

PHARMACOLOGY

(Introduction)

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Drug

- A drug is defined as any chemical that can affect living processes.
- All chemicals can be considered drugs, since, when exposure is sufficiently high, all chemicals will have some effect on life.

Pharmacology

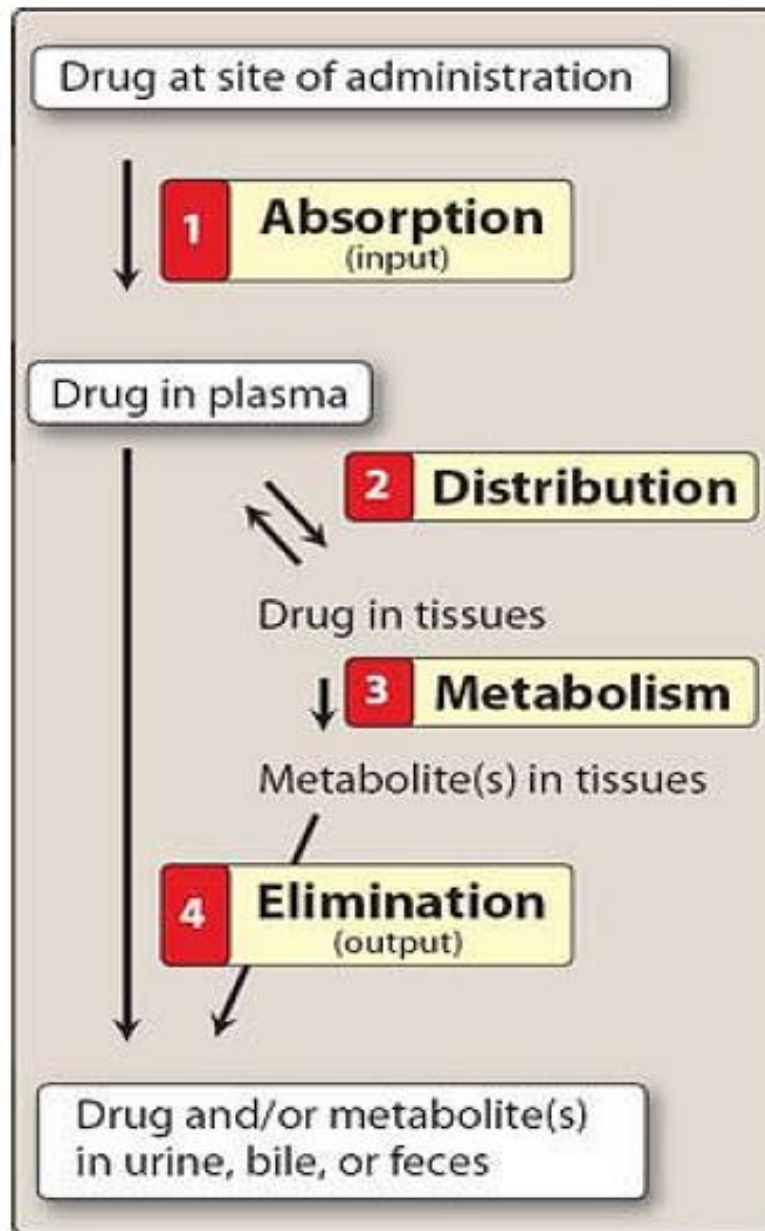
- Pharmacology can be defined as the study of drugs and their interactions with living systems.
- Pharmacology encompasses the study of the physical and chemical properties of drugs as well as their biochemical and physiologic effects.
- Pharmacology includes knowledge of the history, sources, and uses of drugs as well as knowledge of drug absorption, distribution, metabolism, and excretion.

Clinical Pharmacology

- Clinical pharmacology is defined as the study of drugs in humans.
- This discipline includes the study of drugs in patients as well as in healthy volunteers (during new drug development).
- Thus, clinical pharmacology encompasses all aspects of the interaction between drugs and people.

Pharmacokinetics

- The goal of drug therapy is to prevent, cure, or control various disease states.
- To achieve this goal, adequate drug doses must be delivered to the target tissues so that therapeutic yet nontoxic levels are obtained.
- Pharmacokinetics examines the movement of a drug over time through the body.
- Pharmacological as well as toxicological actions of drugs are primarily related to the plasma concentrations of drugs.
- The speed of onset of drug action, the intensity of the drug's effect, and the duration of drug action are controlled by four fundamental pathways of drug movement and modification in the body.



Schematic representation of drug absorption, distribution, metabolism, and elimination.

