



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
الَّذِي عَلَّمَ بِالْقَلَمِ ۖ عَلَّمَ الْإِنْسَانَ مَا لَمْ يَعْلَمْ



PHARMACOLOGY

MID | Lecture 1 & 2

Introduction to Pharmacology

Written by :

Khaled Abdalla / Ali Alsharaeah

Ahmad Mohy / Yaman Khalil

Reviewed by:

Yamen Aljarrah



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LECTURE 1

Introduction to Pharmacology

Definitions, branches of pharmacology, and sources of drugs

Dr. Alia Shatanawi

Introduction to Pharmacology | Second-year Medicine

Content aligned with Katzung, Basic & Clinical Pharmacology

Learning objectives

By the end of this lecture you should be able to:

- 1 Define a drug, pharmacology and the related disciplines (pharmacy, toxicology, pharmacotherapeutics).
- 2 Distinguish therapeutic effects, side effects, adverse effects and toxicity.
- 3 Define tolerance, tachyphylaxis, idiosyncrasy, pharmacogenetics and pharmacogenomics.
- 4 Contrast pharmacodynamics with pharmacokinetics and outline the ADME processes.
- 5 Classify drugs by source and describe the physical nature of drug molecules.

To understand pharmacology, you must know physiology to understand the effects of drugs.

Example: antihistamine; we know (from physiology) that histamine is activated when exposed to allergies causing effects like itching and swelling.

Because we understand the effects of histamine we can assume what antihistamine does to our body (prevent the allergy reactions from occurring)

Drugs commonly have 2 names, a trade name and a scientific name

Example: Panadol (trade name) and Paracetamol (scientific name)

We use the scientific name when prescribing patients with drugs

Think about how drugs work, let's take loratadine (an antihistamine drug) as an example:

For it to prevent the allergy reaction to take place, it binds to the histamine receptors to prevent and block histamine from binding to the receptor and as a result we're able to prevent the effects of histamine

What is a drug?

- **Drug:** any substance that brings about a change in biologic function through its chemical actions.
- A drug modifies an **existing** function. It does **not** create a new function.
- Drugs may be synthesized in the body (hormones- **such as insulin, given to treat type I & II diabetes patients**) or given from outside (xenobiotics – **such as penicillin which comes from fungi**).
- Most drugs act by binding a specific molecule in the body, the receptor.
- Poisons are drugs with almost exclusively harmful effects. **Toxins** are poisons of biologic origin.
- **Any drug at a high dose can be toxic.**
- **Poisons are drugs, because just like drugs they are substances that bring change in the biological function.**



Why are poisons also drugs?

They act through the same chemical interaction with biological molecules. Paracelsus: "the dose makes the poison". Any drug becomes toxic at a high enough dose.

Pharmacology and related disciplines

1 Pharmacology

The study of substances that interact with living systems through chemical processes: source, properties, ADME, actions, uses and toxicity.

4 Pharmacotherapeutics

The medical use of drugs to prevent and treat disease.

2 Medical pharmacology

Use of drugs for the diagnosis, prevention and treatment of human disease.

5 Chemotherapy

Drugs that kill or stop the growth of microorganisms, parasites or cancer cells.

3 Pharmacy

Health science dealing with the preparation, dispensing and proper use of drugs.

Pharmaceutics is a branch of pharmacy which is interested in producing the drug

6 Toxicology

Adverse effects of drugs and toxic effects of household, environmental and industrial chemicals.

How are Toxicology and Pharmacology connected?

Toxicology is a branch of pharmacology focusing on: any drug in high amounts can become toxic which can affect and interact with living systems

Pharmacokinetics: What the body does to the drugs;

- ADME:

A: Absorption → D: Distribution (through blood stream) → M: Metabolism → E: Excretion (GI system & through kidney in the form of urine)

What is the function of Metabolism in ADME?

biotransformation of the drug – resulting in the deactivation of the drug and to turn it into a form that can be easily excreted out of the body

(Note: it can also be turned from an inactive state to an active state) – Depending on the drug, this happens so that it can be easily excreted out

Note: Excretion could happen in a lot of ways such as sweat, the respiratory system (some drugs are excreted by just exhaling), it could be also excreted with the mother's milk, but it most importantly is excreted through the kidney (in the form of urine which is mostly water). So mostly the metabolism's main purpose is to try and make the drug more water soluble so it's able to be excreted easily.

