Basic Principles of Pharmacology

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** PHARMACOLOGY

Pharmakon = Drug; Logos = Science

The study of drugs and their interactions with living systems Wide term which includes:

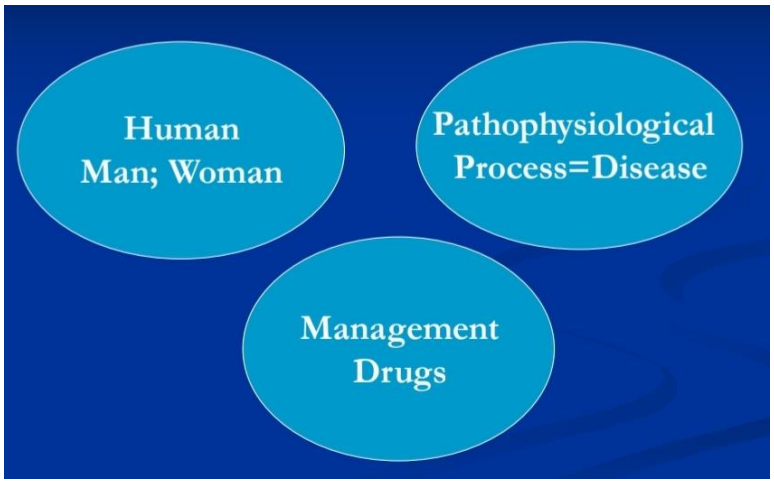
- The investigation of the biochemical and physiological effects of drugs

- The study of drug absorption; distribution; metabolism and excretion

- The knowledge about the history; sources; physical and chemical properties and therapeutic uses of drugs

** DRUG

- A chemical substance that is primarily used to reverse a pathophysiological defect = disease
= Virtually all chemicals may be drugs
= <u>All drugs are toxins but not all toxins are drugs</u>



FDA APPROVED DEFINITION OF DRUGS

A chemical substance that is mainly used to [1]treat, [2]control, [3]prevent, or [4]diagnose a specific disease or to [5]prevent pregnancy!!!

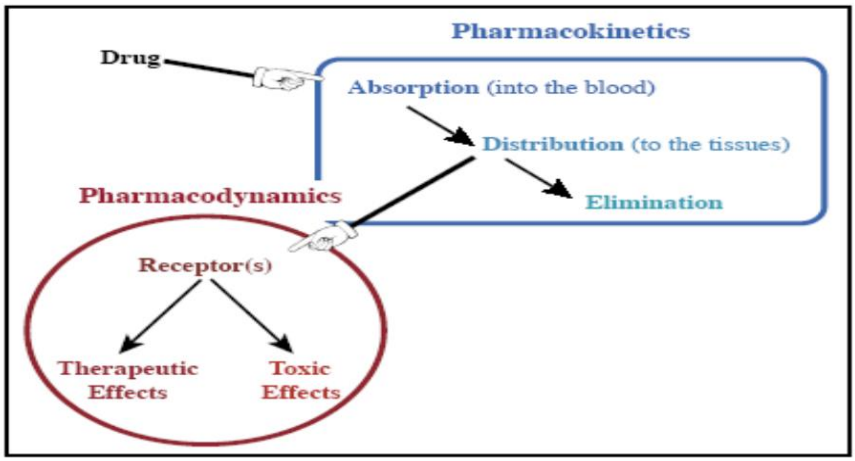
CHEMICAL NATURE OF DRUGS

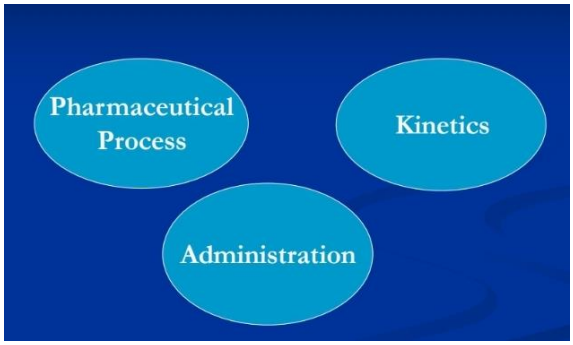
- **Acidic**; Aspirin, barbiturates...etc
- **Basic or alkaline;** Morphine, Atropine, Alkaloids...etc
- **Neutral**; Steroids

MAJOR OBJECTIVE VERY IMPORTANT

TO HAVE DRUG AT [1]SITE OF ACTION IN [2]PROPER CONCENTRATION GOOD [3]ENOUGH TO REVERSE DEFECT [4]WITHOUT PRODUCING SIDE OR TOXIC EFFECTS

DRUG DISCOVERY AND PHARMACEUTICAL PROCESS





■PHARMASTICAL PROCESSES

•Pharmaceutical process; drug in dosage form:

Is the drug getting into patient?

