Shree H.N.Shukla institute of Pharmaceutical Education & Research Rajkot

B.Pharm

Semester IV

Subject Name: Pharmacology I
Subject code:BP404TP

TOPIC:

General Pharmacology

a. Introduction to Pharmacology- Definition, historical landmarks and scope of pharmacology, nature and source of drugs, essential drugs concept and routes of drug administration, Agonists, antagonists(competitive and noncompetitive), spare receptors, addiction, tolerance, dependence, tachyphylaxis, idiosyncrasy, allergy.

b. Pharmacokinetics- Membrane transport, absorption, distribution, metabolism and excretion of drugs .Enzyme induction, enzyme inhibition, kinetics of elimination

Definition:

1. **PHARMACOLOGY**: The word pharmacology is made of two parts, pharmacon (drug) and logus (discourse or study). Pharmacology means study of drugs, their pharmacodynamics, pharmacokinetics and toxicities.

2. **CLINICAL PHARMACOLOGY**: The branch concerned with the scientific studies on the effects of drug treatment in human being.

3. **PHARMACOKINETICS**: It is study of absorption, distribution, metabolism and excretion of

4. **Drugs**. i.e study of what body does to the drug.

5. **PHARMACODYNEMICS**: It is study of mechanism action and site of action of the drugs i.e it is study of what drug does to the body.

6. **ABSORPTION**: Drug goes from site of administration to systemic circulation or blood.

7. **DISTRIBUTION**: Drug goes from systemic circulation to various compartments like fat, muscles, tissue, organ etc.

8. **METABOLISM**: Conversion of drug in to excretion form.

9. **ELIMINATION** OR **EXCRETION**: Removal of drug from the body.

10. **BIOAVAILABILITY**: Fraction of an administered dose of unchanged drug that reaches the systemic circulation

11. **DRUG**: It is the active ingredient which is useful for diagnosis, treatment, mitigation and prevention of any disease or disorder in human beings or animals.

12. **MEDICINE**: The substances used to deliver drug in stable and acceptable form and it consist

13. lubricant, binder, sweetener like other additives constituents with active ingredients.

14. **PHARMACOEPIDEMIOLOGY**: Study of effects of drugs in large numbers of people.

15. **PHARMACOGENOMICS**: Application of genomic technologies to new drug discovery and further characterization of older drugs.

16. **NEUROPHARMACOLOGY**: Effects of medication on central and peripheral nervous system functioning.

17. **PSYCHOPHARMACOLOGY**: Effects of medication on the psyche; observing changed behaviors of the body and mind, and how molecular events are manifest in a measurable behavioral form.

18. **PHARMACOGENETICS**: Clinical testing of genetic variation that gives rise to differing response to drugs.

19. **THEORETICAL PHARMACOLOGY**: Study of metrics in pharmacology.

20. **POSOLOGY**: How medicines are dosed. It also depends upon various factors like age, climate, weight, sex, and so on.

21. **PHARMACOGNOSY**: A branch of pharmacology dealing especially with the composition, use, and development of medicinal substances of biological origin and especially medicinal substances obtained from plants.

22. **PHARMACOVIGILANCE** (PV): It is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

23. **SIDE EFFECTS**: A secondary but predictable effects, typically undesirable effect of a drug or medical treatment.

24. **ADVERSE EFFECTS**: A secondary but unpredictable effects, typically undesirable effect of a drug or medical treatment.

25. **TOXIC EFFECTS**: Harmful effects of the drug which is related to dose (Excess).

History of pharmacology:

Ancient Medicine

Chinese medicine is the earliest and records dated about 2500 B.C. available today give an idea about the medical knowledge of Chinese. In Chinese medicine, the use of Ephedra or Ma huang as a tonic has been reported. Ayurveda or Indian Medicine is equally ancient. To form the science of life namely Ayurveda, Charaka, Sushruta and Vagbhatta (the great three classics) made a compilation of old and new drugs in the cure of diseases. The Charaka Samhita is believed to have arisen around 400-200 BCE. This work is considered a redaction of an older and more voluminous work of Agnivesha Samhita (46,000 verses). Dridhabala, living about 400 A.D, is believed to have filled in many verses of missing text (perhaps up to 20%). The language of Charaka is Sanskrit and its style is poetry, with meter and melody to serve as a memory aid. Most of their theoretical edifice concentrates on the branch of Ayurveda called Kayachikitsa (internal medicine), largely based on the theory of the internal fire - of digestion - or internal medicine, in modern terms. The Sushruta Samhita presents the field of Ayurvedic surgery (Shalya). This branch of medicine arose in part from the exigencies of dealing with the effects of war. Ashtanga Sangraha and Ashtanga Hridayam are the work of a person named Vagbhata. Egyptian medicine is also very ancient. The Ebers Papyrus (a kind of medical encyclopaedia) dated about 1500 B.C. gives a collection of drugs prevalent in Egypt at that time, their classification and their use. Some of the drugs employed now such as, castor oil and pomegranate bark are mentioned in this papyrus.

Pre-Christian Era

Greek medicine is said to be the origin of modern medicine and therapeutics. Hippocrates in fifth century B.C. separated medicine from religion and was known as the father of medicine.

He laid down certain principles on which modern medicine is built. According to Hippocrates the four elements of nature namely water, fire, air and earth gave rise to the four humors of the body namely blood, phlegm, yellow bile or urine and black bile. Any imbalance in one or more of these humors inflicted sufferings. Galen (Aelius Galenus or Claudius Galenus) was a famous Greek physician, surgeon and philosopher in the Roman Empire who practiced in Rome. In Galen's view, an imbalance of each humor (the bodily liquids) corresponded with a particular human temperament (blood—sanguine/cheerful, black bile—melancholic/pensive sadness, yellow bile— choleric/bad-tempered or irritable, and phlegm—phlegmatic/calm). Among Galen's major contributions to medicine was his work on the circulatory system. He was the first to recognize that there are distinct differences between venous (dark) and arterial (bright) blood. His name is still used to refer some drugs as galenical drugs. He was the father of polypharmacy (the concurrent use of multiple medications). Galenical drugs are pharmaceuticals compounded by mechanical means, mostly of the vegetable material.

Mediaeval Medicine

Paracelsus introduced inorganic chemicals like mercury into medicine. He called this 'Iatro Chemistry' or medicinal chemistry. He induced practitioners to use laudanum (an opium preparation), Sulphur, Iron, Copper Sulphate, Potassium Sulphate, Mercurial, tinctures and fluid extract of various plants for treatment of diseases.

Revolts in Medicine

By the beginning of 19th century the principle of shotgun prescription flourished (Shotgun prescription is one that contains a number of substances with no therapeutic efficacy. It is a result of ignorant attempt to cure the disease, no matter what may be its nature).

Gregory advocated methods like venesection, leeching emetics and drastic purgatives. Large doses of purgatives were given. The patient either survived or died. This sort of symptomatic treatment was referred to as allopathy meaning 'other suffering'. This term allopathy is now being used to refer modern medicine. Samuel Hahnemann introduced homeopathy meaning 'similar suffering' at the commencement of 19th century. In Greek, "homos" means same and "patheia" means suffering. He was known as the father of homeopathy. Homeopathy introduced by him had two newer principles that 'like cures like' and 'dilution potentiates the action of drugs'

Modern Medicine

Buccheim, a professor of Dorpat University who was known as the father of Pharmacology set up the first laboratory to study pharmacology. He discarded many remedies because rational scientific action or explanation could not be demonstrated in his laboratory. By the middle of the 19th century, modern medicine had brought to fight disease only one effective weapon i.e. immunization against smallpox.

Later in quick succession came the anesthetics and antiseptics. In the last quarter, the causative organisms for malaria, plaque, cholera etc. were identified. Beginning in the 20th century, the fresh wind of synthetic chemistry began to revolutionize the pharmaceutical industry and with it the science of pharmacology. New synthetic drugs, such as barbiturates and local anesthetics, began to appear and the era of antimicrobial chemotherapy began with the discovery of arsenical compounds for the treatment of syphilis by Paul Ehrlich in 1909. He was known as the father of chemotherapy. Further breakthroughs came with the discovery of sulphonamides by Gerhard Domagk in 1935 and the development of penicillin during world war II.

The addition of drugs to the therapeutic jungle is growing with rapid pace from the latter half of the 20th century.

Scope of pharmacology:

Pharmacology is the science which involves all aspects of the action of drugs on living system. It is the study of the therapeutic value and/or potential toxicity of chemical agents on biological systems. It targets every aspect of the mechanisms for the chemical actions of both traditional and novel therapeutic agents. Important and interrelated areas are: pharmacodynamics and pharmacokinetics.

