3

Pharmacology

Doctor 2018 | Medicine | JU

Sheet ○ Slides

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You may refer back to the slides

Recap:- **The part below is not mentioned in lecture 3, but it was taken from 2017 sheets to be on the safe side**

Drug Approaches:

1- Serendipity: Example: Penicillin *anti-bacterial* was discovered to have an effect on bacteria but the mechanism wasn't discovered until around 40 years later on *inhibition of cell wall synthesis*, then we identified the molecular target. **e.g. Sildenafil – Penicillin**

2- Screening: Willow trees were known to have anesthetic, anti-inflammatory effects. So, we can take the extract of the tree bark and chemically analyze its chemical constituents through analytical chemistry and then screen those compounds to see which of them results in the final .physiological effect. **e.g. aspirin – statins/HMG CoA Reductase inhibitors**

3- Design: You could have a molecular target *let's say an enzyme* that you need to inhibit, so you have a designed compound targeting that enzyme, and by testing you could check on the physiological effect on the body and choose the best one. **e.g. HIV Protease inhibitors – COX2 specific inhibitors.**

4- *You could have some intermixing between these ways like with the **Sildenafil - Viagra** (Serendipity & design) where the side effect was overwhelming that it became the main use of the drug in place of the desired initial use – changed from pulmonary arterial hypertension treatment to erectile dysfunction.

Clinical Trials

Phases of Clinical Investigations:-

TABLE 1.1 Phases of Clinical Investigation

Phase	Purpose
I	Establish safety
II	Establish efficacy and dose
III	Verify efficacy and detect adverse affects
IV	Obtain additional data following approval

Clinical trials:

After effective and complete studies on the drug to make sure it's not toxic, we reached a point that we can test the drug on human beings.

There are 4 phases of clinical trials:

You have to know the purpose of each phase and the differences between them

Phase 1

- The first human encounter, the drug is administered for the first time.

- It's tested on healthy men between ages of 18-45.

- In this phase, the drug is tested on healthy individuals, therefore we're not expecting to test the efficiency of it or whether the drug is treating the disease or not.

- **The purpose:** making sure the drug isn't toxic.

Different doses of drugs are given gradually until the signs and symptoms of toxicity are observed, so the safe dose that should be given to patient can be detected.

-Number of patients is low, 30-100 individuals.

Note:

We don't give the individual a dose that would kill him or threaten his life, we already tested it on animals (monkeys for example) and we'll give him a dose below the tested dose, so it doesn't cause damage to the body. The human would be given the drug gradually till we determine a sign and we'll directly stop.

Volunteers that participate and come to the clinical trials have to sign a contract that they are responsible for the possible risk factors that might take place.

Important questions:

Q1- Can these multiple clinical trials be applied for all kinds of drugs, or do we have some exceptions?

Actually no, we do have some exceptions. For example, chemotherapeutic drugs have severe adverse effects, so they can't be given to a healthy person. They are usually tried on individuals with cancer. So any drug that has the substantial toxicity cannot be given in phase 1.

Q2- Why do we test the toxicity of the drug on men not women?

Because of the variability in hormonal cycle of the female, most drugs are tested on men. But there are some drugs that are specific for women and we have to test them on her.

Phase 2

-The drug is tested on actual patients with diseases, unlike phase 1.

-The dose used is also not toxic , but we still have to test the dose of toxicity to the patient, so the drug is administered for the first time for patients with a larger group, 100-300 patients.

- **The purpose:** to detect whether the drug is efficient and working or not, confirming the effectiveness of the drug and monitoring its side effects.

Phase 3

-Used with a larger number of patients (1000-3000).

-**The purpose:** to fulfill the same objectives of phase 2,(confirm effectiveness, monitor for safety) + to compare the drug to a drug that's already in the market.

For example, let's say that a clinical trial is done on a painkiller, what would be done on phase 3 is comparing the painkiller to another one that's already used, and study which drug is more effective, because what's the purpose of giving a new drug if it doesn't have an added value to the original drug that's already in the market. The new drug may be more effective, have less side effects, or have more absorption than the original one. **Ex. Augmentin compared to Amoclan.**

-The drug is approved and goes to the market, but we don't stop here, the company has to monitor it after being used by many people, that's what'll be discussed in phase 4.

Phase 4

-People start taking the drug, researches won't be stopped.

-After the drug is marketed, researchers continue to monitor the drug as it's used by the population and study if there are any reports of adverse effects.

-**The purpose:** The drug is monitored for safety in the group of patients that was subjected before, and then to the population in general, because the group of patients subjected before may not show distinct adverse adverse effects as they're just 2-4% of the whole population. And sometimes certain differences between individuals can show the adverse side effects.