Pharmacodynamics: What the drugs do to the body

d: drugs → body (shortcut to remember easily).

Branches of toxicology

Branch	Focus	Example
Clinical	Diagnosis and treatment of poisoning in patients	Paracetamol overdose (caused by high intake of a drug which might lead to death) → treated with N-acetylcysteine (within the first few hours- 24 hours)
Analytical	Measuring toxic chemicals in biological and environmental samples	Blood lead <u>level</u> , urine drug screen, <u>lead levels</u>
Forensic الطب الشرعي	Medico-legal link between a poison and illness or death	Post-mortem toxicology report
Environmental	Movement of toxins through air, water, soil and the food chain	Mercury in fish, pesticide residues
Occupational (industrial / toxicology)	Toxic exposure in the workplace; part of industrial hygiene	Organic solvents, heavy metals in factories

Two principles every student should remember

(IMPORTANT)

1. Every substance can be toxic

- Toxicity depends on dose, route, duration and the patient (drug variation in responses between different patients, mentioned later on in the course) .
- Water, oxygen and vitamins A and D are toxic in excess.
- Safety is a question of margin (the limit) , never of absolute certainty.

2. Supplements need the same proof

- Dietary supplements and products promoted as "health-enhancing" should meet the same efficacy and safety standards as drugs.
- "Natural" does not mean safe: St John's wort (The drug increases immunity of the body) induces CYP3A4 and reduces levels of many drugs.

Describing what a drug does

Example: Ibuprofen is a pain reliever drug which is used to reduce pain. It is always recommended to take it after having a meal because ibuprofen is known to increase the acidity of the stomach which will lead to GI problems.

Therapeutic effect: reduce the pain.

Side effect (known and predictable unintended effect): increase the stomach acidity.

1 Therapeutic effect

The **intended primary effect**; the reason the drug is prescribed. Morphine: analgesia.

2 Side effect

An **unintended effect at therapeutic doses**.
Usually predictable; may be harmless or harmful. Morphine: constipation.

3 Adverse effect

Any undesired, harmful response. Ranges from mild to life-threatening.
– Its like side effects but very dangerous

4 Drug toxicity

Harmful effect on an organism or tissue, usually from **overdose or accumulation of the drug**.
Morphine: respiratory depression.

Note: Morphine is less prescribed than other pain relievers because it causes addiction and rewarding effects which could lead to take overdoses of the drug.

Prescription: the written order for preparing and administering a drug to a specific patient.

Terms related to drug use



Drug interaction

-One drug, given before, with or after another, changes the effect of one or both.

- For example : drugs that interacts with certain enzymes that metabolizes other certain drugs could lead to drug interaction.
- Taking warfarin (مميع للدم) and certain drugs that counter stomach acidity would cause a drug interaction.
- Drug interactions can be FATAL, that's why it's important to understand how drugs work to reduce these incidents



Drug misuse

2

Improper use of common medicines causing **acute or chronic toxicity**, e.g. laxatives, antacids, vitamins.

For example: using laxatives (used for constipation) in order to lose weight is drug misuse.



Drug abuse

3

Use of a substance, continually or periodically, for non-medical purposes, in a way that harms the user.

For example: patients using morphine because of addiction.

Terms describing variation in response

G6P dehydrogenase deficiency

1 Idiosyncrasy Due to mutations or certain gene deficiencies

An unusual response seen in **few** patients.
Usually **genetic** (e.g. hemolysis with primaquine in G6PD deficiency) or immunologic.

Usually unpredictable and serious (adverse effect)

2 Hypersensitivity

An **immune-mediated (allergic)** reaction, unrelated to the drug's pharmacologic action.
Not dose-related.

Example: allergies to penicillins

3 Tolerance

Gradual decrease in response with continued use; a higher dose is needed for the same effect (e.g. opioids **such as morphine**, nitrates).

Usually happens upon continuous usage of strong analgesics that act on CNS

4 Tachyphylaxis

Rapid decrease in response after a few doses given at short intervals (e.g. ephedrine, tyramine).

- Side effect is **always predictable** and less serious than Adverse effect
- Adverse effect is usually predictable except when talking about **Idiosyncrasy** (maybe in future it may be predictable by knowing the genome of each individual)
- ❖ Idiosyncrasy and hypersensitivity are similar, but hypersensitivity has more to do with **allergies (immune mediated)** , while Idiosyncrasy happens because of the genetic differences among the patients.