Pharmacodynamics is the study of how drugs act on the body while pharmacokinetics is the study of how the body acts on drugs. Pharmacodynamic and pharmacokinetic aspects of the action of chemical agents are applicable to all related areas of study, including toxicology and therapeutics.

Toxicology is the study of the adverse or toxic effects of drugs and other chemical agents. It is concerned both with drugs used in the treatment of disease and chemicals that may present household, environmental, or industrial hazards.

Therapeutics focuses on the actions and effects of drugs and other chemical agents with physiological, biochemical, microbiological, immunological, or behavioral factors influencing disease. Each of these areas is closely interwoven with the subject matter and experimental techniques of physiology, biochemistry, cellular biology, microbiology, immunology, genetics, and pathology. The ultimate goal of Pharmacology is to design chemical agents to cure, ameliorate, or prevent disease.

Branches of Pharmacology

Neuropharmacology is the study of neurophysiological or neurobiochemical functions of the nervous system including the brain, spinal cord, and the nerves that are modified by drug action.

Cardiovascular pharmacology concerns the effects of drugs on the heart, the vascular system, and those parts of the nervous and endocrine systems that participate in regulating cardiovascular function.

Molecular pharmacology deals with the biochemical and biophysical characteristics of interactions between drug molecules and those of the cell. It is molecular biology applied to pharmacology and toxicology.

Biochemical pharmacology is the study of action of drugs and drug metabolism, how drugs interact with, and influences, the physiology of the organism.

Behavioral pharmacology studies the effects of drugs on behavior of organism. It includes topics such as the effects of psychoactive drugs on the phenomena of learning, memory, wakefulness, sleep and the behavioral consequences of experimental intervention in enzyme activity and brain neurotransmitter levels and metabolism.

Endocrine pharmacology is the study of drugs that are either hormones or hormone derivatives, or drugs that may modify the sections of normally secreted hormones.

Clinical pharmacology is the application of pharmacodynamics and pharmacokinetics to patients with diseases, it also includes pharmacogenetic component. Clinical pharmacologists study how drugs work, how they interact with the genome and with other drugs, how their effects can alter the disease process, and how disease can alter their effects.

Clinical trial design, the prevention of medication errors, and the optimization of rational prescribing are critical components of clinical pharmacology.

Chemotherapy is the area of pharmacology that deals with drugs used for the treatment of microbial infections and malignancies. Chemotherapeutic agents selectively inhibit the growth of, or kill, the infectious agent or cancer cell without seriously impairing the normal functions of the host.

Toxicology is the science of adverse effects of chemicals/ drugs on living systems. It also includes problems of drug safety, effects of drug over dosage.

Pharmacy is a separate discipline in the health sciences. It is the profession responsible for the preparation, dispensing and appropriate use of medication, and provides services to achieve optimal therapeutic outcomes.

Sources of Drugs

Plant Sources of Drugs

Many drugs available from plants are even today used in the treatment of pathological conditions. With the increasing tendency for the use of alternate medicine, this source has gained more importance in the recent past. The pharmacological activities of plants are attributed to certain active principles in plants. They are - Alkaloids, Glycosides, Oils, Tannins, Saponins, Resins, Gums etc.

Alkaloids

Alkaloids are nitrogenous substances obtained from various parts of the plant. Alkaloids containing oxygen are solids and comparatively non-volatile (cocaine) while those that do not contain oxygen are liquids and volatile (nicotine, lobeline and coniine). Alkaloids are insoluble in water while their salts (atropine sulphate, caffeine citrate) are soluble in water. Alkaloids are bitter to taste. They are incompatible with the alkalis, tannic acid and heavy metals. Alkaloids represent the waste products of plant metabolism and their names end with 'ine'. Alkaloids should be administered in small quantities and when given in excess they may produce death without much postmortem changes for diagnosis. (Adrenaline is considered as animal alkaloid)

Glycosides

Glycosides are non-nitrogenous substances obtained from plants. The glycosides on hydrolysis yield two molecules namely a sugar molecule and a 'genine' or 'aglycone' molecule. Sugar helps in the dissolution of the preparation while the pharmacological action rests with the 'aglycone'. When the sugar molecule is glucose, the glycoside is known as glucoside. Cardiac glycosides digitalis, strophanthus and squill play a major role

in the treatment of congestive cardiac failure. Cyanogenetic glycoside is one in which hydrocyanic acid is released on glycolysis

ESSENTIAL DRUG CONCEPT

"Essential drugs are those that satisfy the health care needs of majority of population"

History of the WHO Model List of Essential Drugs

1977 First Model list published, ± 200 active substances

List is revised every two years by WHO Expert Committee

Last essential drug list established in the year 2010

Guidelines for establishing a national programme for essential drugs

National drug regulatory authority should be established

National drug and therapeutic committee (NDTC) should be established

Committee includes people from Medical Clinical Pharmacology Pharmacy

Public health fields Also from other appropriate health care fields

Generic names should be used for all drugs Concise, accurate and comprehensive drug information should be prepared

Stability and bioavailability should be assured

Efficient administration of supply, storage and distribution of drugs

Management of stocks and eliminate waste

Criteria for the selection of essential drugs

Pattern of prevalent disease and treatment facilities

Level of training and experience of the personnel

Financial resources available in the country

Genetic, demographic and environmental factors

Evidence based and not suituation based

Selected drugs should have adequate data on their efficacy and safety

Tasks after the formation of Essential drug list

Updating the essential drug list

Essential drug list for primary health care centres

Specialist control of drug use

Research and development

Drug information and education activities

Making a list of reserve microbials

Post registration drug studies

Essential drug list for primary health care centres

Existing system of medicine

National health infrastructure

Pattern of endemic diseases

Supplies

Routes of Drug Administration

The drug are administered to have effect on the whole body system or have localized effect on certain region.

Based on the purpose, there is systemic administration or local application of drug by various routes are

1.Oral.

2.Sublingual.

3.Per Rectal.

4.Injectable(Parenteral).

5.Local(Topical) Application.

6.Inhalation.

7.Other Method and Devices of drug delivery.

ORAL ROUTE

Drug which are absorbable and stable in GIT are given by this route.

Though majority drugs are administrated by this route but every drug cannot be given by this route or disadvantages of this route=it take some time before drug effect is seen and intensity of effect may not predictable thus , this route will not be suitable for emergency condition.

Patient have vomiting and diarrhoea,this route not prefered.

For majority of situation it serves the purpose or advantage of this route=

Dose adjustment is easy.

Self administration is possible,comparatively it is less costly and possibility of injury or infection is not there so it is most convenient to patient Drug which are not absorbable; which are destroyed in GIT;

Which are destroyed during portal circulation after absorption(having high first pass

metabolism)and drugs which are irritant cannot given by this route.

Patients who are appose non-cooperative unconscious patients should not be given drug by this route

SUBLINGUAL ROUTE

This is a peculiar route for the drugs undergoing high first pass metabolism.

The tablet is kept underneath the tongue and drug is allowed to get absorbed.

The drug rapidly absorbed and immediate systemic effect is produced.

Very few drugs are given by this route. In case of angina pectoris glyceryl trinatrate and isosorbide dinitrate are use sublingually.

Buprenorphine is use sublingually for chronic pain in malingnancy.

PER RECTAL(PR)

It is less preferred route ,being cumbersome.

For the purpose of sysemic action ,very few drugs are used in this route.

Use of diazepam by this route for status epilepticus or febrile convulsion is important in children.

INJECTABLE(Parenteral)

As better and quicker absorption is expected by this route,it is important route in case of emergency situation and for the not absorbable orally.

This will be suitable in unconscious and uncooperative patient.

Accurate dose adjustment is possible by this route When drug cannot be given oral because of irritation or patient has vomiting, diarrhea and dehydration injection route is preferred. There will no problem related to high first pass metabolism in port circulation , because portal circulation being bypassed.

It is not a convenient route for self administration of drug.

Some injection(particular with irritant drugs)are painful.

There is possibility of local damage(be careful to nerve at the site of injection,repeated injection of insulin causes lipodystrophyin diabetic patient).

Aseptic precaution are needed in this route. Various way of injection eg. sc,im,iv, intra-thecal;intra-peritoneal; Intra-articular;intra- arterial;subconjuctival;retro-bulbar;

INTRA-DERMAL(id)

Vary small quantity of the drug is administered(only0.1-0.2ml);the injection is painfull;only test dose is administered(to determine hypersensitivity reaction).

BCG vaccine is given by this route Drug kept under the skin by this route.

INTRAVENOUS(IV)

There is very quick effect as drugs enters the circulation(no process of absorption is involved).

Rapid(bolus)administration into high concentration reaching to the heart may causes cardiac toxicity.

Suspensions and oily preparation cannot be injected(danger of embolism).

Irritation of vein can lead to phlebitis and thrombosis.