For example, Ibuprofen is a painkiller, but sometimes, people suffer from irritation and stomach problems as side effects, so now they're forced to take another drug to get rid of these problems, so companies synthesize drugs that take ibuprofen's job without having these side effects or at least minimizing them. **Ex: Celecoxib and Rofecoxib**, but with adding warning boxes on drugs outside to aware people from the drug's toxicity/ side effects that may develop.

Summary of Phases I-III

	# Subs.	Length	Purpose	% Drugs Successfully Tested
Phase I	20 – 100	Several months	Mainly Safety	70%
Phase II	Up to several 100	Several months- 2 yrs.	Short term safety; mainly effectiveness	33%
Phase III	100s – several 1000	1-4 yrs.	Safety, dosage & effectiveness	25-30%

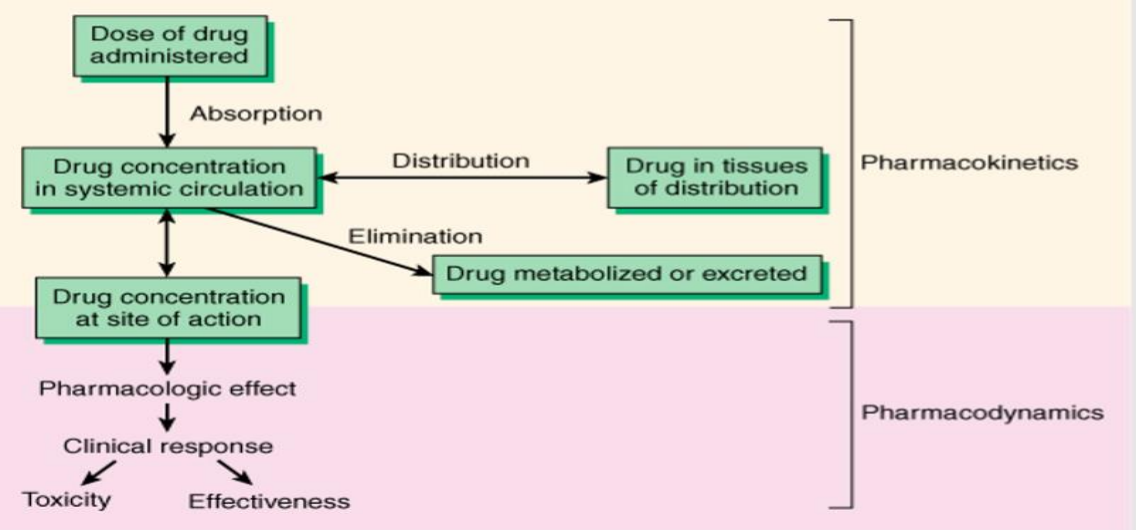
Areas of pharmacology:

1) Pharmacodynamics:
   the study of biochemical and physiological effects of the drug and its mechanism of action.
   (what the drug does to the body)
2) Pharmacokinetics:
   - The way the body handle drug absorption, distribution, biotransformation, and excretion.
     (what the body does to the drug from the moment the drug enters the body, until its excreted)
   - The determination of the fate of substances administered from an exogenous source to a living organism.

-Phases of pharmacokinetics: (ADME/ ADBE)

1) Absorption. 2) Distribution. 3) Biotransformation (metabolism).

4) Excretion.



The figure above shows where do dynamics and kinetics meet in the body.(the next sheer will talk about it more)

-How do people decide the dosage form of the drug? (Orally, capsule, injection, cream,…)

A. It depends on the patient and what way is suitable for him.

B. Lipid and water solubility of the drug also determine the dosage form of the drug.

Lipid soluble >> drug can fuse through the membrane and it can be used orally or as a cream for example.

C. Problem/disease site, for example it's more preferable to use cream for skin rather than injections.

D. How fast do I want the response if the drug(therapeutic objective); during emergency situations, if person X ate peanuts/ nuts for example and he's allergic to it, this might lead to death if not treated quickly as a result of anaphylactic reaction.

Treatment of anaphylactic reactions: **epinephrine**.

E. If the patient is conscious or not, for example if a patient fainted and the doctor wants to give him/her any kind of drug, it shouldn't be given orally as their body won't respond, so the doctor must use another form of administration as injection, one of the therapeutic objectives of the patient.

-There are certain factors related to the drug itself or factors related to the therapeutic objectives of the patient.

Routes of Drug Administration

1-Oral: it can be either by suspension, tablet, capsule..etc.

Advantages:-

1-Easy to take

2-Less expensive, most economical

3-Safest in relation to sterility; patient's body won't be exposed (if compared to injection) to introducing of foreign molecules into the blood stream.

