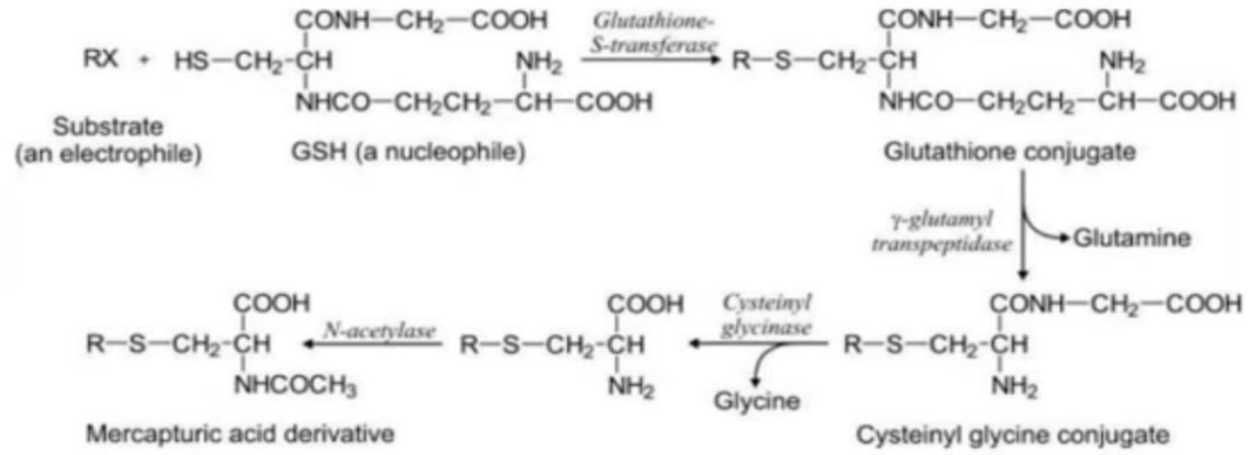
Presence of mercaptopuric acid in urine indicates GSH conjugation occurred.

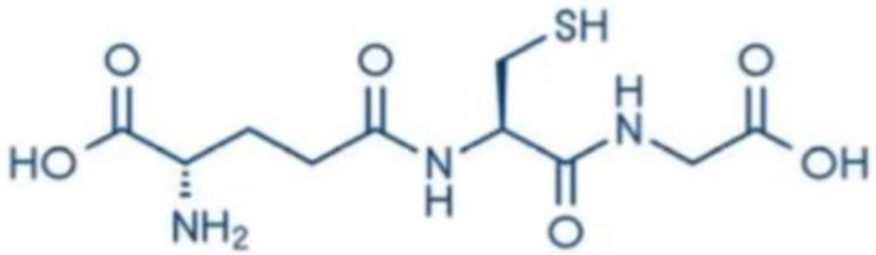
Patients with depleted GSH can develop toxicity.

We cannot give GSH orally (it is digested).

N-acetylcysteine (NAC) can be used as a substitute:
Why? Because it Acts like GSH in detoxification **and**
Provides sulfur to regenerate GSH in the body

Example: Paracetamol overdose
NAC treatment is effective if given early, not late.





glutathione

To increase understanding

Phase II Biotransformation reactions

5. **S-Adenosyl-L-methionine (SAM) mediate O-, N- and S-methylation of drugs and xenobiotics by methyltransferases (MTs).**

Methylation reaction by methyltransferase which use SAM as high energy intermediate...so :

· **Target Molecules:** Drugs and xenobiotics (specifically their O, N, and S atoms for methylation).

· **Donor Molecule:** S-Adenosyl-L-methionine (SAM)

Phase II Biotransformation reactions

- **Certain conjugation reactions may lead to formation of reactive species and drug toxicities.**

Examples:

1. **Acyl glucuronidation of nonsteroidal antiinflammatory drugs**
2. **O-sulfation of N-hydroxyacetylaminofluorine**
3. **N-acetylation of isoniazid**
4. **Sulfation leads to activation of the prodrug minoxidil.**
5. **Morphine-6-glucuronide is more potent than morphine.**

Phase II Biotransformation reactions

- **Certain conjugation reactions may lead to formation of reactive species and drug toxicities.** Conjugation usually makes the drug more polar and secretable & terminates the action of the drug, but here are some exceptions:

Examples:

1. **Acyl glucuronidation of nonsteroidal anti-inflammatory drugs**

   Conjugation of glucuronic acid (that are found on non-steroidal anti-inflammatory drugs) with a carboxylic group, then they become toxic reactive oxygen species.

2. **O-sulfation of N-hydroxyacetylaminofluorine**

   It will turn into a carcinogen

3. N-acetylation of isoniazid

4. Sulfation leads to activation of the prodrug minoxidil.

Remember prodrugs: not active by itself, it needs to be metabolized in the body in order to be activated.