It is easy to adjust the rate of administration with accuracy by this route.

By this route the drug is administered as

(A)Bolus injection(diazepam for status epilepticus,diazoxide for the hypertansive emergency).

(B) as slow intravenous administration after adequate dilution of drug(adrenaline for anaphylatic shock 1ml of adrenaline solution diluted to 10ml saline and 5ml of it is injected over a few minutes)

(C)as intra venous infusion drug dilute in a large volume of suitable vehicle is given over a period of a few hours.insuline50 units added to 500ml of saline and infused as

15 drops per min. in a patient of 60kg for t/t of diabetic coma.Dopamine 10-12 drops per min for t/t of cardiogenic shock.

Intra venous infusion needed when continuous blood level of drug is to be maintained.Drug having very short half life(like insuline,dopamine,oxytocin,lignocaine etc.)are preffered given by this route.

SUCUTANEOUS(SC)

About 1-5ml can be injected.

Non-irritant drugs are injected.

There is slow and steady absorption occur.

If peripheral circulation is not maintained,absorption is poor and drug is not effective.

Insulin and adrenaline are usually administered by this route.

Lignocaine is given by this route for surgical procedure.

In this route adrenaline retard the absorption of lignocaine and local aneasthetic effect is prolonged.

Irritation of vein can lead to phlebitis and thrombosis.

INTRAMUSCULAR(IM)

Deltoid,triceps and gluteus maximus muscles

are usual sites. Injection is less painful.

Soluble drugs are quickly absorbed.

In case of repository(depot) preparation like oily solution and suspensions are absorbed slow and steady. Exercise and blood flow in the area are determinant of rate of absorption.

Some special routes of injection=

Intra-thecal=for spinal anaesthesia

Intra-peritoneal=large volume can be given;used for peritoneal dialysis.

Intra-arterial =Radio-opaque dyes are injected for radiography.

Intra-articular=Steroids can be given in joint cavity.

Sub –conjuctival,retro-bulbar are specialized route in ophthalmology.

LOCAL (TROPICAL)APPLICATION

Application on the skin,mucous membrane or in body cavities for localized action is local application.

Skin,mucous membrane including of the body cavities like mouth,vagina and rectum are common sites of local application.

There is quick and localized action. As there is minimal systemic absorption chances of systemic unwanted effects are less.However,local irritation may occur.

INHALATION

By this route, the drug in the form of gas,volatile liquiq,aerosols or fine powder are inhaled.

They get absorbed and produce systemic effecs(general anaesthesia by halothane,isoflurane,oxygen correct hypoxia and carbon di oxide stimulates respiration and corrects pH balance).

If drug is not absorbed it produces local effect in respiration tract without producing systemic(unwanted)effects.

Action is expected to be quick.

Anti-asthma drugs salbutamol,beclomethasone are commenly used by this route.

OTHER METHODS AND DEVICES OF DRUG DELIVERY=

OCUSERT: Adevice place under eyelid,delivers pilocarpine continuously over a long time(seven days)for treatment of glaucoma.

PROGESTASERT: It produce continuous release of progesterone for long period(a year) useful as intrauterine contraceptive.

DRUG ELUTING STENTS:

Metallic stents are covered with polymer containing drug; used in coronary angioplasty to reduce restenosis.

SUBCUTANEOUS IMPLANTS:

Solid pellets or drug packed in a capsule of suitable material is implanted underneath the skin is one the new drug delivery systems.

PRO-DRUG: The drug is administered In an inactive form.Inside the body, it is converted into an active compound.

By use of pro-drug availability of the active drug is increased(talampicillin,bacampicillin leads to better avaibility of ampicillin)or its distribution to particular sites is increased(levodopa reaches to brain and converted to dopamine to be effective in parkinsons disease).

TARGETED DELIVERY:It is a new advancement in drug delivery system.A cytotoxic drug is atteched to the monoclonal antibodies specific to cancer cell antigen;drug produces intense effect on cancer cells and general toxicity is very much reduced.

Anti-cancer drugs and amphotericin B for kala-azar are ued in this manner.

Types of Drug Action

Agonist

Antagonist

Partial agonist

Inverse agonist

Agonists

An agonist is a chemical that binds to a receptor and activates the receptor to produce a biological response. Whereas an agonist causes an action, an antagonist blocks the action of the agonist, and an inverse agonist causes an action opposite to that of the agonist. Receptors can be activated by either endogenous agonists (such as hormones and neurotransmitters) or exogenous agonists (such as drugs), resulting in a biological response. A physiological agonist is a substance that creates the same bodily responses but does not bind to the same receptor.

Antagonist

Antagonist: A substance that acts against and blocks an action. Antagonist is the opposite of agonist. Antagonists and agonists are key players in the chemistry of the human body and in pharmacology. A receptor antagonist is a type of receptor ligand or drug that blocks or dampens a biological response by binding to and blocking a receptor rather than activating it like an agonist. They are sometimes called blockers; examples include alpha blockers, beta blockers, and calcium channel blockers.

Partial agonist

A partial agonist is a substance that binds to and activates a receptor in the body, but with less efficacy or strength compared to a full agonist. In pharmacology, agonists are molecules that activate a receptor and produce a biological response. However, the extent to which they activate the receptor can vary.

A partial agonist binds to the receptor and activates it to a certain degree, but it does not produce the maximal response that a full agonist would. This partial activation can be due to a variety of factors, including the affinity of the partial agonist for the receptor or its intrinsic activity.

Inverse agonist

Most receptors have some level of basal activity, meaning they are active even in the absence of any agonist. Inverse agonists bind to these receptors and reduce this basal activity, effectively exerting an inhibitory effect. This is in contrast to antagonists, which simply block the action of agonists without affecting the basal activity of the receptor.

Inverse agonists are particularly relevant in systems where receptors exhibit constitutive activity, such as certain G protein-coupled receptors (GPCRs). They have potential therapeutic applications in conditions where reducing the basal activity of a receptor is beneficial, such as in the treatment of anxiety, insomnia, or certain psychiatric disorders.

Spare Receptor

The concept of spare receptors was first proposed by pharmacologist Alfred G. Gilman and mathematician Martin Rodbell in the early 1980s to explain certain observations related to receptor-effector coupling and cellular signaling. It has since

been widely studied and has become an important consideration in the field of pharmacology and drug development.

The presence of spare receptors can also provide a buffer against receptor desensitization or downregulation in response to chronic exposure to agonists. This can help maintain the responsiveness of the system to agonist stimulation over time.

Drug addiction

drug addiction refers to a condition where an individual becomes dependent on a particular substance due to its pharmacological effects on the brain and body. Drug addiction involves a complex interplay of biological, psychological, and environmental factors. From a pharmacological perspective, drug addiction is studied in terms of how drugs interact with the brain's neurotransmitter systems, particularly those involved in reward, motivation, and reinforcement.

Drug tolerance

Drug tolerance refers to a phenomenon in which an individual requires increasing doses of a drug to achieve the same effects that were initially experienced with lower doses. It develops as a result of the body's adaptive response to repeated exposure to the drug. Tolerance can occur with various types of drugs, including prescription medications, illicit substances, and even certain therapeutic interventions like opioids or anxiolytics.

Drug Dependence

drug dependence refers to a state where the body has adapted to the presence of a drug, leading to physiological changes that result in tolerance, withdrawal symptoms upon cessation of drug use, and a compulsive need to continue using the drug despite negative consequences.

Tachyphylaxis

refers to a rapid decrease in response to a drug after repeated or continuous administration. It is also known as "acute tolerance" or "rapid tolerance." Tachyphylaxis can occur within minutes to hours of drug exposure and may result in a diminished therapeutic effect or complete loss of response.

Idiosyncrasy

In pharmacology, an idiosyncratic reaction refers to an unusual or unexpected response to a drug that is not typically observed in most individuals. These reactions are unpredictable and often unrelated to the drug's pharmacological actions. Idiosyncratic reactions can manifest as unusual side effects, toxicity, or allergic reactions.

Allergy

an allergy refers to an abnormal immune response triggered by exposure to a specific substance, known as an allergen. Allergic reactions can range from mild to severe and can affect various systems of the body, including the skin, respiratory tract, gastrointestinal tract, and cardiovascular system.

PHARMACOKINETICS:

Pharmacokinetics is derived from two words: Pharmacon meaning drug and kinesis meaning movement. In short, it is 'what the body does to the drug'. It includes absorption (A), distribution (D), metabolism (M) and excretion (E). All these processes involve movement of the drug molecule through various biological membranes. All biological membranes are made up of a lipid bilayer. Drugs cross various biological membranes by the following mechanisms:

1. **Passive diffusion**: It is a bidirectional process. The drug molecules move from a region of higher to lower concentration until equilibrium is attained. The rate of diffusion is directly proportional to the concentration gradient across the membrane. Lipid-soluble drugs are transported across the membrane by passive diffusion. It does not require energy and is the process by which majority of the drugs are absorbed.