- First, drug absorption from the site of administration (Absorption) permits entry of the therapeutic agent into plasma.
- Second, the drug may then reversibly leave the bloodstream and distribute into the intracellular fluids (Distribution).
- Third, the drug may be metabolized by the liver, kidney, or other tissues (Metabolism).
- Finally, the drug and its metabolites are removed from the body in urine, bile, or feces (Elimination).
- The processes (Absorption, Distribution, Metabolism, and Elimination) influence the decision of the route of administration for a drug, the amount of each dose, and the dosing intervals.

Routes of Drug Administration

- **Enteral**

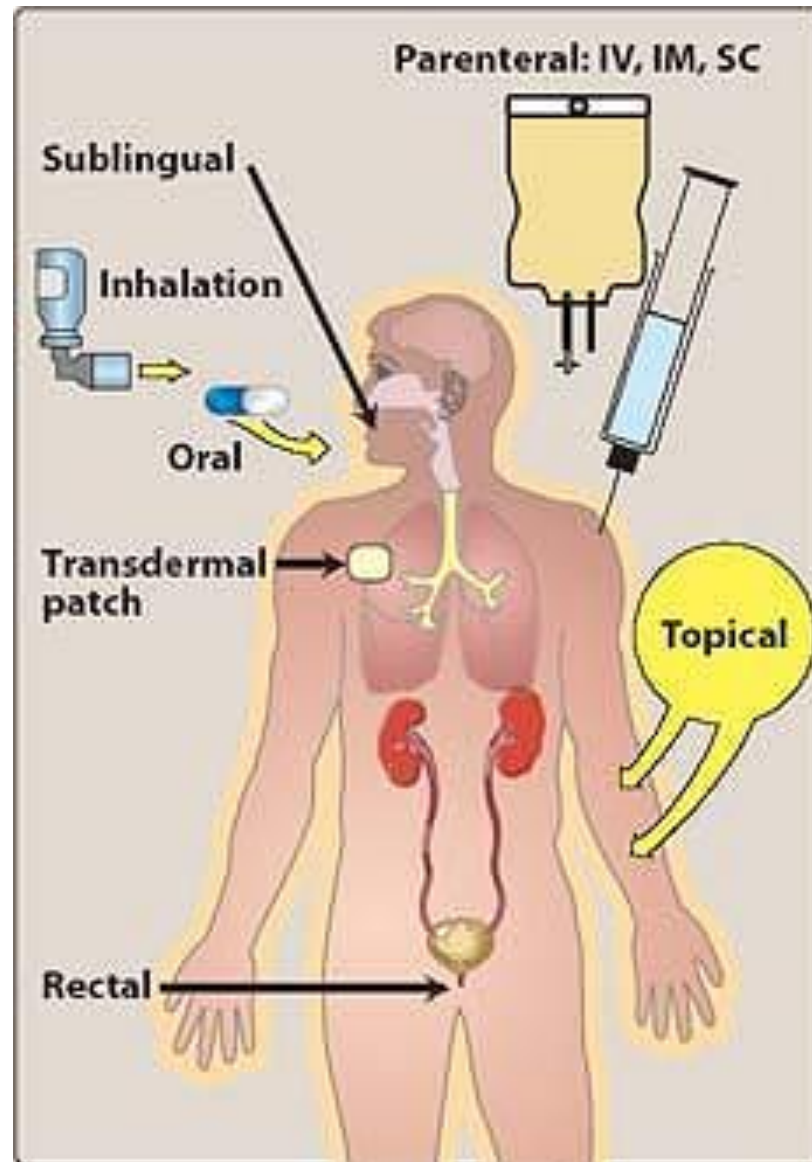
- Oral
- Sublingual

- **Parenteral**

- Intravenous (IV)
- Intramuscular (IM)
- Subcutaneous (SC)

- **Other**

- Inhalation
- Intranasal
- Intrathecal
- Topical
- Transdermal
- Rectal



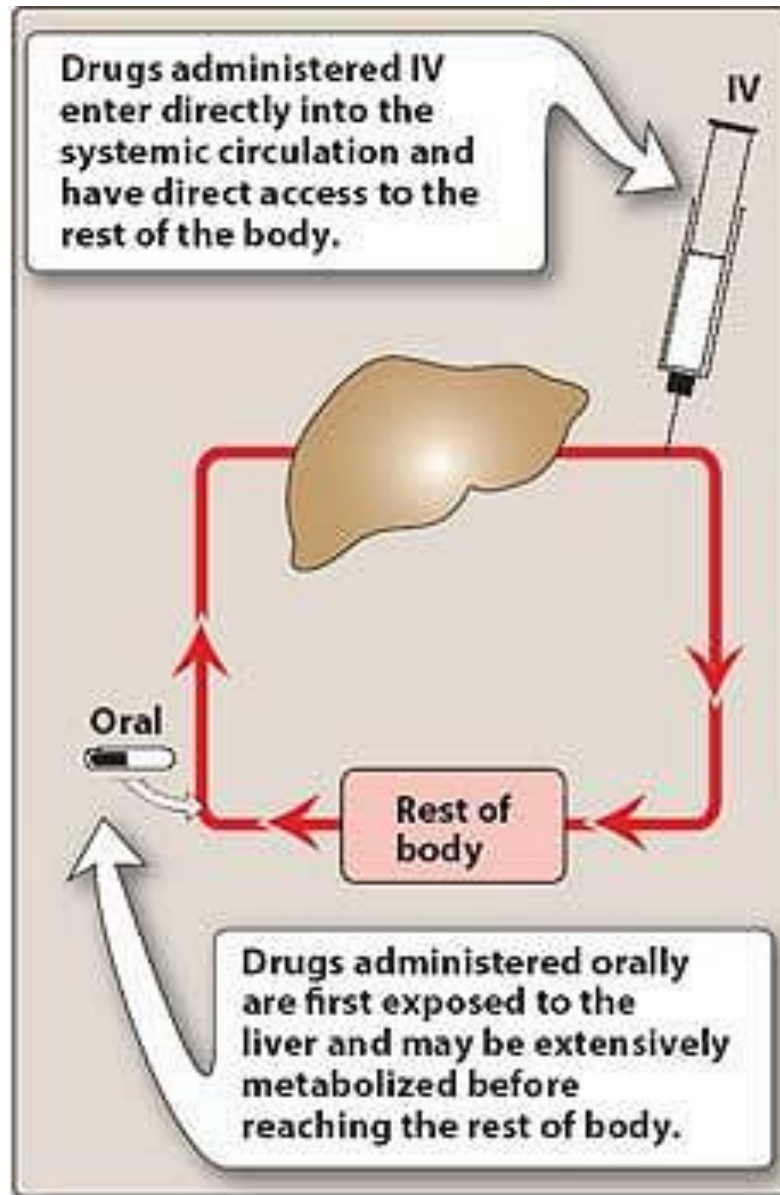
Commonly used routes of drug administration

Enteral

A. Oral

- Giving a drug by mouth provides many advantages to the patient.
- Oral drugs are easily self-administered and limit the number of systemic infections that could complicate treatment.
- Moreover, toxicities or overdose by the oral route may be overcome with antidotes such as activated charcoal.

- On the other hand, the pathways involved in drug absorption are the most complicated, and the drug is exposed to harsh gastrointestinal environments that may limit its absorption.
- Some drugs are absorbed from the stomach; however, the duodenum is a major site of entry to the systemic circulation because of its larger absorptive surface.
- Most drugs absorbed from the GI tract enter the portal circulation and encounter the liver before they are distributed into the general circulation.
- These drugs undergo first-pass metabolism in the liver, where they may be extensively metabolized before entering the systemic circulation.



First-pass metabolism occurs with orally administered drugs.

- First-pass metabolism by the intestine or liver limits the efficacy of many drugs when taken orally.
- For example, more than 90% of *nitroglycerin* is cleared during a single passage through the liver, which is the primary reason why this agent is not administered orally.
- Drugs that exhibit high first-pass metabolism should be given in sufficient quantities to ensure that enough of the active drug reaches the target organ.

- Ingestion of drugs with food, or in combination with other drugs, can influence absorption.
- Drugs that are destroyed by acid (for example, *penicillin*) become unavailable for absorption.
- Enteric coating of a drug protects it from the acidic environment.
- The coating may prevent gastric irritation, and depending on the formulation, the release of the drug may be prolonged, producing a sustained release effect.

B. Sublingual

- Placement under the tongue allows a drug to diffuse into the capillary network.
- Thus, enter the systemic circulation directly.
- Administration of an agent, sublingually, has several advantages including:
 - Rapid absorption
 - Convenience of administration
 - Low incidence of infection
 - Avoidance of the harsh GI environment
 - Avoidance of first-pass metabolism.

Parenteral

- The parenteral route introduces drugs directly across the body's barrier defenses into the systemic circulation or other vascular tissue.
- Parenteral administration is used for drugs that are poorly absorbed from the GI tract (for example *heparin*) and for agents that are unstable in the GI tract (for example, *insulin*).
- Parenteral administration is also used for treatment of unconscious patients and under circumstances that require a rapid onset of action.

- In addition, these routes have the highest bioavailability and are not subject to first-pass metabolism or harsh GI environments.
- Parenteral administration provides the most control over the actual dose of drug delivered to the body.
- However, these routes are irreversible and may cause pain, fear, and infections.
- The three major parenteral routes are intravenous (or intra-arterial), intramuscular, and subcutaneous.

