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LECTURE 1

Introduction to Pharmacology

Definitions, branches of pharmacology, and sources of drugs

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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.

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) or given from outside (xenobiotics).
- 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.

? 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.

2 Medical pharmacology

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

3 Pharmacy

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

4 Pharmacotherapeutics

The medical use of drugs to prevent and treat disease.

5 Chemotherapy

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

6 Toxicology

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

Branches of toxicology

Branch	Focus	Example
Clinical	Diagnosis and treatment of poisoning in patients	Paracetamol overdose treated with N-acetylcysteine
Analytical	Measuring toxic chemicals in biological and environmental samples	Blood lead level, urine drug screen
Forensic	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)	Toxic exposure in the workplace; part of industrial hygiene	Organic solvents, heavy metals in factories

Two principles every student should remember

1. Every substance can be toxic

- Toxicity depends on dose, route, duration and the patient.
- Water, oxygen and vitamins A and D are toxic in excess.
- Safety is a question of margin, 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 induces CYP3A4 and reduces levels of many drugs.

Describing what a drug does

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.

4 Drug toxicity

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

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

Terms related to drug use

1 Drug interaction

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

2 Drug misuse

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

3 Drug abuse

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

Terms describing variation in response

1 Idiosyncrasy

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

2 Hypersensitivity

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

3 Tolerance

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

4 Tachyphylaxis

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

Pharmacogenetics and pharmacogenomics

Pharmacogenetics

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

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

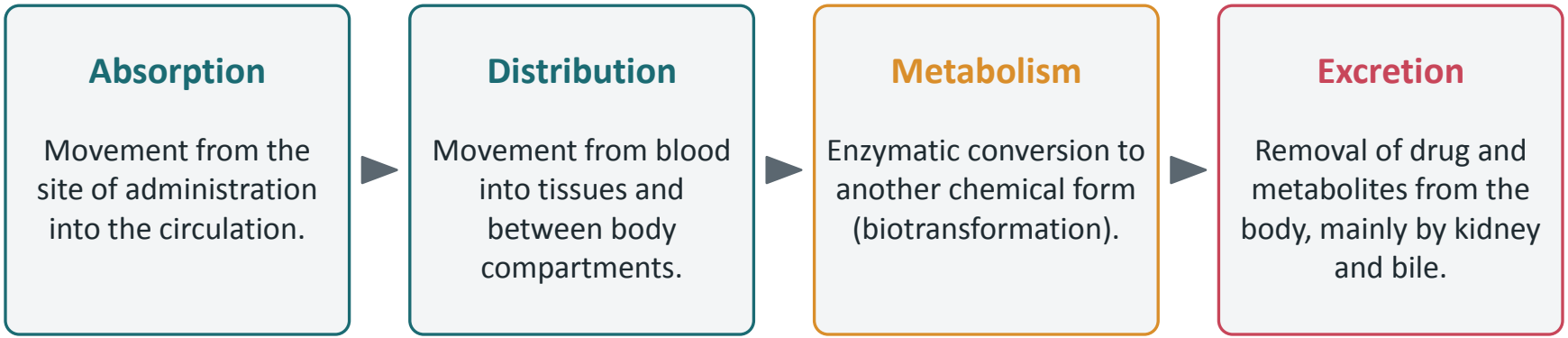
Pharmacodynamics

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

Pharmacokinetics

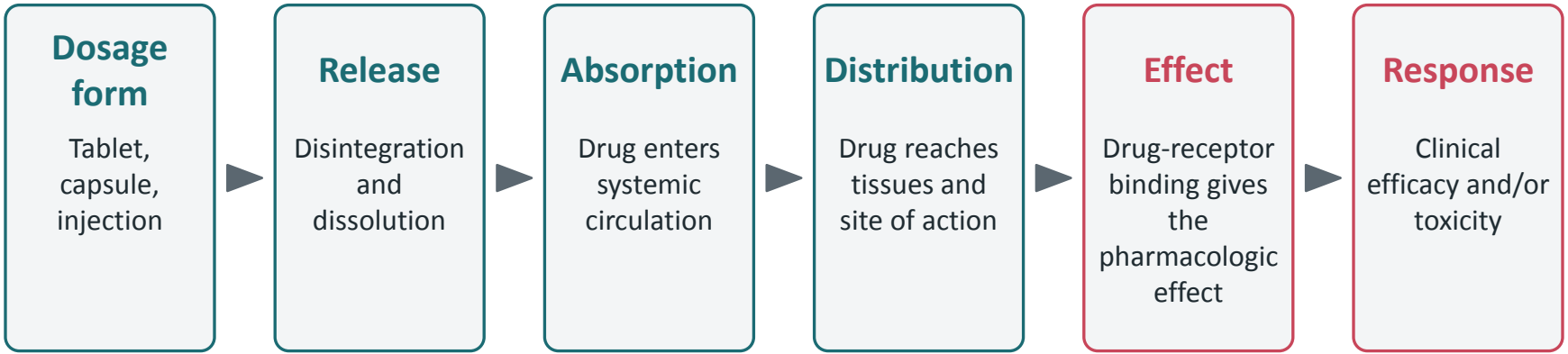
- What the body does to the drug.
- Absorption, distribution, metabolism, excretion (ADME).
- Determines the concentration at the site of action over time.
- Basis for choosing dose, route and interval.

Pharmacokinetics: the ADME processes



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

From dose to clinical response



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 crosses membranes, reaches receptors and is filtered by the kidney.
- 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.
- 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

Source	Examples
Plants	Alkaloids (nitrogen-containing bases): morphine, atropine, quinine, cocaine. Also digoxin (Digitalis), paclitaxel, artemisinin
Microorganisms	Antibiotics from Penicillium (penicillin) and Streptomyces (streptomycin, tetracyclines). Statins from fungal metabolites
Animal tissues	Hormones for replacement: insulin, thyroid hormone, heparin (historically from animal tissue)
Minerals	Lithium salts (bipolar disorder), iron, 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. Monoclonal antibodies (-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).
- **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).
- **Bonds with receptors:** covalent (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.

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.

Check your understanding

Three questions on this lecture. Answers follow each question.

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.