2. **Active transport**: Drug molecules move from a region of lower to higher concentration against the concentration gradient. It requires energy, e.g. transport of sympathomimetic amines into neural tissue, transport of choline into cholinergic neurons and absorption of levodopa from the intestine. In primary active transport, energy is obtained by hydrolysis of ATP. In secondary active transport, energy is derived from transport of another substrate (either symport or antiport).

3. **Facilitated diffusion**: This is a type of carrier-mediated transport and does not require energy. The drug attaches to a carrier in the membrane, which facilitates its diffusion across the membrane. The transport of molecules is from the region of higher to lower concentration, e.g. transport of glucose across muscle cell membrane by a transporter GLUT 4.

4. **Filtration**: Filtration depends on the molecular size and weight of the drug. If drug molecules are smaller than the pores, they are filtered easily through the membrane.

5. **Endocytosis**: The drug is taken up by the cell through vesicle formation. Absorption of vitamin B12–intrinsic factor complex in the gut is by endocytosis.

DRUG ABSORPTION PH1.4

Movement of a drug from the site of administration into the blood stream is known as absorption.

Factors Influencing Drug Absorption

1. **Physicochemical properties of the drug**:

a. **Physical state**: Liquid form of the drug is better absorbed than solid formulations.

b. Lipid-soluble and unionized form of the drug is better absorbed than watersoluble and ionized form.

c. **Particle size**: Drugs with smaller particle size are absorbed better than larger ones, e.g. microfine aspirin, digoxin and griseofulvin are well absorbed from the gut and produce better effects. Some of the anthelmintics have larger particle size. They are poorly absorbed through gastrointestinal (GI) tract, hence they produce better effect on gut helminths.

d. **Disintegration time**: It is the time taken for the formulation (tablet or capsule) to break up into small particles and its variation may affect the bioavailability.

e. **Dissolution time**: It is the time taken for the particles to go into solution. Shorter the time, better is the absorption.

f. **Formulations**: Pharmacologically inert substances like lactose, starch, calcium

sulphate, gum, etc. are added to formulations as binding agents. These are not totally inert and may affect the absorption of drugs, e.g. calcium reduces the absorption of tetracyclines.

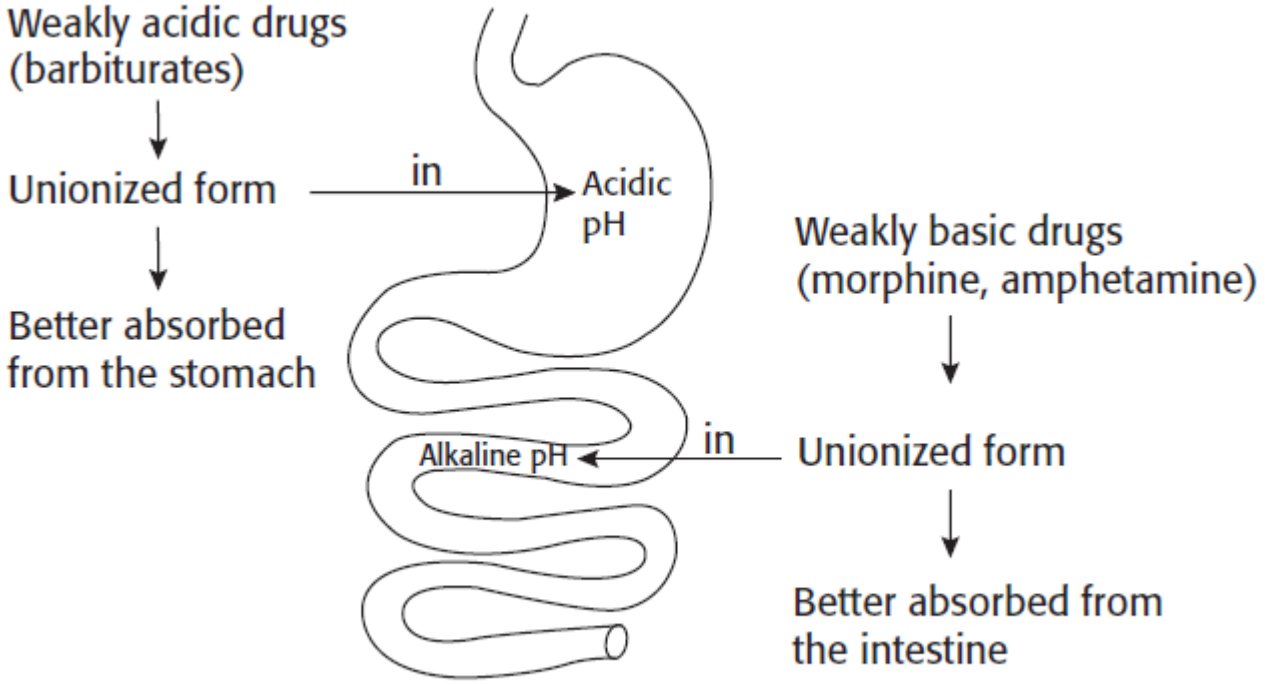


Fig. 1.3 Effect of pH and ionization on drug absorption.

2. **Route of drug administration**: A drug administered by intravenous route bypasses the process of absorption as it directly enters the circulation. Some drugs are highly polar compounds, ionize in solution and are not absorbed through GI tract, hence are given parenterally, e.g. gentamicin. Drugs like insulin are administered parenterally because they are degraded in the GI tract on oral administration.

3. **pH and ionization**: Strongly acidic (heparin) and strongly basic (aminoglycosides) drugs usually remain ionized at all pH, hence they are poorly absorbed (Fig. 1.3).

4. **Food**: Presence of food in the stomach can affect the absorption of some drugs. Food decreases the absorption of rifampicin, levodopa, etc., hence they should be

taken on an empty stomach for better effect. Milk and milk products decrease the absorption of tetracyclines. Fatty meal increases the absorption of griseofulvin.

5. **Presence of other drugs**: Concurrent administration of two or more drugs may affect their absorption, e.g. ascorbic acid increases the absorption of oral iron. Antacids reduce the absorption of tetracyclines.

6. **Area of the absorbing surface**: Normally, drugs are better absorbed in small intestine because of a larger surface area. Resection of the gut decreases absorption of drugs due to a reduced surface area.

7. **Gastrointestinal and other diseases**: In gastroenteritis, there is increased peristaltic movement that decreases drug absorption. In achlorhydria, absorption of iron from the gut is reduced. In congestive cardiac failure, there is GI mucosal oedema that reduces absorption of drugs.

BIOAVAILABILITY

It is the fraction of a drug that reaches systemic circulation from a given dose. Intravenous route of drug administration gives 100% bioavailability as it directly enters the circulation. The term bioavailability is used commonly for drugs given by oral route. If two formulations of the same drug produce equal bioavailability, they are said to be bioequivalent. If formulations differ in their bioavailability, they are said to be bioinequivalent.

Factors Affecting Bioavailability.

The factors which affect drug absorption (physicochemical properties of the drug, route of drug administration, pH and ionization, food, presence of other drugs, area of absorbing surface, GI and other diseases) also affect bioavailability of a drug. Other factors that affect the bioavailability of a drug are discussed as follows:

1. **First-pass metabolism (First-pass effect, presystemic elimination):** When drugs are administered orally, they have to pass via gut wall n portal vein n liver n systemic circulation (Fig. 1.4). During this passage, certain drugs get metabolized and are removed or inactivated before they reach the systemic circulation. This process is known as first-pass metabolism. The net result is a decreased bioavailability of the drug and diminished therapeutic response, e.g. drugs like lignocaine (liver), isoprenaline (gut wall), etc.

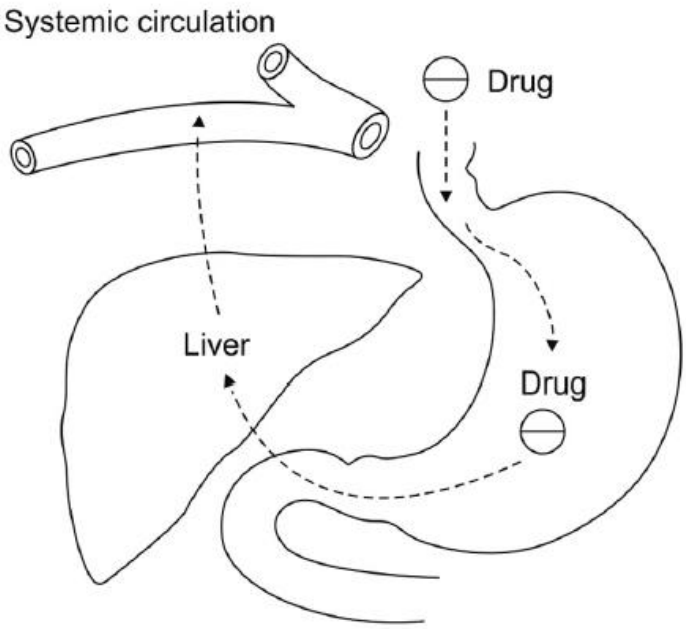
Consequences of high first-pass metabolism:

1) Drugs which undergo extensive first-pass metabolism are administered parenterally, e.g. lignocaine is administered intravenously in ventricular arrhythmias.