Minoxidil is a vasodilator used for hair growth. It becomes active by sulfation
conjugation reaction.

(friendly advice: do **not** use it for your hair, it's just going to fall off once you stop using it)

5. Morphine-6-glucuronide is more potent than morphine.

More potent means less amount of morphine-6-glucuronide makes same effect as morphine when given at a higher dose.

Metabolism of Drugs to Toxic Product

- **Several drugs may be metabolically transformed to reactive intermediates that are toxic to various organs.**

Another exception:

Both are scientific names

- **An example is acetaminophen (paracetamol)- induced hepatotoxicity.**

Damage to the liver & the lungs when overdose because of toxic metabolites (in three days).
It produces minor toxic metabolites when taken at regular dose, but it's insignificant.

- **It normally undergoes glucuronidation and sulfation, which make up 95% of the total excreted metabolites.**

Metabolism of Drugs to Toxic Product

- **A minor toxic metabolite (P450-dependent) may accumulate in case of paracetamol over dose.**
- **This metabolite can be eliminated normally by GSH conjugation pathway.**
- **No hepatotoxicity results as long as hepatic GSH is available for conjugation.**
- **At high paracetamol dose and when GSH is depleted, the toxic metabolite accumulates resulting in hepatotoxicity.**

Glutathion is **available**: no hepatotoxicity
Depletion of glutathion: hepatotoxicity

Metabolism of Drugs to Toxic Product

- **Administration of N-acetylcysteine (antidote) within 8–16 hours after acetaminophen overdosage protects victims from fulminant hepatotoxicity and death.**
- **Administration of GSH is not effective because it does not cross cell membranes readily.**

Treatment: n-acetylcysteine (given orally or by injection) turns into and compensates for glutathione. This treatment requires early detection. We can't give glutathione directly because it's going to be digested.

Enzyme Induction

- It means 1) Mainly enhanced rate of enzyme synthesis, 2) or reduced rate of degradation.
- **Results in accelerated drug metabolism, and usually in a decrease in the pharmacological action of the drug.**

More enzymes more metabolism

- Except **Toxicity may increase if the drug is metabolized to reactive metabolites.**

If the metabolites were reactive or if it was a prodrug: the action will increase.
If the metabolites were reactive and can react with tissues and cause damage to cells: toxicity will increase

- **Induction mostly starts at the gene level.**
- Transcription > mRNA > protein synthesis It takes days.

Enzyme Induction

Inducers include (but are not limited to):

1. **Environmental chemicals and pollutants such as polycyclic aromatic hydrocarbons present in tobacco smoke and charcoal-broiled meat.**

The drugs used for epilepsy include antiepileptics, barbiturates, phenytoin, and carbamazepine

2. **Drugs: barbiturates, phenytoin, carbamazepine, rifampin.**

The drugs used for tuberculosis include rifampin or rifamycin.

3. **Cruciferous vegetables.**

Cabbage, cauliflower, broccoli

4. **St. John's wort.**

A herb in America that is used to treat depression.

- **Polycyclic aromatic hydrocarbons are the products of incomplete combustion of organic matter.**
- **Polycyclic aromatic hydrocarbons are carcinogenic to the lung and urinary bladder .**
- **The grilled foods contain polycyclic aromatic hydrocarbons, which are carcinogenic to the stomach , because stomach receive most of toxins.**

Enzyme Induction

- Autoinduction refers to a drug that induces its own metabolism, like carbamazepine. anti-seizure drug
- **Autoinduction may lead to tolerance to drug action.**

Induction occurs after four half-lives of the drug, reaching its maximum level, which means it is in a steady state.
When we start the treatment by giving a specific dose, the drug reaches the steady state, and the metabolizing enzymes reach their maximum activity, leading to increased metabolism of the drug, which reduces the therapeutic concentration.
As a result, the patient may experience seizures again, so after three weeks, the dose needs to be increased. This highlights the importance of autoinduction, as it leads to what is called drug tolerance that means the drug is no longer effective or has become less effective. Therefore, the importance of autoinduction is that it may lead to tolerance to drug action and requires increasing the dose.

Enzyme Inhibition

1. **Macrolide antibiotics such as erythromycin, inactivate (CYP3A).**
2. **Suicide inhibitors (inactivators) include grapefruit furanocoumarins**

1) Inhibit CYP3A (suicidal means that they kill the enzyme) and they inhibit P-glycoprotein .
2) If you drink 250 mL, it will shut down CYP3A4 for one to two days, but you drink it consistently, it will stop performing adequate metabolism for 50% of the drugs that are metabolized.