Pharmacogenetics and pharmacogenomics

Pharmacogenetics

- **Variation in drug response** due to a **single gene. (due to polymorphism of a gene)**
- Example: CYP2D6 poor metabolizers get little analgesia from codeine.
- Example: TPMT deficiency causes severe marrow toxicity with azathioprine.



Change in CYP2D6 will lower the metabolic rate leading to the change of drug concentration

Pharmacogenomics

- Relates the **whole genome** of an individual to drug response.
- Uses genome-wide data to predict efficacy and toxicity.
- Aim: precision medicine, choosing drug and dose from the patient's genotype.

The two terms are often used interchangeably in practice.

The two main areas of pharmacology

Pharmacodynamics

- **What the drug does to the body.**
- Mechanism of action and receptor interactions.
- Concentration-effect relationships.
- Therapeutic and adverse effects.

Pharmacokinetics

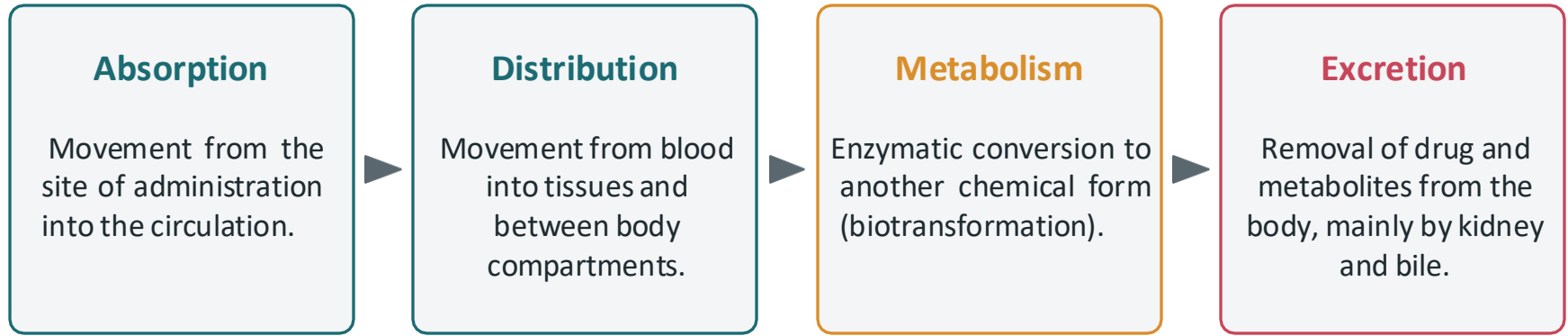
- **What the body does to the drug.**
- Absorption, distribution, metabolism, excretion (**ADME**).
- Determines the concentration at the site of action over time.
- Basis for choosing dose, route and interval.

Example of pharmacodynamics:

Paracetamol (and Ibuprofen) targets **cyclooxygenase** (an enzyme that produces prostaglandins- inflammatory mediators: responsible for pain, fever, swelling...) and inhibit it, which causes a decrease in the level of prostaglandins and, in turn, reduces pain and fever (**therapeutic effect**).

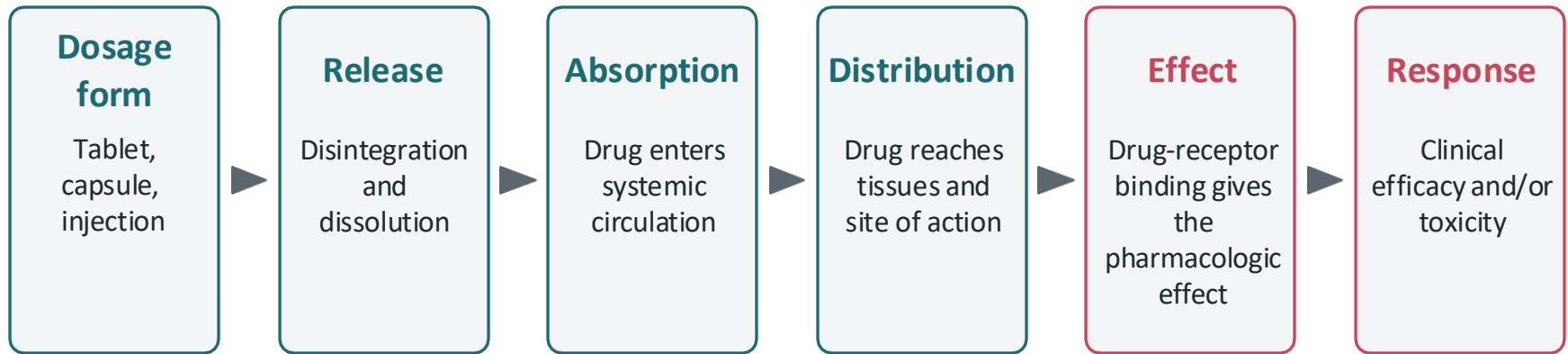
*Note: Ibuprofen causes the prostaglandins' levels in the stomach to decrease which leads to more HCL secreted, less Bicarbonate ion secretion and less mucous to protect the stomach. All these lead to losing the protective layer of the stomach which causes peptic ulceration قرحة المعدة. Understanding the mechanism of action of ibuprofen and other drugs is very important to make their side effects more predictable.