2) Dose of a drug required for oral administration is more than that given by other systemic routes, e.g. nitroglycerin.

2. Hepatic diseases: They result in a decrease in drug metabolism, thus increasing the bioavailability of drugs that undergo high first-pass metabolism, e.g. propranolol and lignocaine.

3. Enterohepatic cycling: Some drugs are excreted via bile but after reaching the intestine they are reabsorbed n liver n bile n intestine and the cycle is repeated– such recycling is called enterohepatic circulation and it increases bioavailability as well as the duration of action of the drug, e.g. morphine and doxycycline.



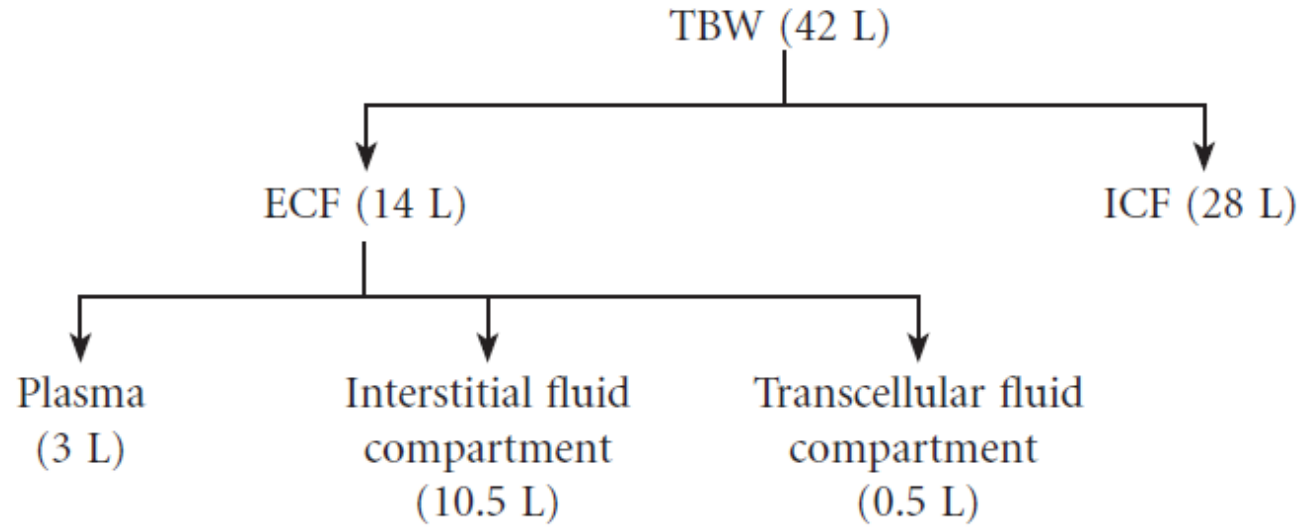
Factors affecting bioavailability of a drug

1. Physicochemical properties of the drug
2. Route of drug administration
3. pH and ionization
4. Food
5. Presence of other drugs
6. Area of absorbing surface
7. Gastrointestinal and other diseases
8. First-pass metabolism
9. Hepatic diseases
10. Enterohepatic cycling

Fig. 1.4 First-pass metabolism.

DRUG DISTRIBUTION

Distribution is defined as the reversible transfer of drugs between body-fluid compartments. After absorption, a drug enters the systemic circulation and is distributed in the body fluids. Various body-fluid compartments for a 70-kg person can be depicted as follows:



ECF, extracellular fluid; ICF, intracellular fluid; TBW, total body water.

Apparent Volume of Distribution

Apparent volume of distribution (aVd) is defined as the hypothetical volume of body fluid into which a drug is uniformly distributed at a concentration equal to that in plasma, assuming the body to be a single compartment.

$$aV_d = \frac{\text{Total administered amount of drug}}{\text{Concentration of the drug in plasma}}$$

Drugs with high molecular weight (e.g. heparin) or extensively bound to plasma protein (e.g. warfarin) are largely restricted to the vascular compartment, hence their aVd is low.

If aVd of a drug is about 14–16 L (0.25 mL/kg in a person weighing 70 kg), it indicates that the drug is distributed in the ECF, e.g. gentamicin, streptomycin, etc. Small water soluble molecules like ethanol are distributed in total body water – aVd is approximately 42 L. Drugs which accumulate in tissues have a volume of distribution which exceeds total body water, e.g. chloroquine (13,000 L) and digoxin (500 L). Haemodialysis is not useful for removal of drugs with large aVd in case of overdosage.

In congestive cardiac failure, Vd of some drugs can increase due to an increase in ECF volume (e.g. alcohol) or decrease because of reduced perfusion of tissues.

In uraemia, the total body water can increase which increases Vd of small watersoluble drugs. Toxins which accumulate can displace drugs from plasma protein binding sites resulting in increased concentration of free form of drug which can leave the vascular compartment leading to an increase in Vd.

Fat:lean body mass ratio – highly lipid-soluble drugs get distributed to the adipose tissue. If the ratio is high, the volume of distribution for such a drug will be higher; fat acts as a reservoir for such drugs.

Redistribution

Highly lipid-soluble drug, such as thiopentone, on intravenous administration, immediately gets distributed to the areas of high blood flow, such as brain, and causes general anaesthesia. Immediately within few minutes, it diffuses across the blood–brain barrier (BBB) into blood and then to the less perfused tissues, such as muscle and adipose tissue. This is called redistribution, which results in termination of drug action. Thiopentone has a very short duration of action (5–10 minutes) and is used for induction of general anaesthesia.

Drug Reservoirs or Tissue Storage

Some drugs are concentrated or accumulated in tissues or some organs of the body,

which can lead to toxicity on chronic use, e.g. tetracyclines – bones and teeth; thiopentone

and DDT – adipose tissue; chloroquine – liver and retina; digoxin – heart, etc.

Blood–Brain Barrier

The capillary boundary that is present between blood and brain is called blood—brain

barrier (BBB). In the brain capillaries, the endothelial cells are joined by tight junctions.

Only the lipid-soluble and unionized form of drugs can pass through BBB and reach the

brain, e.g. barbiturates, diazepam, volatile anaesthetics, amphetamine, etc. Lipid-insoluble

and ionized particles do not cross the BBB, e.g. dopamine and aminoglycosides.

Pathological states like meningitis and encephalitis increase the permeability of the

BBB and allow the normally impermeable substances to enter the brain, e.g. penicillin

G in normal conditions has poor penetration through BBB, but its penetrability increases

during meningitis and encephalitis.

Placental Barrier

Drugs administered to a pregnant woman can cross placenta and reach the fetus. Passage

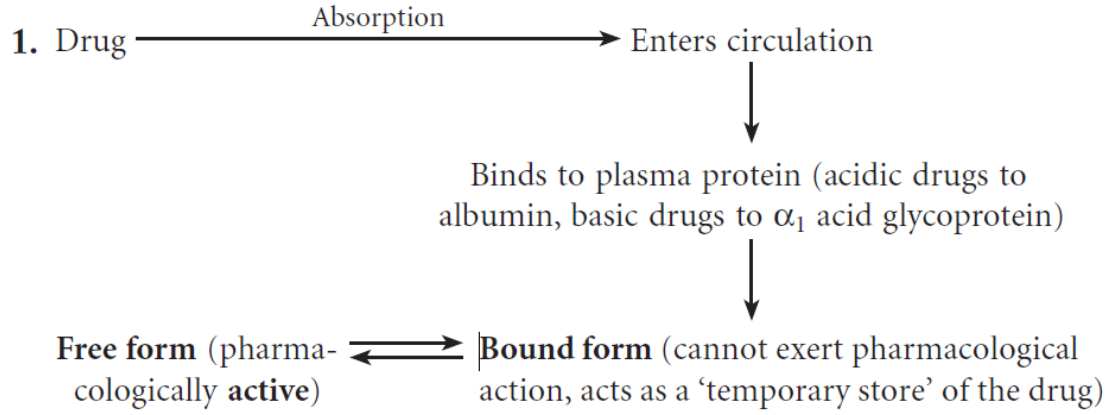
across placenta is affected by lipid solubility, degree of plasma protein binding, presence

of transporters, etc. Quaternary ammonium compounds, e.g. d-tubocurarine (d-TC)

and substances with high molecular weight like insulin cannot cross the placental barrier.