• **Pharmacokinetic process:**

Is the drug getting to its site of action?

• **Pharmacodynamic process:**

Is the drug producing the required pharmacological effect?

• **Therapeutic process (clinical pharmacology):**

Is the pharmacological effect being translated into therapeutic effect?

• **Pharmacogenetics**

Individual variations in responding to drugs + gene therapy.

■ DRUG DISCOVERY & DEVELOPMENT

1. **Starts with prediction=an idea & hypothesis**

   What helps?

   - Awareness of the beneficial effects of plants and animal products (natural sources)
   - Chemical identification of a wide variety of natural mediators and the possibility of modifying them chemically
   e.g. epinephrine, norepinephrine, acetylcholine, histamine, prostaglandins, endogenous opioids ,hormones…etc
   - Avoid chemicals with highly reactive groups (toxic)

2. **Design and synthesis of useful drugs or substances through simple techniques or with the help of advanced technology**

   e.g.

   ▪A plant ⟶ fractionation, chromatographic experiments ⟶identification of the active ingredients ⟶ isolation ⟶ purification ⟶ good drug (recently most drugs of plant source could be synthesized)

   ▪An animal → isolation of a substance (Thyroid hormones; insulin…)

   ▪Human → isolation of a substance (HMG's)

   ▪Simple peptides → a.a (amnio acid) sequencing machine

   ▪Complex proteins → recombinant DNA technology=genetic engineering

   - Receptology studies Allowed synthesis of huge number of agonists and antagonists

An agonist is a molecule capable of binding to and functionally activating a target. An antagonist is a molecule that binds to a target and prevents other molecules (e.g., agonists) from binding.

3. Preclinical studies

Studies on tissues and whole animals

▪**Determine efficacy**(the ability to produce a desired or intended result)

~Isolated tissue e.g. bronchi → organ path → testing drug…etc

~Animal models

→ drug ↓ BP

→ drug ↓ blood sugar level

▪**Determine pharmacokinetic parameters**

Absorption, distribution, metabolism…etc

▪**Determine pharmacodynamics (MOA)**

MOA= Mechanism Of Action

▪**Assessment of drug toxicity=safety**

✓ Acute toxicity studies

Determination of **LD50**; margin of safety…etc

Acute, short-term tests are usually 48- or 96-h exposures and measure mortality. Acute toxicity is a single-dose test that identifies symptoms and the extent to which toxicity affects animals

VERY IMPORTANT NOTES

- **LD** stands for "Lethal Dose". **LD_{50}** is the amount of a material, given all at once, which causes the death of 50% (one half) of a group of test animals.

Doctor example: if 100 gram of drug kills ½ of the rats means 100 is LD50 and 200 gram would kill all the tested Rats. اعذروني على الصياغة

-Margin of safety: The difference between the usual effective dose and the dose that causes severe or life-threatening side effects -or death-.

The larger the margin between the lethal dose and effective dose of a drug means the higher the therapeutic index and safety of that drug.

✓ Subacute and chronic toxicity studies

Repeated dose studies

occurs from small doses of toxins administered to an organism over time, usually weeks or months till reaching the end point when the organism dies.

-Daily observation of animals (wt., food and water intake ..)

-Obtaining biological samples (blood; urine)

-Obtaining tissues (liver; spleen; stomach …etc) for histopathological exam or studies

✓ Special toxicology studies

a. Mutagenicity (genotoxicity) tests:
   -Could delineate the induction of gene mutations (bacterial mutagenicity test or administration of drug to pregnant animals…etc)
   -Some mutations could result in the development of cancer

b. Carcinogenicity studies:
   -Not always required prior to early studies in man unless there is a high suspicion that the drug could be carcinogenic e.g. suspicion of mutagenicity; highly reactive groups on drug; histopathological abnormalities…etc
   -Required if the use of drug in man for more than one year or +ve mutagenic test.