A. Intravenous (IV)

- IV injection is the most common parenteral route.
- For drugs that are not absorbed orally, such as the neuromuscular blocker *atracurium*, there is often no other choice.
- With IV administration, the drug avoids the GI tract and therefore, first-pass metabolism by the liver.
- Intravenous delivery permits a rapid effect and a maximal degree of control over the circulating levels of the drug.

- However, unlike drugs in the GI tract, those that are injected cannot be recalled by strategies such as emesis or by binding to activated charcoal.
- Intravenous injection may inadvertently introduce bacteria through contamination at the site of injection.
- IV injection may also induce hemolysis or cause other adverse reactions by the too-rapid delivery of high concentrations of drug to the plasma and tissues.
- Therefore, the rate of infusion must be carefully controlled.
- Similar concerns apply to intra-arterially injected drugs.

B. Intramuscular (IM)

- Drugs administered IM can be aqueous solutions or specialized depot preparations “often a suspension of drug in a nonaqueous vehicle” such as polyethylene glycol.
- Absorption of drugs in an aqueous solution is fast, whereas that from depot preparations is slow.
- As the vehicle diffuses out of the muscle, the drug precipitates at the site of injection.

- The drug then dissolves slowly, providing a sustained dose over an extended period of time.
- An example is sustained-release *haloperidol decanoate*, which slowly diffuses from the muscle and produces an extended neuroleptic effect.

C. Subcutaneous (SC)

- This route of administration, like that of IM injection, requires absorption and is somewhat slower than the IV route.
- Subcutaneous injection minimizes the risks associated with intravascular injection.
- Minute amounts of *epinephrine* are sometimes combined with a drug to restrict its area of action.

- *Epinephrine* acts as a local vasoconstrictor and decreases removal of a drug, such as *lidocaine*, from the site of administration.
- Other examples of drugs utilizing SC administration include solids, such as a single rod containing the contraceptive *etonogestrel* that is implanted for long-term activity.
- Also programmable mechanical pumps that can be implanted to deliver *insulin* in diabetic patients.

Other routes

A. Inhalation

- Inhalation provides the rapid delivery of a drug across the large surface area of the mucous membranes of the respiratory tract and pulmonary epithelium.
- Produce an effect almost as rapidly as with IV injection.
- This route of administration is used for drugs that are gases (for example, some anesthetics) or those that can be dispersed in an aerosol.

- This route is particularly effective and convenient for patients with respiratory complaints (such as asthma, or chronic obstructive pulmonary disease).
- The drug is delivered directly to the site of action and systemic side effects are minimized.
- Examples of drugs administered via this route include *albuterol*, and corticosteroids, such as *fluticasone*.

B. Intranasal

- This route involves administration of drugs directly into the nose.
- Agents include nasal decongestants such as the anti-inflammatory corticosteroid *mometasone furoate*.
- *Desmopressin* is administered intranasally for the treatment of diabetes insipidus.
- Salmon *calcitonin*, a peptide hormone used in the treatment of osteoporosis, is also available as a nasal spray.
- The abused drug, *cocaine*, is generally taken by intranasal sniffing.

C. Intrathecal

- It is sometimes necessary to introduce drugs directly into the cerebrospinal fluid.
- For example, *amphotericin B* is used in treating cryptococcal meningitis.

D. Topical

- Topical application is used when a local effect of the drug is desired.
- For example, *clotrimazole* is applied as a cream directly to the skin in the treatment of dermatophytosis.
- *Tropicamide* or *cyclopentolate* are instilled (administered drop by drop) directly into the eye to dilate the pupil and permit measurement of refractive errors.

E. Transdermal

- This route of administration achieves systemic effects by application of drugs to the skin, usually via a transdermal patch.
- The rate of absorption can vary markedly, depending on the physical characteristics of the skin at the site of application.
- This route is most often used for the sustained delivery of drugs, such as the antianginal drug *nitroglycerin*, the antiemetic *scopolamine*, and the once-a-week contraceptive patch (Ortho Evra) that has an efficacy similar to oral birth control pills.

F. Rectal

- Fifty percent of the drainage of the rectal region bypasses the portal circulation; thus, the biotransformation of drugs by the liver is minimized.
- Like the sublingual route of administration, the rectal route of administration has the additional advantage of preventing the destruction of the drug by intestinal enzymes or by low pH in the stomach.

- The rectal route is also useful if the drug induces vomiting when given orally, if the patient is already vomiting, or if the patient is unconscious.
- The rectal route is commonly used to administer antiemetic agents.
- On the other hand, rectal absorption is often erratic and incomplete, and many drugs irritate the rectal mucosa.