PLASMA PROTEIN BINDING

Many drugs bind to plasma proteins like albumin, "1 acid glycoprotein, etc.



2. Drugs that are highly bound to plasma proteins have a low volume of distribution.

3. Plasma protein binding delays the metabolism of drugs.

4. Bound form is not available for filtration at the glomeruli. Hence, excretion of highly plasma protein bound drugs by filtration is delayed.

5. Highly protein bound drugs have a longer duration of action, e.g. sulphadiazine is less plasma protein bound and has a duration of action of 6 hours, whereas sulphadoxine is highly plasma protein bound and has a duration of action of 1 week.

6. In case of poisoning, highly plasma protein bound drugs are difficult to be removed by haemodialysis.

7. In disease states like anaemia, renal failure, chronic liver diseases, etc. plasma albumin levels are low (hypoalbuminaemia). So, there will be a decrease in bound form and an increase in free form of the drug, which can lead to drug toxicity.

8. Plasma protein binding can cause displacement interactions. More than one drug can bind to the same site on plasma protein. The drug with higher affinity will displace the one having lower affinity and may result in a sudden increase in the free concentration of the drug with lower affinity.

BIOTRANSFORMATION (Drug Metabolism)

Chemical alteration of the drug in a living organism is called biotransformation. The metabolism of a drug usually converts lipid-soluble and unionized compounds into water-soluble and ionized compounds, hence not reabsorbed in the renal tubules and are excreted. If the parent drug is highly polar (ionized), then it may not get metabolized and is excreted as such. Sites: Liver is the main site for drug metabolism; other sites are GI tract, kidney, lungs, blood, skin and placenta. The end result of drug metabolism is inactivation, but sometimes a compound with pharmacological activity may be formed as shown below:

The end result of drug metabolism is inactivation, but sometimes a compound with pharmacological activity may be formed as shown below:

1. *Active drug to inactive metabolite*: This is the most common type of metabolic transformation.
   Phenobarbitone ⟶ Hydroxyphenobarbitone
   Phenytoin ⟶ *p*-Hydroxyphenytoin
2. *Active drug to active metabolite*
   Codeine ⟶ Morphine
   Diazepam ⟶ Oxazepam
3. *Inactive drug (prodrug) to active metabolite*
   Levodopa ⟶ Dopamine
   Prednisone ⟶ Prednisolone

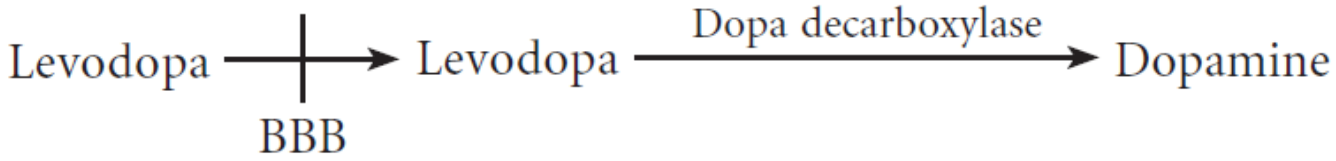
Prodrug

It is an **inactive** form of a drug, which is converted to an active form after metabolism.

Uses of Prodrugs (Advantages)

1. To improve bioavailability: Parkinsonism is due to deficiency of dopamine. Dopamine

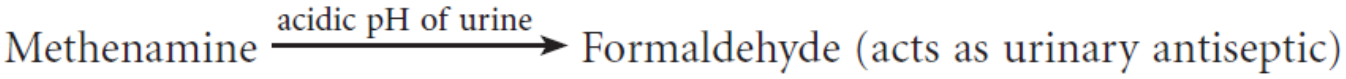
itself cannot be used since it does not cross BBB. So, it is given in the form of a prodrug, levodopa. Levodopa crosses the BBB and is then converted into dopamine.



2. To prolong the duration of action: Phenothiazines have a short duration of action, whereas esters of phenothiazine (fluphenazine) have a longer duration of action.

3. To improve taste: Clindamycin has a bitter taste, so clindamycin palmitate suspension has been developed for paediatric use to improve the taste.

4. To provide site-specific drug delivery:



Pathways of Drug Metabolism. Drug metabolic reactions are grouped into two phases. They are Phase I or nonsynthetic reactions and Phase II or synthetic reactions. Phase I Reactions (Table 1.1). Oxidation: Addition of oxygen or removal of hydrogen is called oxidation. It is the most important and common metabolic reaction. Oxidation reactions are mainly carried out by cytochrome P450, cytochrome P450 reductase, molecular O2 and NADPH. There are several cytochrome P450 isoenzymes.

Table 1.1 ■ **Phase I reactions**

Oxidation	Addition of oxygen/removal of hydrogen	Phenytoin, phenobarbitone, pento-barbitone, propranolol
Reduction	Removal of oxygen/addition of hydrogen	Chloramphenicol, methadone
Hydrolysis	Break down of compound by addition of water	Esters – procaine, succinylcholine Amides – lignocaine, procainamide
Cyclization	Conversion of straight chain compound into ring structure	Proguanil
Decyclization	Breaking up of the ring structure of the drug	Phenobarbitone, phenytoin

Phase II Reactions. Phase II consists of conjugation reactions. If the phase I metabolite is polar, it is excreted in urine or bile. However, many metabolites are lipophilic and undergo subsequent conjugation with an endogenous substrate, such as glucuronic acid, sulphuric acid, acetic acid or amino acid. These conjugates are polar, usually water-soluble and inactive. Not all drugs undergo phase I and phase II reactions in that order. In case of isoniazid (INH), phase II reaction precedes phase I reaction.

Table 1.2 ■ **Phase II reactions**

Conjugation reaction	Enzyme	Examples
Glucuronidation	UDP glucuronosyl transferase	• Aspirin • Morphine
Acetylation	N-acetyltransferase	• Isoniazid • Dapsone
Sulphation	Sulphotransferase	• Paracetamol • Methyldopa
Methylation	Transmethylase	• Adrenaline • Dopamine
Glutathione conjugation	Glutathione transferase	• Paracetamol
Glycine conjugation	Acyl CoA glycine transferase	• Salicylates

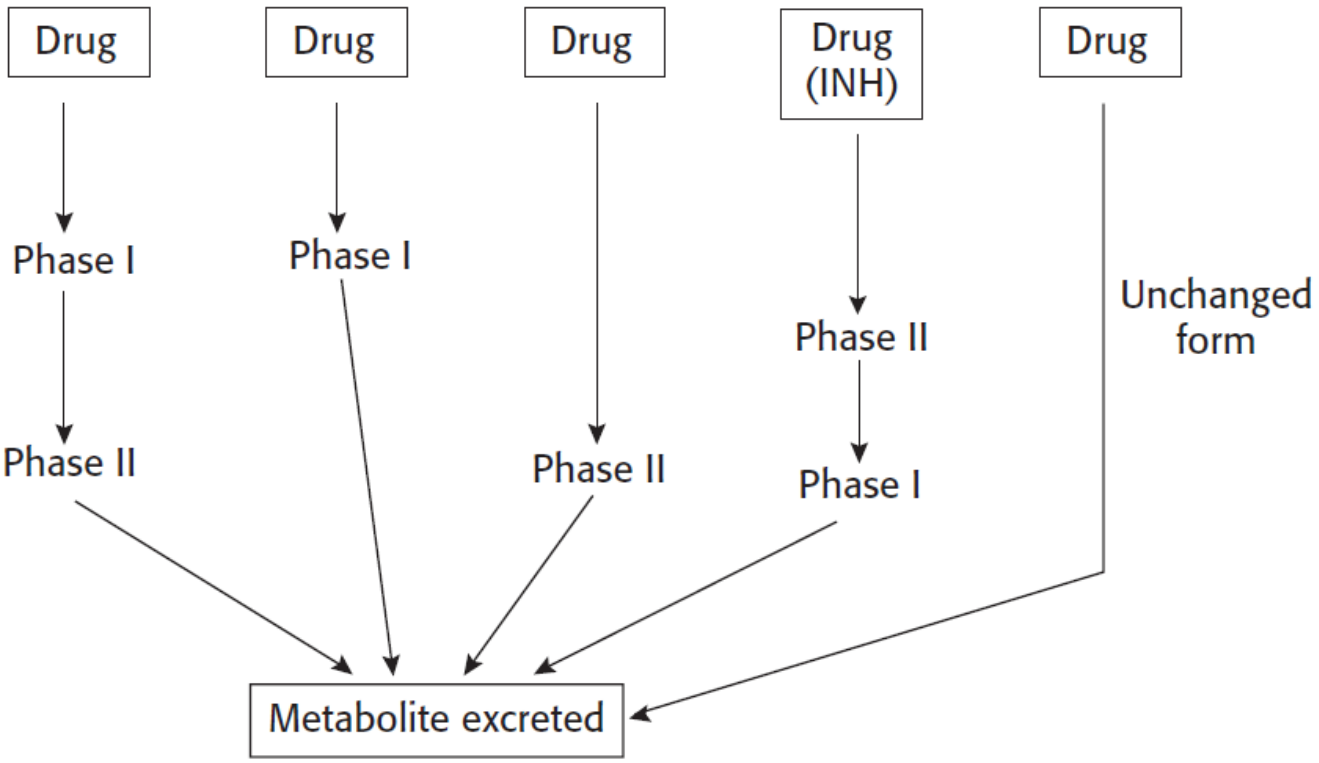


Fig. 1.5 Phases of biotransformation.

Table 1.3 ■ **Microsomal and nonmicrosomal enzymes**

Microsomal enzymes	Nonmicrosomal enzymes
Location	
Smooth endoplasmic reticulum of cells, liver, kidney, lungs, e.g. cytochrome P450, monooxygenase, glucuronyl transferase	Cytoplasm, mitochondria, plasma, e.g. conjugases, esterases, amidases, flavoprotein oxidases
Reactions	
Most of the phase I reactions, Glucuronide conjugation	Oxidation, reduction (few), hydrolysis. All conjugations except glucuronide conjugation
Inducible	Not inducible – may show genetic polymorphism

Drug-Metabolizing Enzymes

They are broadly divided into two groups – microsomal and nonmicrosomal enzyme systems (Table 1.3).

Hofmann Elimination

Drugs can be inactivated without the need of enzymes – this is known as Hofmann elimination. Atracurium, a skeletal muscle relaxant, undergoes Hofmann elimination.

Factors Affecting Drug Metabolism

1. Age: Neonates and elderly metabolize some drugs to a lesser extent than adults. In these cases, it is due to diminished amount/activity of hepatic microsomal enzymes. Neonates conjugate chloramphenicol more slowly, hence develop toxicity – grey baby syndrome. Increased incidence of toxicity with propranolol and lignocaine in elderly is due to their decreased hepatic metabolism.

2. Diet: Poor nutrition can decrease enzyme function.

3. Diseases: Chronic diseases of liver may affect hepatic metabolism of some drugs, e.g. increased duration of action of diazepam, in patients with cirrhosis, due to its impaired metabolism.

4. Genetic factors (pharmacogenetics): These factors also influence drug metabolism. The study of genetically determined variation in drug response is called pharmacogenetics

a. Slow and fast acetylators of isoniazid: There is an increased incidence of peripheral neuritis with isoniazid in slow acetylators. The fast acetylators require a larger dose of the drug to produce therapeutic effect.

b. Succinylcholine apnoea: Succinylcholine, a neuromuscular blocker, is metabolized by plasma pseudocholinesterase enzyme. The duration of action of succinylcholine is 3–6 minutes. However, some individuals have atypical pseudocholinesterase that metabolizes the drug very slowly. This results in prolonged succinylcholine apnoea due to paralysis of respiratory muscles, which is dangerous.

c. Glucose-6-phosphate dehydrogenase (G6PD) deficiency and haemolytic anaemia: G6PD activity is important to maintain the integrity of the RBCs. A person with G6PD deficiency may develop haemolysis when exposed to certain drugs like sulphonamides, primaquine, salicylates, dapsone, etc.

5. Simultaneous administration of drugs: This can result in increased or decreased metabolism of drugs (see enzyme induction or inhibition).

Enzyme Induction

Repeated administration of certain drugs increases the synthesis of microsomal enzymes. This is known as enzyme induction. The drug is referred to as an enzyme inducer, e.g. rifampicin, phenytoin, barbiturates, carbamazepine, griseofulvin, etc.

Clinical Importance of Microsomal Enzyme Induction

1. Enzyme induction may accelerate the metabolism of drugs, thus reducing the duration

and intensity of drug action leading to therapeutic failure, e.g. rifampicin and oral contraceptives. Rifampicin induces the drug metabolizing enzyme of oral contraceptives, thus enhancing its metabolism and leading to contraceptive failure.

2. Autoinduction may lead to development of drug tolerance, e.g. carbamazepine enhances its own metabolism.

3. Enzyme induction can lead to drug toxicity, e.g. increased incidence of hepatotoxicity with paracetamol in alcoholics is due to overproduction of toxic metabolite of paracetamol.

4. Prolonged phenytoin therapy may produce osteomalacia due to enhanced metabolism of vitamin D3.

5. Enzyme inducers, e.g. barbiturates, can precipitate porphyria due to overproduction of porphobilinogen.

6. Enzyme induction can also be beneficial, e.g. phenobarbitone in neonatal jaundice – phenobarbitone induces glucuronyl transferase enzyme, hence bilirubin is conjugated and jaundice is resolved.

Enzyme Inhibition

Certain drugs, e.g. chloramphenicol, ciprofloxacin, erythromycin, etc. inhibit the activity of drug metabolizing enzymes and are known as enzyme inhibitors. Inhibition of metabolism of one drug by another can occur when both are metabolized by the same enzyme. Enzyme inhibition is a rapid process as compared to enzyme induction.

Clinical Relevance of Enzyme Inhibition

Enzyme inhibition can result in drug toxicity, e.g. increased incidence of bleeding with warfarin, due to concomitant administration of erythromycin or chloramphenicol, etc. These drugs inhibit drug metabolizing enzyme of warfarin resulting in increased plasma concentration of warfarin and enhanced anticoagulant effect (bleeding). Toxicity following inhibition of metabolism is significant for those drugs which have saturation kinetics of metabolism. Enzyme inhibition can be beneficial,

e.g. boosted protease inhibitor regimen used for treatment of HIV infection (see p. 436).

DRUG EXCRETION

Removal of the drug and its metabolite from the body is known as drug excretion. The main channel of excretion of drugs is the kidney; others include lungs, bile, faeces, sweat, saliva, tears, milk, etc.

1. **Kidney**: The processes involved in the excretion of drugs via kidney are glomerular

filtration, passive tubular reabsorption and active tubular secretion. Glomerular filtration and active tubular secretion facilitate drug excretion, whereas tubular reabsorption decreases drug excretion. Rate of renal excretion (Rate of filtration + Rate of secretion) – Rate of reabsorption

1) **Glomerular filtration**: Drugs with small molecular size are more readily filtered. The extent of filtration is directly proportional to the glomerular filtration rate (GFR) and to the fraction of the unbound drug in plasma.

2) **Passive tubular reabsorption**: The main factor affecting passive reabsorption is the pH of renal tubular fluid and the degree of ionization. Strongly acidic and strongly basic drugs remain in ionized form at any pH of urine, hence are excreted in urine.

a) Weakly acidic drugs (e.g. salicylates, barbiturates) in acidic urine remain mainly in 'unionized' form, so they are reabsorbed into the circulation. If the pH of urine is made alkaline by sodium bicarbonate, the weakly acidic drugs get 'ionized' and are excreted easily.

b) Similarly, weakly basic drugs (e.g. morphine, amphetamine, etc.) in alkaline urine remain in 'unionized' form, hence are reabsorbed. If the pH of urine is made acidic by vitamin C (ascorbic acid), these weakly basic drugs get 'ionized' and are excreted easily.

3) Active tubular secretion: It is a carrier-mediated active transport which requires energy. Active secretion is unaffected by changes in the pH of urine and protein binding. Most of the acidic drugs (e.g. penicillin, diuretics, probenecid, sulphonamides, etc.) and basic drugs (e.g. quinine, procaine, morphine, etc.) are secreted by the renal tubular cells. The carrier system is relatively nonselective and therefore drugs having similar physicochemical properties compete for the same carrier system, e.g. probenecid competitively inhibits the tubular secretion of penicillins, thereby increasing the duration of action as well as the plasma half-life and effectiveness of penicillins in the treatment of diseases, such as gonococcal infections.

2. **Lungs**: Alcohol and volatile general anaesthetics, such as ether, halothane, isoflurane,

sevoflurane and ether are excreted via lungs.

3. **Faeces**: Drugs like purgatives, e.g. senna, cascara, etc. are excreted in faeces

4. **Bile**: Some drugs are secreted in bile. They are reabsorbed in the gut while a small

portion is excreted in faeces, e.g. tetracyclines.

5. **Skin**: Metals like arsenic and mercury are excreted through skin.

6. **Saliva**: Certain drugs like potassium iodide, phenytoin, metronidazole and lithium are excreted in saliva. Salivary estimation of lithium may be used for noninvasive monitoring of lithium therapy.