■ CLINICAL DRUG TRIALS (MAINLY *4* PHASES)

PHASE 0

-Phase 0 or first-in-human trials is a recent phase approved in accordance with the United States FDA's 2006 Guidelines

-Phase 0 trials are also known as human microdosing studies and are designed to speed up the development of promising drugs by establishing very early on whether the drug or agent behaves in human subjects as was expected from preclinical studies

-**Distinctive features** of Phase 0 trials include the administration of single subtherapeutic doses of the study drug to a small number of subjects (**10 to 15)** to gather preliminary data on the agent's pharmacokinetics and pharmacodynamics

-A Phase 0 study gives no data on safety or efficacy, being by definition a dose too low to cause any therapeutic effect. Drug development companies carry out Phase 0 studies to rank drug candidates in order to decide which has the best pharmacokinetic parameters in humans to take forward into further development

-Phase 0 studies enable go/no-go decisions to be based on relevant human models instead of relying on sometimes inconsistent animal data

-Questions have been raised by experts about whether Phase 0 trials are useful, ethically acceptable, feasible, speed up the drug development process or save money, and whether there is room for improvement.

PHASE I

-Involves the use of a drug in humans for the first time

-It establishes dose level at which signs of toxicity first appear Conducted on **20-80 healthy** men with ages 18-45 yrs.

-Usually a single dose is used initially and if no side effects exhibited, the dose is increased progressively until sufficient serum level is achieved (therapeutic level) or some toxic effects appear

-Such studies are conducted in hospital

-If no side effects result from single dose, multiple dose studies should be initiated =bioavailability-bioequivalence studies. * Doctor said that these studies are similar to phase 0, but we have controls. * I'm not sure about this note, you should ask doctor about it.

PHASE II

-If phase I studies prove that the drug is safe to continue, the new drug is administered to **patients** for the first time.

- All patients should have only one problem (one disease)

- It assesses efficacy and establishes optimal dose range in patients (dose-response studies are important)

-Phase II studies are conducted on **80-100 patients** (certain countries ask for 50-300 patients)

-Also, patients are observed for toxicity to assess safety of the drug

PHASE III

Similar to phase II but conducted on large number of patients (several hundreds to thousands; 250-1000 reasonable)

- It also assesses safety and efficacy

-Could detect effects/side effects not observed in phase II

PHASE IV

-Post-marketing studies

-Controlled and uncontrolled studies are often conducted after drug approval and marketing

-It further assesses safety & efficacy of drugsIt allows for comparisons between different drugs used for the same disease

In addition, phase IV studies could provide evidence of a new use to the drug e.g.
aspirin-antiplatelet
sildenafil citrate-ED

-Double-blind; single-blind placebo controlled studies are usually conducted

In a single-blind study, patients do not know which study group they are in (for example whether they are taking the experimental drug or a placebo). In a double-blind study, neither the patients nor the researchers/doctors know which study group the patients are in.

Placebo: a treatment that appears real, but is designed to have no therapeutic benefit.

AFTER ALL THESE CLINICAL DRUG TRIALS THE DRUG IS USUALLY APPROVED BY NATIONAL OR INTERNATIONAL REGULATORY AUTHORITIES AND IS LICENSED FOR GENERAL PRESCRIBING

■ ETHICS OF THE USE OF DRUGS IN HUMANS

•Full detailed protocol has to be approved by the ethical committee, the institutional review board (IRB)
• All subjects should sign an informed consent form
• All subjects should be insured for life and damage

BRANCHES OF PHARMACOLOGY USUALLY ANSWER ALL OF THE FOLLOWING QUESTIONS:

- How much of a drug to give? Dose
- How frequent a drug should be given?

Related to the biological half-life (t1/2)

- When to give it? Before or after meals; at bed time, PRN... PRN is an acronym for the Latin term "pro re nata," which means "as the situation demands," or simply, "as needed."
- How to give it? administration ... etc

****ADMINISTRATION** (ROUTES) = SYSTEMIC OR LOCAL

- Oral (tablets [IR immediate release; SR Sustained Release; MR Modified Release :according to the activity, Details later on)], syrups, suspension...),
- Parenteral route = Subcutaneous S.C (solution), intramuscular I.M (sol.) intravenous = I.V (sol.); depo-injectable
- Buccal (tab.) sublingual (tab.) rectal (suppositories)
- Transdermal (patches); subdermal implants
- Inhalational (sprays)

****TOPICAL = LOCAL ADMINISTRATION**

- Liquid forms (sprays, lotions, solutions = ear or ophthalmic drops, mouth washes, S.C infiltration e.g. local anesthetics...)
- Semisolid forms (creams, ointments...)
- Solid forms (suppositories, pessaries = vaginal tablet...)

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