PHARMACOLOGY

بسم الله الرحمن الرحيم

MID – Lecture 6

Routes of Drug Administration & Drug Biotransformation (pt.1)

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

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Quiz for the last lecture

Routes of Drug Administration

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Routes of Drug Administration

A. **Enteral** — Means: administration of drug through GI tract.

B. **Parenteral** — Other tracts, Not the GI tract, include injections.

C. **Others**

Abbreviations of route administration **are required** .

Enteral Routes

1. **Oral route (PO):** Os (Latin): means "mouth"

- **The drug should be swallowed.** Swallowed whole
- **Most commonly used route.** Because it's most convenient
- **Safest** Doesn't mean safe
- **most convenient, and most economical**

  Cheaper than injections because it doesn't need aseptic techniques and multiple procedures .

- **Duodenum is the major site of absorption, but stomach, jejunum and ileum may be involved.**

WHY ?

-Because Duodenum contain folds in mucosa, **mucosa** is not smooth it's a folding structure and it has villi for increasing the surface area.

-Is the most important site for absorption due to its largest surface area.

FLUX = (C1-C2) [(AREA * PERMEABILITY COEFFICIENT)/THICKNESS]

Remember from previous lectures: increasing surface area enhances absorption, making the duodenum a suitable site for absorption.

-In Stomach: acidic drugs can be absorbed because they are **unionized** while basic drugs can't because they are **ionized** .

In conclusion: the absorbed is unionized fraction of the drug.

In Stomach: acidic drugs can be absorbed because they are **unionized** while basic drugs can't because they are **ionized** .

In conclusion: the absorbed is unionized fraction of the drug.

- Different sites in the gastrointestinal tract (such as the stomach, duodenum, jejunum, ileum, and colon) have different pH levels, influencing drug absorption.

-The colon and rectum are not primary absorption sites for most drugs; instead, they primarily reabsorb water and electrolytes after digestion.

-Degree of ionization depends on :

1) Pka of the drug.
2) PH of the medium.

-Absorption window of the Drug: is the site where the drug is absorbed mostly (absorption happens at the highest degree of the unionized fraction) .

-When does the adequate absorption happen?

1) When absorption happen at proper time .
2) Last for proper duration at that site.

If the drug pass quickly at state of high motility in GI tract or cramps, the drug may not last enough at the site of absorption.

-Every drug has suitable site of absorption differ than the others.

Some of those are mentioned before in the low bioavailability lecture.

Enteral Routes

Disadvantages:

Those patients are not cooperative (عنيد).

1. **The patient must be cooperative (compliant).**
2. **Absorption is variable because of several factors affecting the rate and extent of absorption:**

a) **Vomiting.** Patients who vomit the drug (we can't treat them with oral drugs) .
b) **Failure of disintegration and dissolution.**
c) **First-pass effect.**
d) **Drug may be destroyed by gastric acid or intestinal flora.**

Enteral Routes

Food may delay absorption.(majority of the drugs)

EXCEPTIONS:

-In some cases, food does not affect absorption, while in others, it can enhance it.

-Which drugs their absorption will be increased by food ?

Highly lipid-soluble drugs taken with foods **high in lipid** content (e.g., fats) are solubilized in lipids, allowing them to be absorbed through the **lymphatic system**, where they then circulate in the form of **chylomicrons**.

-In conclusion: food may increase the absorption of certain drugs, but generally, for the majority of drugs, food may delay their absorption.

- Alteration in intestinal motility may affect absorption.

(In cases of increased gastrointestinal motility, the drug may pass through its absorption window too quickly, resulting in decreased absorption)

- Absorption may be affected by splanchnic blood flow.

(Very limited role of administration)

Enteral Routes

2. Sublingual route (SL): تحت اللسان

- **The drug is placed under the tongue.** Highly vascular area, absorption can be fast.
- **Avoids the first-pass effect.** (So it's provided with a smaller dose compared to the oral dose)

  It doesn't go to portal circulation. It goes directly to the systemic circulation.
- **Used when a rapid onset is required – such as in angina pectoris.** See the next slide
- **Not commonly used.** (Very few indications but it's fast and has a significant role)

Angina pectoris (الذبحة الصدرية): is a cardiac condition caused by reduced blood flow to the heart, often due to platelet aggregation in the coronary arteries.

If a patient experiences this condition at home and immediate treatment is needed, but no injection is available, we advise the patient to chew an **aspirin tablet** to release it quickly in the mouth for fast absorption.

Additionally, a **nitroglycerin** tablet can be placed under the tongue (sublingually) to promote rapid absorption. This approach provides initial treatment until the patient can reach a hospital.

Aspirin -> **inhibits** platelet aggregation almost immediately, which is essential in small doses to prevent clotting.

The anti-platelet (cardiac) dose ranges from 60-100 mg, whereas the dose for analgesic and antipyretic effects (pain and fever relief) ranges from 700-10,000 mg. If a patient has a 350 mg tablet and only requires 60 mg, chewing the tablet can help achieve the effective dose quickly.

For a required dose of 325 mg, if each tablet is 100 mg, the patient would need to take 3 tablets.

1. Aspirin is absorbed in a highly vascular area (the mouth) when chewed, allowing for rapid action.
2. It is released locally for quick effect.
3. This method of administration is particularly useful for patients experiencing heart ischemia.

Nitroglycerin-> acts as a vasodilator, helping to relieve angina by widening blood vessels to improve blood flow to the heart.

Can we chew the drug then swallow it ? (Not for all drugs)

All slow- or controlled-release drug preparations should not be chewed and must be swallowed whole to ensure proper drug release.

-Children may be tempted to chew flavored medications, but they should not chew any slow-release drugs.

Enteral Routes

-The rectal route can be used for either **systemic** or **topical effects**.
-**Systemic**: Medications absorbed into the bloodstream for a full-body effect.(PR or per rectum)
-**Topical**: Direct treatment within the rectum, such as suppositories for localized rectal diseases.

3. Rectal route (PR):

- **Avoids first-pass effect partially (~ 50%). Why?** (Average first-pass effect)

Rectal circulation divides, with the upper part entering the portal circulation and the lower part going directly into systemic circulation. This distribution reduces the first-pass effect, as only part of the drug is processed by the liver.

- **Useful in unconscious or vomiting patients.**

Since vomiting reduces or prevents oral absorption, if a patient is experiencing vomiting and is in need of medication, we can administer the drug rectally. Alternatively, if the patient is unconscious, we may administer the medication as a suppository(تحميلة) via the rectum.

Enteral Routes

3. Rectal route (PR):

- **Absorption is often irregular, incomplete and unpredictable.**

Why?

Because the rectum, like the rest of the large intestine, is not primarily an organ of absorption. As mentioned earlier, absorption is not the main function of the rectum.

- **Can be used for a local effect.**
- **Used for drugs poorly absorbed from, or unstable in the GIT.**

For example, if a drug is destroyed by gastric acid, it can be administered via the rectum. This bypasses the stomach and the digestive process that could degrade the drug

- **Used for rapid effect for local diseases.**
- **Aseptic technique is not required.**(Also oral and sublingual routes)

تعقيم

Parenteral Routes (Injections)

1. Intravenous route (IV):

- **Bolus vs infusion.**

-We can administer an IV bolus as a single dose, or an infusion slowly over time.
-The infusion can be delivered using various methods:
either **mixed with IV fluids** or **through specialized pumps**. For example, heparin, an anticoagulant, is often administered via an infusion pump.

- **Only aqueous solutions may be injected IV.**

It must be watery. For example, if someone mentions that a patient was given an IV that was not aqueous but instead milky or turbid in appearance, this would ***not*** be considered drug administration. This is called ***parenteral nutrition***, which is given to patients who lack appetite or those with ***anorexia nervosa***, a psychiatric illness affecting some individuals who have a fear of eating. This is not a drug administration, but rather nutritional support. Drugs, on the other hand, should be administered in an aqueous solution to ensure proper absorption and safety.

Parenteral Routes (Injections)

1. Intravenous route (IV):

- **Rapid onset of action.**
- **Oily vehicles or those that precipitate blood constituents should NOT be given IV.**
- **No first-pass hepatic metabolism, the drug goes first to the right side of the heart, the lung, the left side of the heart, then to the systemic circulation.**

IV dose is lower than the oral dose for drugs that undergo the first-pass effect.

Parenteral Routes

Disadvantages:

1. **Produce high initial concentration of the drug that might be toxic.**

However, this initial concentration is not sustainable because, through distribution, it will decrease very quickly over a short period of time.

2. **Once injected, the drug is there…??**

- Once an overdose is administered intravenously, few options exist for intervention unless the drug is dialyzable.

-If the drug is dialyzable, contacting a kidney unit for hemodialysis may be an option, but success is not guaranteed, and the patient may not survive long enough for the intervention to take effect.

-**Medical errors**, including medication errors, are a leading cause of death in the U.S., ranking as the fourth to sixth most common cause.

-**Medical errors** can increase hospital stays by 7 to 21 days, significantly driving up healthcare costs.

-Medication errors are the most frequent type of medical error and contribute to extended hospitalizations and added healthcare expenses.

Make sure you can distinguish between medical errors and medication errors.

Parenteral Routes

2. Intramuscular route (IM):

Because of the bulk

- **The drug is injected within muscle fibers of the deltoid, gluteus maximus or vastus lateralis** (lateral part of the leg).
- **Absorption of drugs depends on the blood supply (slower for g.m) Why?**

-If the injection doesn't reach the muscle, absorption is affected.
-The drug is absorbed slowly in the gluteus maximus muscle due to fat.
-Fat decreases blood flow to the area, leading to reduced absorption.

- **Absorption is reduced in circulatory failure or shock.**

In heart failure or shock, low blood flow reduces absorption, so IM injections are not effective for treatment.

- **To be injected IM, the drug must be non- irritating to tissues.**

Irritating drugs are not given via IM or subcutaneous routes. If administered IM, the patient will experience pain and itching.

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).**

-What do we mean by “Depot” ?

It refers to a drug formulation that is placed in a specific solution or vehicle, which prevents immediate absorption into the bloodstream. Instead, the drug remains at the injection site or in a reservoir, where it is gradually released over time into the circulation for extended therapeutic effects.

- **Can accommodate large volumes.**

See the next slide for explanation

- **Can accommodate large volumes.**

-Large-volume intramuscular (IM) injections can be administered, but this topic is not directly related to routes of administration; however, it's important to understand the risks. IM injections should be avoided in patients taking anticoagulants because the needle can penetrate small blood vessels within the muscle, leading to bleeding. In patients on anticoagulants, significant bleeding can occur, with blood leaking into the muscle. While muscles can accommodate some bleeding, large volumes may eventually lead to anemia and symptoms such as weakness and fatigue. In severe cases, excessive bleeding can cause systemic issues, including shock, cause hyperthermia in the kidneys,etc.

-Regarding large-volume injections, it's important to understand that "large volume" doesn't mean administering 1 or 2 liters IM. Typically, large-volume IM injections range from 100 to 200 mL maximum, anything more than that should not be given via IM.

Parenteral Routes

3. Subcutaneous injections (SC, or SQ):

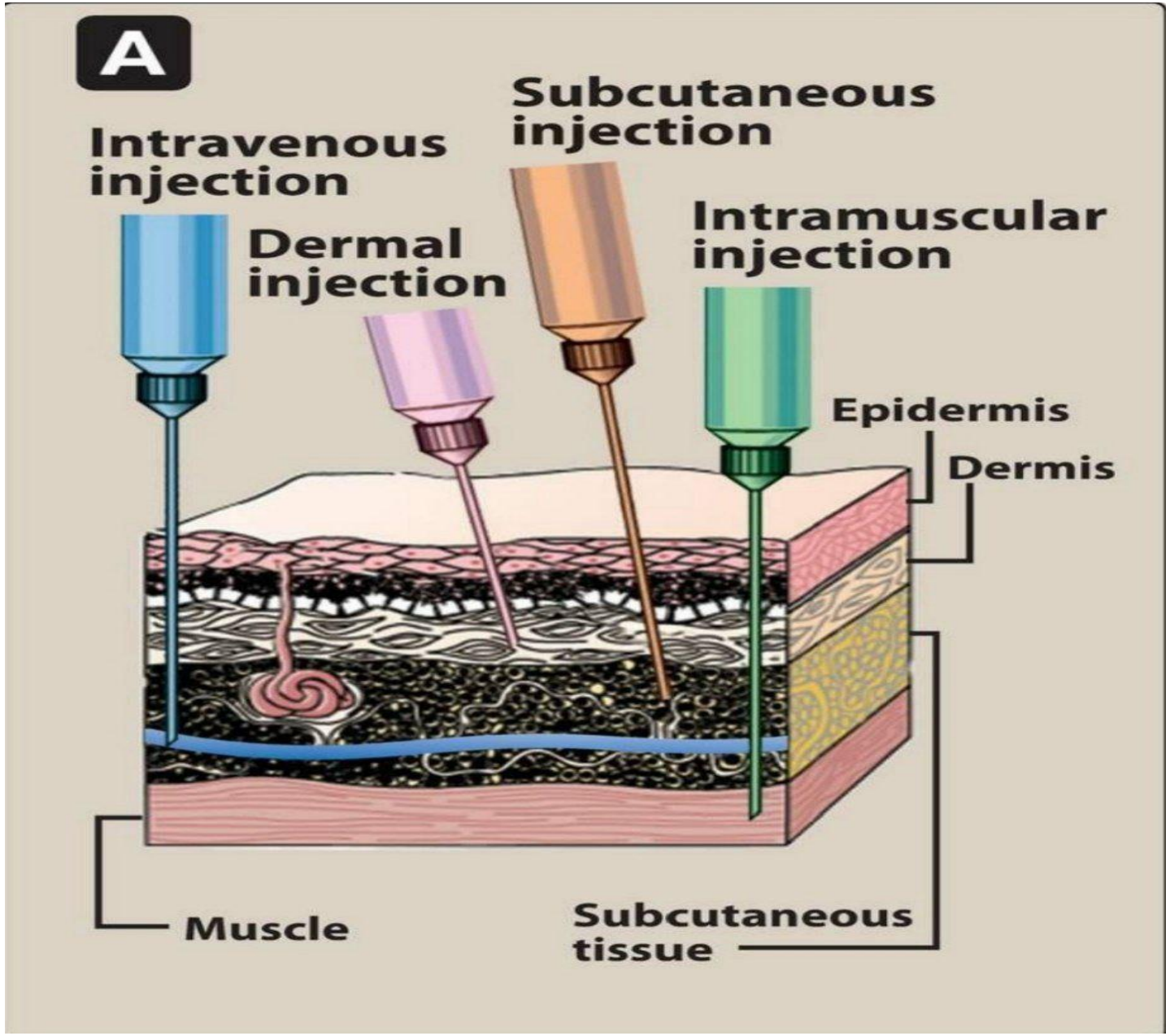
- **The drug is injected under the skin.**

The main sites for subcutaneous injections are the upper arm, the abdomen and thigh.
For patients requiring chronic subcutaneous injections, such as insulin for diabetes, it's important to change the injection site each time.

- **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.**

Solid pellets are a type of solid dosage form used for long-term drug delivery. To administer, a small incision is made in the skin, the pellet is placed under the skin, and the site is then stitched closed. This method allows the drug to release slowly, reducing the need for daily dosing. Depending on the pellet's size and the drug type, the release can last from weeks to months, with some pellets providing effects for up to two years. This is an example of utilizing the subcutaneous route for sustained drug delivery.

EXTRA IMAGE


A
Intravenous injection
Subcutaneous injection
Dermal injection
Intramuscular injection
Epidermis
Dermis
Muscle
Subcutaneous tissue

The **inhalational route** is not considered parenteral because "parenteral" typically refers to injections.

Other Routes

Parenteral = not oral

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 (هَباء), such as drugs for bronchial asthma.** In aerosols, solid particles are dispersed and suspended in the air, rather than dissolving.
- **Drugs are absorbed across pulmonary epithelium and mucous membranes of respiratory tract.**
- **Absorption is rapid.**

A patient given inhalational anesthetics typically can't finish counting to ten!

- **Avoids first-pass effect.** Because there is no portal circulation to the lung.
- **The lung acts as a route of elimination also.**

Other Routes

2. **Topical application:**

- **For a local effect on:**

  a. mucous membranes: conjunctiva, nose, mouth, nasopharynx, oropharynx, vagina, rectum, colon, urethra, and urinary bladder.

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

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

Other Routes

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

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

Required

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

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You're not overdosing on information—you're just in the loading dose phase! ☺

Drug Biotransformation

Xeno = foreign
Biotic: affects living organisms

They affect the body negatively

- **Humans are always exposed to foreign compounds called xenobiotics through the GIT, skin, lungs, etc.**
- **Xenobiotics include drugs, environmental toxins and industrial toxins.**
  - The body has defense mechanisms for handling these substances. **For microbes**, we rely on the immune system. **For chemicals**, if they are small, they are excreted in urine.
  - If they are large and lipid-soluble, they undergo metabolism in the liver, and the resulting metabolites are excreted in the urine or bile.
- **Xenobiotics excreted by the kidney are usually small polar molecules or ionized at physiologic pH.**

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.** Because they are large .
- **Such drugs are metabolized in the liver to more polar molecules that can be excreted in urine and/or bile.**

These metabolites are excreted in urine if they are 500 MW or less. If they are 1000 MW or more, they get excreted in bile. For medium-sized metabolites, excretion can occur through either route.

Drug Biotransformation

- **Metabolic products are often less active than the parent drug and maybe even inactive.**
  - This serves as a defence mechanism in the body to protect us from toxic substances.

Exception:

1. Some drug metabolites have enhanced activity or even toxicity.

Morphine, a centrally acting analgesic, is metabolized by the liver, and its metabolite is more potent as an analgesic than the parent drug.

2. Some drugs are inactive and need to activation by metabolism (prodrugs) like levodopa, codeine.

If the drug isn't metabolized, it won't be effective. For example, levodopa, used in Parkinsonism, needs to cross the blood-brain barrier and convert to dopamine in the brain to work, as dopamine itself cannot cross. Similarly, codeine must be metabolized into morphine to act as an analgesic.

For more explanation click here

1. Some drugs are metabolized into toxins.

Drug Biotransformation

Examples:

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

-One metabolite, N-acetyl-p-benzoquinone imine, is usually produced in small amounts.
-In large doses or overdose, this metabolite can cause severe liver damage.
-Toxic effects on the liver are delayed, often taking around three days to appear.
-Paracetamol overdose can also damage the lungs through the same mechanism.

Read more about the effects of paracetamol overdose on the lungs.
(Click here)

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

1. Halothane was one of the first volatile general anesthetics used.
2. It is primarily eliminated via the lungs once administration stops.
3. Halothane metabolism can produce hepatotoxic free radicals.
4. Glutathione is part of the body's defense system against free radicals.
5. If glutathione levels are depleted, the risk of hepatotoxicity increases.

Test yourself (added slide)

1) An 18 years old female patient is brought to the emergency department due to drug overdose. Which of the following routes of administration is the most desirable for administering the antidote for the drug overdose?

A) intramuscular
B) intravenous
c) subcutaneous
D) transdermal

2) Which route of administration is most likely to subject a drug to first pass metabolism?

A. Intravenous
B. Sublingual
C. Oral
D. Inhalation
E. Intramuscular

1) B 2) C

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	20	but it does not typically cause hyperthermia in the kidneys.	cause hyperthermia in the kidneys,etc.
V1 → V2			

Additional Resources:

References Used:

Lippincott Chapter 1

Clinical pharmacology

رسالة من الفريق العلمي:

"منك السعي، ومن اللهِ السّعة".

لا يهم كم استغرقت لتنهض، ولا يهم
كم الغبار الذي يعلوك، انهض كأنك
لم تقع وانفض غبارك، كأن شيئًا
لم يعلق بك