3. **Substrates compete with each other for the same active site of the enzyme.**
4. **Deficiency of cofactors impair drug metabolism.**

Enzyme Inhibition

5. **Inhibitors of nucleic acid and protein synthesis impair enzyme synthesis and, thus, drug metabolism.** Because they prevent the transcription and formation of the gene of the metabolizing enzyme .
6. **Malnutrition.**
7. **Impairment of hepatic function.** Cirrhosis of the liver

Enzyme Inhibition

- **Enzyme inhibition leads to accumulation of the drug in the body, thus increasing its adverse reactions and toxicity.**
- **In case of prodrugs, there will be failure of drug response.**
- **Both enzyme inhibition and induction are mechanisms of certain drug-drug interactions.**

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:

1. Photos for deep understanding
https://youtu.be/uYbJKqtDDG0?si=T8R6ne0nLC0M6azb

لا تنسونا من صالح دعائكم

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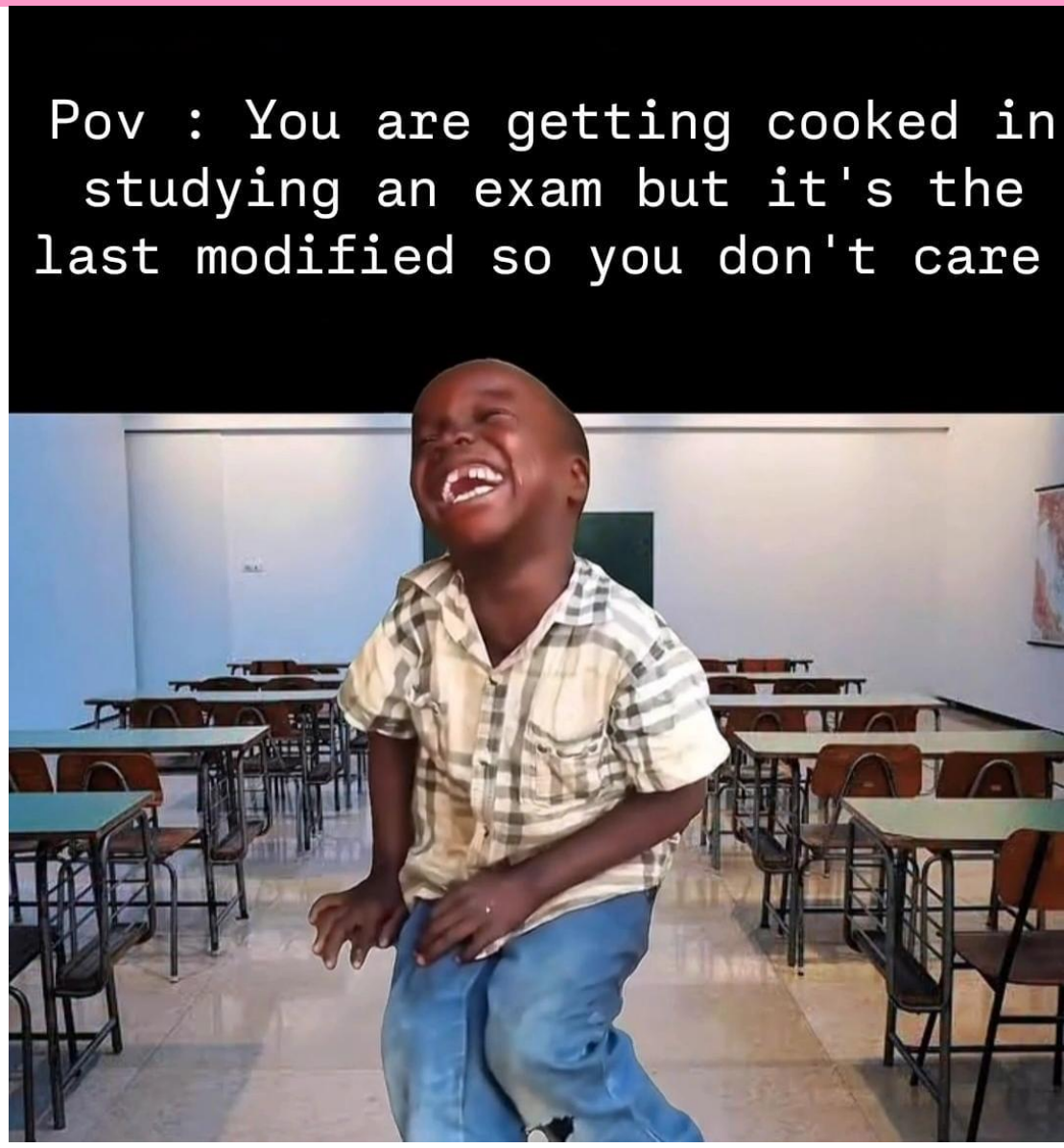

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	**Slides 44-54 were added**		**From DST, related to the last part of the last mid lecture**
V1 → V2			