7

Pharmacology

Doctor 2017 | Medicine | JU

Sheet ○ Slides

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DOCTOR

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Pharmacokinetics

- May be simply defined as what the body does to the drug.

- The determination of the fate of substances administered from an exogenous source to a living organism.

- The study of the movement of drugs in the body, including the processes of absorption, distribution, localization in tissues (where it meets the pharmacodynamics), biotransformation (Metabolism) and excretion.

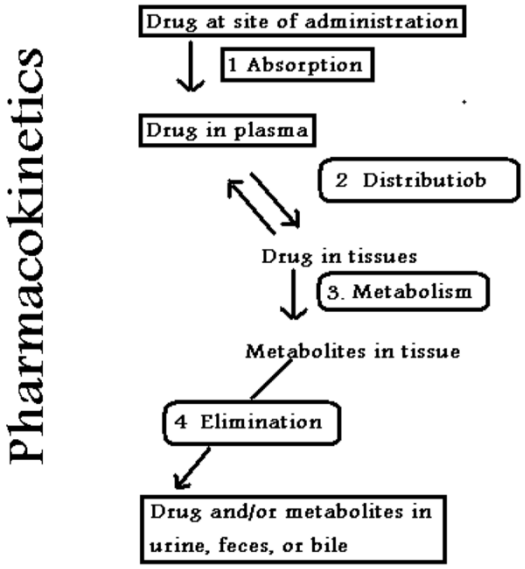
*Usually it's considered as 4 processes, absorption, distribution, metabolism and excretion. For short ADME.

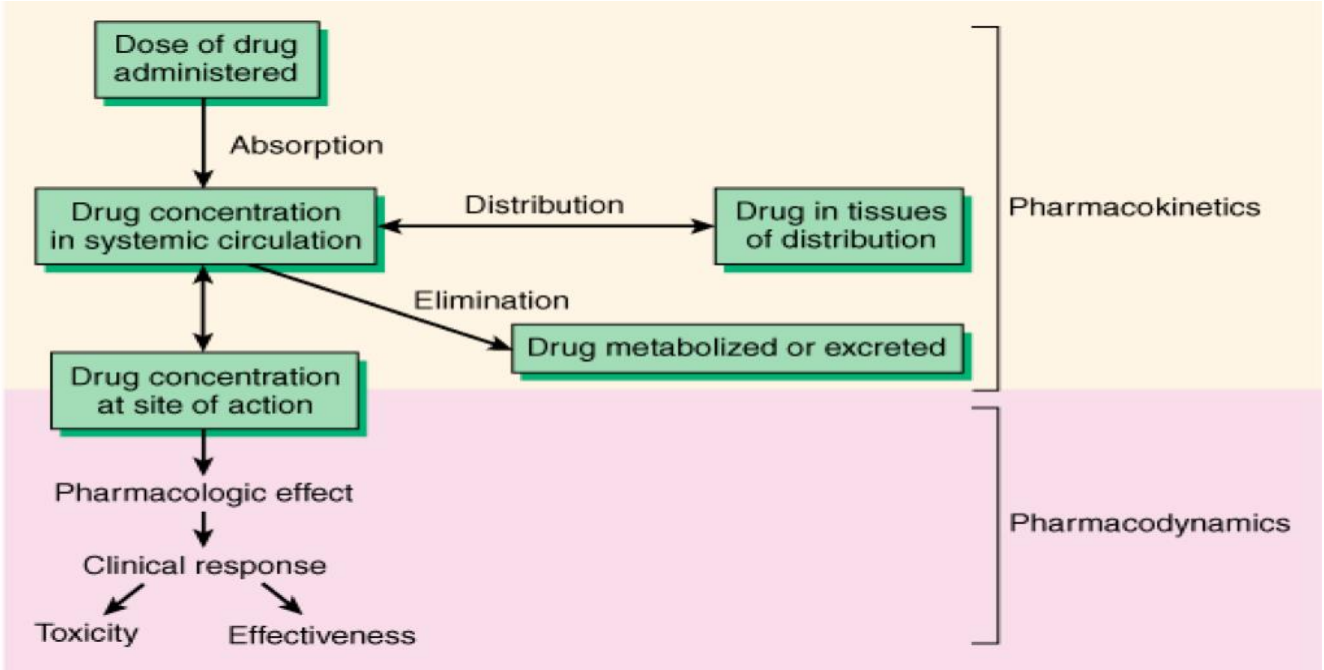
Absorption - drug gets into bloodstream

Distribution - gets to site of action

Metabolism – change the form of the drug to a form to a form that is excreted more easily

Elimination - leaves the body





Routes of drug administration

Determined by the properties of the drug:

- Water solubility – could then be injected.
- Lipid solubility – could be given topically.
- Ionization – depending on the Pka of each drug, we will know where the drug be absorbed more and by how much.