4-Most common

5-Convenient for most people

Disadvantages:-

1-A slow method; the patient has to wait for the absorption of the drug to take place; therefore, it can't be used during emergency situations.

2-Some of the drugs, acid labile drugs can be easily destroyed in acidic environments (in our stomach for example). Stomach is the main site for drug absorption mainly by oral rout. The pH of the stomach is low (acidic) so the absorption of drugs through the stomach is difficult.

3-The body might break down the drug before it being absorbed and this is called **First Pass Effect.** Which is a phenomenon of drug metabolism whereby the drug concentration is greatly reduced before it reaches the systemic circulation. It is the fraction of drug lost during the process of absorption which is generally related to the liver and gut wall.

4-Patients may forget to take it

5-Young patients may not be able to swallow it

6-Taste may not be favored

2-Injections: taken in three possible ways; 1- Intravenous

2- Intramuscular

3- Subcutaneous

The three methods share an advantage which is that they are faster than oral administration, faster absorption of the drug when injected rather than through the GI tract.

Advantages of intravenous injection:-

1-All of the dose gets into the blood; large doses can be given but slowly. Although the patient must be careful of large volume of solution which might cause **bolus injection** that can cause adverse effects.

2-It overcomes the problem we mentioned before when we talked about the oral administration. When someone is unconscious or vomiting all the time in which drug can't be given orally.

3-The titration of the dose of injection can be monitored, example; how much of the drug should the doctor give for a certain period of time. It's easier when it's given by intravenously.

4-Some drugs are digested by digestive enzymes in the stomach if taken orally; such peptides as insulin, hormones, heparin...etc. A better way for such drugs to be administered is through intravenous injection.

Disadvantages of intravenous injection:-

1-It could be dangerous, as some viruses and bacteria might pass through; so you need a sterilizer.

2-If it's not someone's specialty, a nerve or muscle can get injured (hematoma or hemorrhage)

Now**, Intramuscular and subcutaneous** injections are given whether in the muscle or below the skin.

Advantages:

1-Overcoming problems mentioned before

Disadvantages:-

1-They might cause irritation in the muscle causing serious issues. It might cause muscle injury resulting in bleeding, hematoma or hemorrhage.

2-They can be painful.

3-Can't be used in anticoagulant therapy as this might block blood vessels and stop blood flowing to organs such as the brain, heart or liver if they form in the wrong place as anticoagulants work by interrupting the process involved in the formation of blood clots.

So, according to the condition of the patient and to the characteristics of the drug, the most suitable way of administration is decided.

3-Sublingual:- involves placing the drug under your tongue to be dissolved and absorbed into the blood through the tissue there.

Advantages:-

1-It is another rapid way of administration where it will reach the systemic circulation more rapid; because it's a highly vascular area.

2-Avoids First Pass Effect

3-Drug stability is maintained as the pH of saliva is relatively neutral

Disadvantages:-

1-Limited to certain types of drugs

2-Limited to drugs that can be taken in small doses

3-May lose part of the drug dose swallowed.

Example: Nitroglycerin; it is absorbed rapidly and causes the quick release of NO gas to the blood vessels causing dilation. The benefit of it is that it expands blood vessels of the heart muscle. If someone is affected by ischemic heart disease, coronary arteries must dilate to pass/ deliver more oxygen to the heart.

4-Topical: creams, shampoo, sun screen, inhalation giving drugs…etc.

If someone's hand got burnt, topical antibacterial cream can be given.

Advantages:

1-The drug arrives quickly to the place it should get activated at.

2-It can be very lipid soluble to be able to penetrate the skin and pass through the membrane to perform its function.

3-Inhalation drugs such as bitrolin can be used to treat asthma, and it works by expanding the bronchi directly, in advance; the adverse effects that might arise in the systemic absorption will decrease. The patient inhales the drug where it goes to the lungs and then it is administered directly to the cycle it should work in.

4- Effective for patients with respiratory problems.
5- Dose can be titrated.

Disadvantages:-

1-The lung is a highly vascular organ; it has a large surface area, therefore **part** of the drug will be absorbed in the blood stream. By default, drug will be absorbed and this might cause adverse effects. Therefore, higher dose is needed if the drug is administered orally as most of it will be absorbed into its way to the lung than it would be taken by inhalation.

2-It is the most addictive method/rout because gases mostly are lipid soluble in which they enter the brain quickly.

3-Patient may have difficulty regulating the dose and some patients will experience technical difficulties with the use of inhalers.

PLEASE REFER TO THE TABLE BELOW:-

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)
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

"The struggle you're in today is developing the strength you need for tomorrow"