Pharmacokinetics: the ADME processes



Elimination = metabolism + excretion. Both end the drug's action.

From dose to clinical response



Pharmacodynamics and kinetics meet together at **distribution phase** (the drug reaches its receptor when its distributed).

Pharmacokinetics governs the first four boxes. Pharmacodynamics governs the last two.

Drug disposition: only free drug acts

- In plasma, drug exists as free drug and drug bound to proteins (mainly albumin; alpha-1-acid glycoprotein for basic drugs).
- Only free (unbound) drug **are active**, as they crosses membranes, reaches receptors and is filtered by the kidney. **An example is ibuprofen, as 90% of the drug is bound to plasma proteins and just 10% are active. But that doesn't mean the 90% aren't useful as the body uses them when the previous 10% is used.**
- Free drug binds receptors in tissues and produces the clinical response.
- Liver: drug is converted by enzymes to metabolites, excreted in urine or bile.
- Kidney: glomerular filtration of free drug and active tubular secretion by carriers.



Key point

Bound drug is a reservoir. It is pharmacologically inactive until released.

Studying drugs in populations

Pharmacoepidemiology

- Study of the use and effects of drugs in large numbers of people (in population). An example is to study the usage of opioids at homes in a specific population.
- Applies epidemiological methods (cohort, case-control studies) to drug use.
- Epidemiology: factors that determine the occurrence and distribution of disease in populations.

Pharmacovigilance

- Detection, assessment and prevention of adverse drug reactions after marketing.
- Relies on spontaneous reporting (e.g. FDA MedWatch, national reporting centres).
- Detects rare reactions missed in clinical trials.

Sources of drugs: natural

The drugs underlined are the ones mentioned by the director in the lecture.

Aspirin is a drug that has anti-platelet activity, in doses that range from 80-100 mg , but in higher doses like 325-700 mg it can be used as a pain killer and anti-inflammatory. Its called acetylsalicylic acid and considered as semisynthetic drug. People were using the bark of willow trees to reduce pain , turns out it contains salicylic acid but we modify this to make the aspirin that has better properties.

Source	Examples
Plants	<u>Alkaloids (nitrogen-containing bases): morphine, atropine, quinine, cocaine.</u> Also digoxin (Digitalis), paclitaxel, artemisinin
Microorganisms	Antibiotics from <u>a fungus called Penicillium (penicillin)</u> and <u>Streptomyces (streptomycin, tetracyclines).</u> Statins from fungal metabolites , <u>statins are drugs used to reduce lipids proportion in blood like liptol.</u>
Animal tissues	Hormones for replacement: <u>insulin, thyroid hormone</u> , heparin (historically from animal tissue). <u>Later on, we start using recombinant DNA technology to produce insulin (we will take it in molecular) which is more compatible with humans. ++ make sure the source doesn't contain a substance taken from pigs.</u>
Minerals	<u>Lithium salts (bipolar disorder), iron</u> <u>which can be prescribed to patients with anemia</u> , magnesium sulfate

Sources of drugs: synthetic and biotechnology

1 Fully synthetic

Designed and made in the laboratory. Early examples: aspirin, barbiturates, local anesthetics. Most modern small-molecule drugs.

2 Semisynthetic

Chemical modification of a natural compound. Oxycodone from thebaine; amoxicillin from the penicillin nucleus.