7. **Milk**: Drugs taken by lactating women may appear in milk. They may or may not adversely affect the breast fed infant. Drugs like penicillins, erythromycin, etc. are safe for use but amiodarone is to be avoided in mothers during breast feeding.

PHARMACOKINETIC PARAMETERS

The important pharmacokinetic parameters are bioavailability, volume of distribution,

plasma half-life (t1/2) and clearance.

Plasma Half-Life (t1/2)

It is the time required for the plasma concentration of a drug to decrease by 50% of its original value (Fig. 1.6A). Plasma half-life of lignocaine is 1 hour and for aspirin it is 4 hours.

Clinical Importance of Plasma Half-Life. It helps to

determine the duration of drug action.

determine the frequency of drug administration.

estimate the time required to reach the steady state. At steady state, the amount of drug administered is equal to the amount of drug eliminated in the dose interval. It takes approximately four to five half-lives to reach the steady state during repeated administration of the drug. A drug is almost completely eliminated in four to five half-lives after single administration.

Clearance

Clearance (CL) of a drug is defined as that volume of plasma from which the drug is

removed in unit time.

$$\text{Clearance} = \frac{\text{Rate of elimination}}{\text{Plasma concentration of the drug}}$$

1. **First-order kinetics**: A constant fraction of the drug in the body is eliminated per unit time. For example, assume drug 'A' with plasma t1/2 of 1 hour following first-order kinetics of elimination and having an initial plasma concentration of 100 mcg/mL.

$$100 \text{ mcg/mL} \xrightarrow[\frac{1}{2}]{1 \text{ hour}} 50 \text{ mcg/mL} \xrightarrow[\frac{1}{2}]{1 \text{ hour}} 25 \text{ mcg/mL}$$

If its concentration is increased to 200 mcg/mL, a constant fraction (1/2) gets eliminated in unit time, i.e. after 1 hour, concentration is 100 mcg/mL. The rate of drug elimination is directly proportional to its plasma concentration. The t1/2 of the drugs following first-order kinetics will always remain constant. The drug will be almost completely eliminated in four to five plasma half-lives if administered at a constant rate at each half-life. Most of the drugs follow first-order kinetics.

2. **Zero-order kinetics**: A constant amount of a drug in the body is eliminated per unit time. For example, ethanol is eliminated from the body at the rate of about 10 mL/h. Assume a drug 'B' with an initial plasma concentration of 200 mcg/mL and eliminated at a constant amount of 10 mcg per unit time. The concentration will be 190 mcg/mL after 1 hour and 100 mcg/mL after 10 hours. So, half-life is 10 hours.

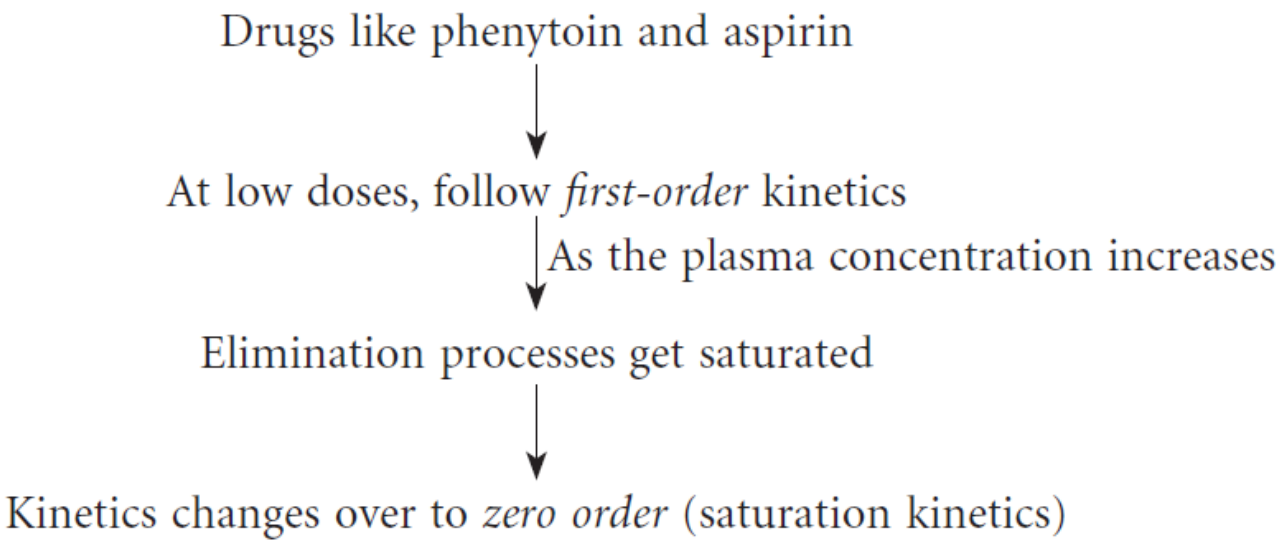
$$200 \text{ mcg/mL} \xrightarrow[10 \text{ mcg}]{1 \text{ hour}} 190 \text{ mcg/mL} \xrightarrow[10 \text{ mcg}]{1 \text{ hour}} 180 \text{ mcg/mL}$$

If its concentration is increased to 300 mcg/mL, concentration will be 290 mcg/mL

after 1 hour (as constant amount 10 mcg per unit time is eliminated) and 150 mcg/mL after 15 hours. The half-life increases to 15 hours. Thus, the t1/2

of the drug following zero-order kinetics is never constant. The rate of elimination

is independent of plasma drug concentration



Note: Phenytoin exhibits saturation kinetics and its plasma concentration has to be carefully monitored (therapeutic drug monitoring, TDM) when used in the treatment of epilepsy. Once the kinetics changes to zero order, an increase in dose will result in a marked increase in plasma concentration leading to drug toxicity.

Steady-State Concentration

If constant dose of a drug is given at constant intervals at its t1/2, plasma concentration of the drug increases due to its absorption and falls due to elimination in each dosing interval. Finally, the amount of drug eliminated will equal the amount of drug administered in the dosing interval. The drug is said to have reached steady-state or plateau level. It is attained after approximately four to five half-lives.

Target Level Strategy

The dosage of drug is calculated to achieve the desired plasma steady state concentration of the drug which produces therapeutic effect with minimal side effects.

Loading dose: Initially, a large dose or series of doses of a drug is given with the aim of rapidly attaining the target level in plasma. This is known as loading dose. A loading dose is administered if the time taken to reach steady state is relatively more as compared to the patient's condition, e.g. the half-life of lignocaine is more than 1 hour, so it takes more than 4–6 hours to reach the target concentration at steady state. When a patient has life-threatening ventricular arrhythmias after myocardial infarction, initially a large dose of lignocaine has to be given to achieve desired plasma concentration quickly. Once it is achieved, it is maintained by giving the drug as an intravenous infusion.

Maintenance dose: The dose of a drug which is repeated at fixed intervals or given as a continuous infusion to maintain target level in plasma or steady-state concentration is known as maintenance dose. The dose administered is equal to dose eliminated in a dosing interval.

Therapeutic Drug Monitoring

Monitoring drug therapy by measuring plasma concentration of a drug is known as

therapeutic drug monitoring (TDM).

Indications of TDM

1. Drugs with narrow therapeutic index, e.g. lithium, digoxin, phenytoin, aminoglycosides, etc.

2. Drugs showing wide interindividual variations, e.g. tricyclic antidepressants.

3. To ascertain patient compliance.

4. For drugs whose toxicity is increased in the presence of renal failure, e.g. aminoglycosides.

5. In patients who do not respond to therapy without any known reason. In drug poisoning, estimation of plasma drug concentration is done. TDM is not required in the following situations:

1. When clinical and biochemical parameters are available to assess response:

a. Blood pressure measurement for antihypertensives.

b. Blood sugar estimation for antidiabetic agents.

c. Prothrombin time, aPTT and International Normalized Ratio (INR) for anticoagulants.

2. Drugs producing tolerance, e.g. opioids.

3. Drugs whose effect persists longer than the drug itself, e.g. omeprazole.

Fixed-Dose Combinations (FDCs; Fixed-Dose Ratio Combinations)

It is the combination of two or more drugs in a fixed-dose ratio in a single formulation.

Some of the examples of WHO approved FDCs are

Levodopa + carbidopa for parkinsonism

Isoniazid + rifampicin + pyrazinamide + ethambutol for tuberculosis.

Ferrous sulphate + folic acid for anaemia of pregnancy

Sulphamethoxazole + trimethoprim in cotrimoxazole (antimicrobial agent)

Amoxicillin + clavulanic acid (antimicrobial agent)

Oestrogen + progesterone (oral contraceptive)