Determined by the therapeutic objective:

- Duration of treatment – you can't keep the patients in hospital for days for IV therapy when you can simply give him pills to take at home.
- Desirability of the rapid onset (response) – in case of an anaphylactic shock you need a quick response so you give the drug by IV (intravenous) and also you will be able to correctly administer the dose.
- Restrictions – explained by the disadvantages in the next table:

ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES
Oral	• Variable; affected by many factors	• Safest and most common, convenient, and economical route of administration	• Limited absorption of some drugs • Food may affect absorption • Patient compliance is necessary • Drugs may be metabolized before systemic absorption
Intravenous	• Absorption not required	• Can have immediate effects • Ideal if dosed in large volumes • Suitable for irritating substances and complex mixtures • Valuable in emergency situations • Dosage titration permissible • Ideal for high-molecular-weight proteins and peptide drugs	• Unsuitable for oily or poorly absorbed substances • Bolus injection may result in adverse effects • Most substances must be slowly injected • Strict aseptic techniques needed
Subcutaneous	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable for slow-release drugs • Ideal for some poorly soluble suspensions	• Pain or necrosis if drug is irritating • Unsuitable for drugs administered in large volumes
Intramuscular	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable if drug volume is moderate • Suitable for oily vehicles and certain irritating substances • Preferable to intravenous if patient must self administer	• Affects certain lab tests (creatine kinase) • Can be painful • Can cause intramuscular hemorrhage (precluded during anticoagulation therapy)

Oral:-

**the safest route;* you don't need to be in a sterile environment, you don't need to go to the hospital, you don't get injected and you don't get very high concentration of the drug administered immediately to your body.

* mainly affected by food that it might interact with some chemicals in food that might stop its absorption. example: an antibiotic called tetracycline is used to treat acne and bone inflammation. Tetracycline should be taken on an empty stomach, at least 1 hour before or 2 hours after meals. Do not take tetracycline with food, especially **dairy products** such as **milk**, **yogurt**, **cheese**, and **ice cream**; because the drug will bind with calcium and prevents gut absorption.

*some drugs are acid labile; they are metabolized by the acidity of the stomach. For example: insulin, being a protein, will be destructed by the acidity of the stomach if given orally and the patient won't receive any part of the drug; that's why it's given intravenously and subcutaneously.

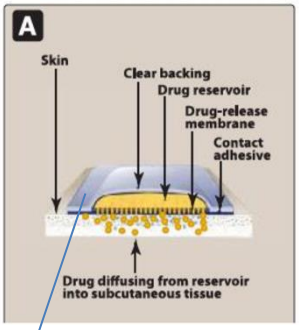
Intravenous (IV): -

**Ideal if dosed in large volumes;* we have high compartment of blood in the body, so we can give high concentration of the drug for a long period of time, because the blood can accommodate high volumes of the drug, unlike other routes such as subcutaneous and intramuscular.

***suitable for irritating substances and complex mixtures;* we don't have irritability in the bloodstream, because it lacks the tissues which will interact with the drug.

20 mins mark

Transdermal Patch



First-pass effect: Most of the drugs given orally are destroyed by enzymes from the liver and in the stomach and intestines. You can pass this effect by giving the drug by **IV, Transdermal patch, Rectally (partial) and sublingually**

Transdermal (patch)	• Slow and sustained	• Bypasses the first-pass effect • Convenient and painless • Ideal for drugs that are lipophilic, thus requiring prolonged administration • Ideal for drugs that are quickly eliminated from the body	• Some patients are allergic to patches, which can cause irritation • Drug must be highly lipophilic • May cause delayed delivery of drug to pharmacological site of action • Limited to drugs that can be taken in small daily doses
Rectal	• Erratic and variable	• Partially bypasses first-pass effect • Bypasses destruction by stomach acid • Ideal if drug causes vomiting • Ideal in patients who are vomiting, or comatose	• Drugs may irritate the rectal mucosa • Not a well-accepted route.
Inhalation	• Systemic absorption may occur. This is not always desirable	• Absorption is rapid; can have immediate effects • Ideal for gases • Effective for patients with respiratory problems • Dose can be titrated • Localized effect to target lungs: lower doses used compared to that with oral or parental administration • Fewer systemic side effects	• Most addictive route (drug can enter the brain quickly) • Patient may have difficulty regulating dose • Some patients may have difficulty using inhalers
Sublingual	• Depends on the drug: Few drugs (for example, *nitroglycerin*) have rapid, direct systemic absorption Most drugs erratically or incompletely absorbed	• Bypasses first-pass effect • Bypasses destruction by stomach acid • Drug stability maintained because the pH of saliva relatively neutral • May cause immediate pharmacological effects	• Limited to certain types of drugs • Limited to drugs that can be taken in small doses • May lose part of the drug dose if swallowed

*Immediate effect: IV, Inhalation, Sublingual.

*Slow release: Subcutaneous, Transdermal patch, some types of Orally given pills.

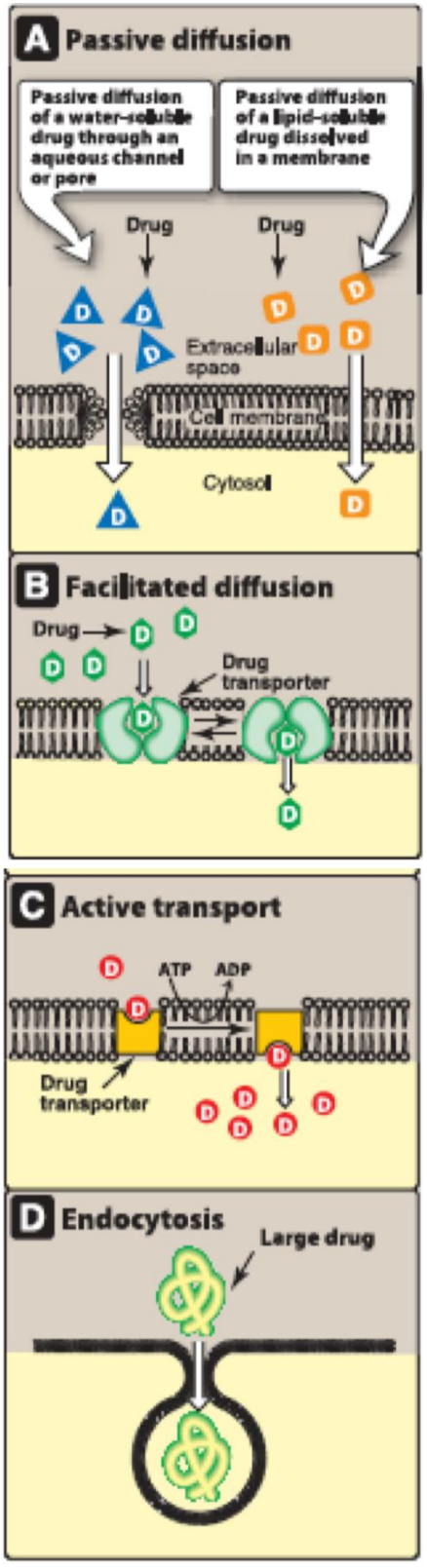
Mechanisms of absorption of drugs from the GI tract

1- Passive diffusion: The driving force for passive absorption of a drug is the concentration gradient across a membrane separating two body compartments.
   Passive diffusion does not involve a carrier, is not saturable, and shows a low structural specificity.
   - Water soluble drugs move through channels or pores.
   - Lipid soluble drugs move across the membrane.

2- Facilitated diffusion: Agents move through the cell by using specialized transmembrane carrier proteins that facilitate the movement of those agents and large molecules.
   It doesn't require energy and it moves along the concentration gradient. Can be saturated and **May be inhibited by other compounds. Ex: Glucose transport.**

3- Active transport: involves carrier proteins spanning the cell membrane except that it requires hydrolysis of ATP to function and it's capable of moving drugs against the concentration gradient.
   It works with only a few drugs that resemble the structure of some naturally occurring metabolites that are actively transported into the cell.
   Saturable, Selective and could be Competitively inhibited by other co-transported substances.
   Ex. Sodium Potassium Pump.

4- Endocytosis & Exocytosis: Used to transport exceptionally large drugs across the membrane.
   Vitamin B12 is transported across the gut wall by endocytosis.



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Absorption & Bioavailability:

Absorption is the transfer of a drug from the site of administration to the bloodstream.

The Bioavilability of the drug: The fraction of an administered dose of an unchanged drug that reaches the systemic circulation.

$$Bioavilability = \frac{plasma\ levels\ of\ a\ drug}{levels\ achived\ by\ IV\ administration} \times 100\%$$

- IV: 100%, Complete bioavilability.
- Variable for all other routes of administration.

Weak acidic drugs are absorbed faster and more completely in the stomach, because it is an acidic medium; high [H+], so the drug will be protonated, and a protonated weak acid **has no charge** and can pass the lipid membrane unlike the charged species.

$$pH = pK_a + \log \frac{[\text{nonprotonated species}]}{[\text{protonated species}]}$$

For acids: $pH = pK_a + \log \frac{[A^-]}{[HA]}$

For bases: $pH = pK_a + \log \frac{[B]}{[BH^+]}$

Weak basic drugs are absorbed faster and more completely in the intestines (alkaline medium).

Bioequivalent: Drug products are considered bioequivalent when the raise and expend of bioavailability of the active ingredient in two different products not significantly different under suitable test conditions. Thus, making the two have the same physiological effect.

The following part wasn't given by the Dr. but explained thoroughly in the Slides, so I will summarize them here

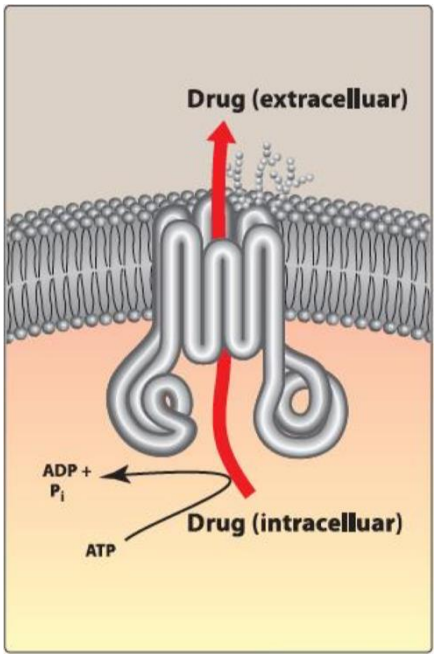
Factors influencing Absorption:

1- PH: Acids and Bases donate or accept protons, but a drug usually passes the membrane if it was uncharged. Therefore, the effective concentration of the permeable form of each drug at its absorption site is determined by the relative concentrations of the charged and uncharged forms. So the more uncharged particles there are the more permeable the drug is (causing the case above were acids are absorbed in stomach and bases are absorbed at the intestines).

2- Blood flow to the absorption site: The intestines receive much more blood flow than the stomach, so absorption from the intestine is favored over the stomach.

3- Total surface area available for absorption: With a surface rich in brush borders containing microvilli, the intestine has a surface area about 1000-fold that of the stomach, making absorption of the drug across the intestine more efficient.

4- Contact time at the absorption surface: If a drug moves through the GI tract very quickly, as can happen with severe diarrhea, it is not well absorbed. Anything that delays the transport of the drug from the stomach to the intestine delays the rate of absorption of the drug. Also, The presence of food in the stomach both dilutes the drug and slows gastric emptying. a drug taken with a meal is generally absorbed more slowly.



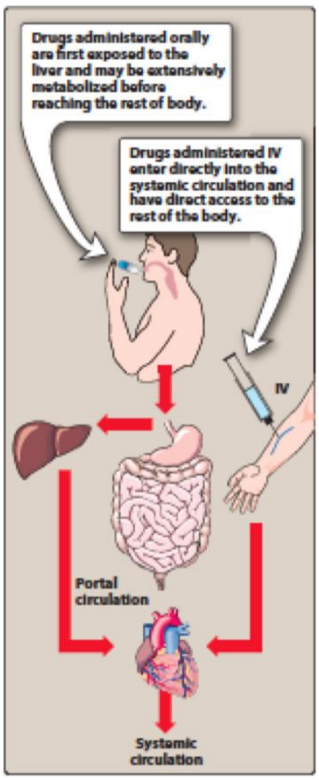
5- Expression of P-glycoprotein: P- glycoprotein is a transmembrane transporter protein responsible for transporting various molecules, including drugs, across cell membranes.

- Where: liver, kidneys, placenta, intestines, and brain capillaries
- Involved in transportation of drugs from tissues to blood. “pumps” drugs out of the cells.
- Areas of high expression P-glycoprotein reduces drug absorption.
- Associated with multi drug resistance.

Factors influencing Bioavailability:

- **First-pass metabolism:**

When a drug is absorbed from the GI tract, it enters the portal circulation before entering the systemic circulation. If the drug is rapidly metabolized in the liver or gut wall during this initial passage, the amount of unchanged drug entering the systemic circulation is decreased.



• First-pass metabolism by the intestine or liver limits the efficacy of many oral medications.

• Example: more than 90% of nitroglycerin is cleared during first-pass metabolism.

• Drugs with high first-pass metabolism should be given in doses sufficient to ensure that enough active drug reaches the desired site of action.

- **Solubility of the drug:**

• Very hydrophilic drugs are poorly absorbed because of their inability to cross lipid-rich cell membranes.

• Drugs that are extremely lipophilic are also poorly absorbed, because they are totally insoluble in aqueous body fluids and, therefore, cannot gain access to the surface of cells.

• For a drug to be readily absorbed, it must be largely lipophilic, yet have some solubility in aqueous solutions.

• This is one reason why many drugs are either weak acids or weak bases.

- **Chemical instability:**

• Some drugs, such as penicillin G, are unstable in the pH of the gastric contents.

• Insulin is destroyed in the GI tract by degradative enzymes.

- **Nature of the drug formulation**:

Drug absorption may be altered by factors unrelated to the chemistry of the drug.

For example, particle size, salt form, crystal polymorphism, enteric coatings, and the presence of excipients (such as binders and dispersing agents) can influence the ease of dissolution and, therefore, alter the rate of absorption.

And here finishes the part the Dr. didn't mention in lecture 7 for section 1

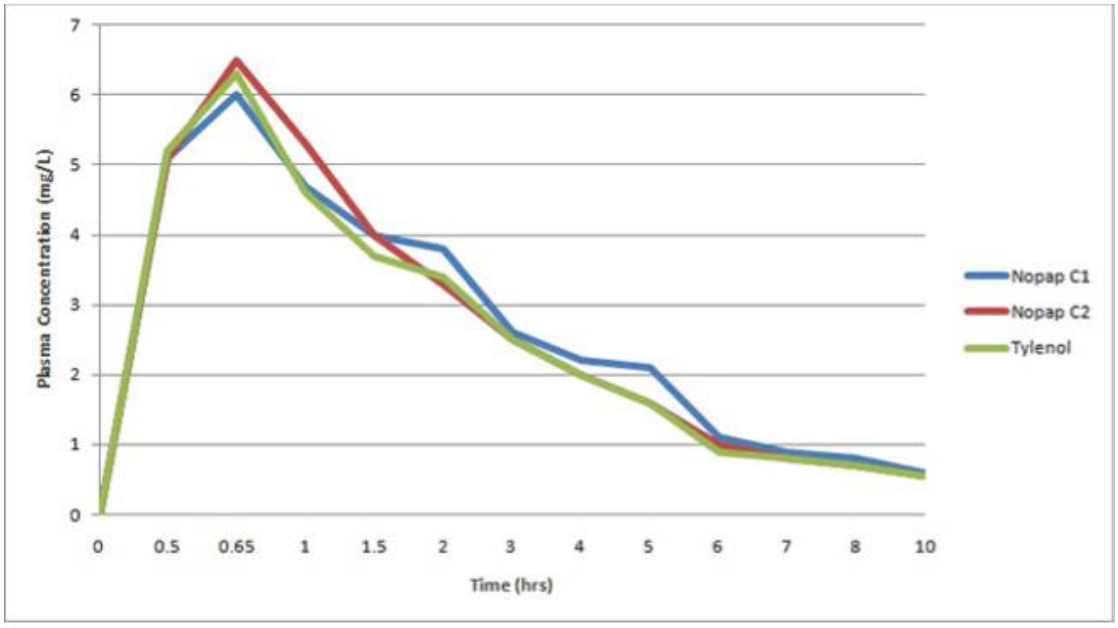
Topical Administration:

Topical administration of a drug is when the drug is applied to the desired type of tissue directly, like using body creams or eye drops.

Advantages: The drug is quickly applied to the site of effect and we reduce the side effects of the drug (Less systemic absorption).

Bioequivalence

Two drug formulations are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations.



- Drug products are considered to be *bioequivalent* when the rates and extents of bioavailability of the active ingredient in the two products are not significantly different under suitable test conditions

it will be discussed more thoroughly in the next sheet