3 Biotechnology

Recombinant DNA proteins: human insulin, growth hormone, erythropoietin **which is a hormone produced by the kidney and induces bone marrow to produce RBC's**. Monoclonal antibodies **produced in special cases like autoimmune diseases** (-mab), e.g. trastuzumab.

4 Nucleic acid based

Antisense oligonucleotides, siRNA, mRNA vaccines and gene therapies. A growing class.

The physical nature of drugs

- Drugs may be solid (aspirin), liquid (ethanol) or gas (nitrous Oxide **that is used to dilate blood vessels as it's produced in endothelial cells to relax the smooth muscles. It can be used fast by the pills that we put under our tongue which are nitrates. It releases NO directly into the blood stream for patients who have ischemic heart disease (ذبحۃ صدریة).**
- **Size:** most drugs have a molecular weight of 100 to 1000 Da.
 - Lower limit set by the need for **selective binding**. Lithium ion (MW 7) is an exception.
 - Above ~1000 Da, drugs cross membranes poorly and usually need injection (e.g. alteplase, antibodies, **insulin and heparin**) **if we use intravenous injection and the drug has big MW that usually means that it's intended to make the drug stay in the blood like heparin because it is an anti-coagulant .**
- **Bonds with receptors:** covalent **irreversible** (rare, long-lasting), electrostatic and hydrophobic.
- **Shape and chirality:** many drugs are racemic mixtures; one enantiomer is often more potent (e.g. S-ketamine, S-warfarin).

S Structure-activity relationship

Medicinal chemists use molecular modelling to relate drug structure, receptor fit and activity, and to design better drugs.

Loratadine is a racemic mixture , but it was figured out that D-loratadine is more potent so they made a new drug only containing this enantiomer which is more powerful than the original loratadine drug.

Key take-home points

- ✓ A drug changes an existing biologic function through chemical action; it creates nothing new.
- ✓ Toxicity is a matter of dose: every substance can be toxic.
- ✓ Side effects are predictable and unintended; idiosyncrasy and hypersensitivity are not dose-related in the usual way.
- ✓ Tolerance develops gradually; tachyphylaxis develops rapidly after a few doses.
- ✓ Pharmacodynamics is what the drug does to the body; pharmacokinetics (ADME) is what the body does to the drug.
- ✓ Only free, unbound drug reaches receptors and is eliminated.
- ✓ Drugs come from plants, microbes, animals, minerals, synthesis and biotechnology.

Q1

Check your understanding

A patient of Mediterranean origin develops acute hemolysis after a standard dose of primaquine. Other patients tolerate the same dose. This reaction is best described as:

A

Tolerance

B

An idiosyncratic response of genetic origin

C

A predictable side effect of therapeutic doses

D

Toxicity due to overdose

A1

Answer: B

- **Idiosyncrasy:** an unusual response in a small subset of patients, usually genetic or immunologic.
- Here the cause is G6PD deficiency, which leaves red cells unable to cope with oxidant drugs.
- Not a side effect: most patients at this dose do not hemolyse. Not overdose: the dose was standard.

Q2

Check your understanding

Ephedrine is given as repeated doses at 10-minute intervals. The rise in blood pressure becomes smaller with each dose and is lost within an hour. The best term for this is:

A Tolerance

B Drug resistance

C Tachyphylaxis

D Idiosyncrasy

A2

Answer: C

- **Tachyphylaxis:** a rapid loss of response after a few closely spaced doses.
- Ephedrine acts partly by releasing noradrenaline; stores are depleted quickly.
- Tolerance develops more slowly over days to weeks. Resistance refers to microbes or tumours.

Q3

Check your understanding

Which observation is a pharmacokinetic rather than a pharmacodynamic finding?

A Buprenorphine gives a lower maximal effect than morphine at the mu receptor

B Theophylline clearance is higher in a heavy smoker

C Propranolol has high affinity for beta-adrenoceptors

D Aspirin shows a ceiling to its analgesic effect

A3

Answer: B

- Clearance is a pharmacokinetic parameter: what the body does to the drug.
- Cigarette smoke induces CYP1A2, which metabolizes theophylline, so clearance rises.
- Efficacy, affinity and ceiling effects are pharmacodynamic properties.

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



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Additional resources:

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رسالة من الفريق العلمي: