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General Terms

PHARMACOLOGY

It deals with interaction of exogenously administered chemical molecules wit living systems, or any single chemical substance which can produce a biological response is a 'drug'. It is the study of Influence of drug on living system, ability of drug to induce response such as pharmacological, physiological, biological, physicochemical.

PHARMACODYNMICS _ *Drugs activity over the body*

This includes physiological and biochemical effects of drugs and their mechanism of action at organ system/subcellular/macromolecular levels drug induced response

PHARMACOKINETICS _ *body activity over the drug*

This refers to movement of the drug in and alteration of the drug by the body; includes absorption, distribution, binding/localization/storage, biotransformation and excretion of the drug whatever happens during drugs movement inside the body such as ADME.

DRUG

The WHO (1966) has given a more comprehensive definition—"Drug is any substance or product that is used or is intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient."

PHARMACOTHERAPEUTICS

It is the application of pharmacological information together with knowledge of the disease for its prevention, mitigation or cure. Selection of the most appropriate drug, dosage and duration of treatment taking into account the specific features of a patient are a part of pharmacotherapeutics.

CLINICAL PHARMACOLOGY

It is the scientific study of drugs (both old and new) in man. It includes pharmacodynamic and pharmacokinetic investigation in healthy volunteers and in patients; evaluation of efficacy and safety of drugs and comparative trials with other forms of treatment; surveillance of patterns of drug use, adverse effects

CHEMOTHERAPY

It is the treatment of systemic infection/malignancy with specific drugs that have selective toxicity for the infecting organism/ malignant cell with no/minimal effects on the host cells. **Drugs in general, can thus be divided into:**

- ✓ **Pharmacodynamic agents** - These are designed to have pharmacodynamic effects in the recipient.
- ✓ **Chemotherapeutic agents** - These are designed to inhibit/kill invading parasite/malignant cell and have no/minimal pharmacodynamic effects in the recipient.

PHARMACY

It is the art and science of compounding and dispensing drugs or preparing suitable dosage forms for administration of drugs to man or animals. It includes collection, identification, purification, isolation, synthesis, standardization and quality control of medicinal substances. The large scale manufacture of drugs is called Pharmaceutics. It is primarily a technological science.

TOXICOLOGY

It is the study of poisonous effect of drugs and other chemicals (household, environmental pollutant, industrial, agricultural, homicidal) with emphasis on detection, prevention and treatment of poisonings. It also includes the study of adverse effects of drugs, since the same substance can be a drug or a poison, depending on the dose.

PHARMACOGENETICS - Study of genetic influence on drugs pk pd

PHARMACOGENOMICS - Use of genetic information to guide drug therapy

PHARMACOEPIDEMIOLOGY - The study of drug effects at population level, it is concerned with variability of drugs effects between individuals in population and between populations**. Responders and non-responders to LT antagonist therapy in case of asthma**

PHARMACOECONOMICS - Branch of pharmacology dealing with cost and benefits of drugs used therapeutically.

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Routes of Drug Administration

Factors governing selection of route

Factor	Condition
Physicochemical properties of drugs	(solid/liquid/gas; solubility, stability, pH, irritancy)
Site of desired action	—localized + approachable or generalized + not approachable
Rate and extent of absorption	Absosrption of drug from different routes
Effect of digestive juices / stomach acidic enviorment and first pass metabolism on the drug	Drugs stability and half life
Accuracy of dosage required	(i.v. and inhalational can provide fine tuning)
Physical and psychological Condition of the patient	(unconscious, vomiting)
Rapidity with which the response is desired	(routine treatment or emergency).

Classification of routes of administration

- Pareneteral: Intra-Vascular and extra vascular
  - Intra-Vascular: iv and ia
  - extra vascular: Im sc Sl buccal oral
- Local and systemic

Important features of the intravascular route of drug administration

1. no absorption phase.

2. immediate onset of action.

3. administered dose is available to produce pharmacological effects.

4. used in life-threatening situations.

5. Adverse reactions are difficult to reverse or control

6. accuracy in calculations and administration of drug dose

Important features of extravascular routes of drug administration

1. An absorption phase is present.

2. The onset of action is determined by factors such as formulation and type of dosage form, route of administration, physicochemical properties of drugs and other physiological variables.

3. The entire administered dose of a drug may not always reach the general circulation (i.e. incomplete absorption).

1 Local routes

1.1 Topical routes & drug candidates features

This refers to **external application** of the drug to the surface for localized action. It is often more convenient as well as encouraging to the patient. Drugs can be efficiently delivered to the localized lesions on **skin, oropharyngeal / nasal mucosa, eyes, ear canal, anal canal or vagina** in the form of **lotion, ointment, cream, powder, rinse, paints, drops, spray, lozengens, suppositories or pesseries**.

Nonabsorbable drugs given orally for action on g.i. mucosa (sucralfate, vancomycin), inhalation of drugs for action on bronchi (salbutamol, cromolyn sodium) and irrigating solutions/jellys (povidone iodine, lidocaine) applied to urethra are other forms of topical medication.

Topical route	Conditions	Drugs
Skin	**Spasmodic conditions** **Spasmodic conditions** **Spasmodic conditions** **Hypogonadism** **Menopause** **Anaethtic**	**Ibuprofen** **Nimusilide** **Diclofenac** **DHT gel** **Estradiol-TTS** **Oxythazine**
Eyes	Glaucoma	Pilocarpine

	As an mitotic Corneal anaesthesia (tonometry)	Physostigmine Benoxinate
Ear	Painful	Dibucaine (cinchocaine)
nasal mucosa	Nasal conditions	Lipophilic

1.2 Deeper tissue

Certain deep areas can be approached by using a syringe and needle, but the drug should be in such a form that systemic absorption is slow, to avoid serious consequences. Also mostly such therapy is for localized treatment, and not for systemic purpose.

Route	**Drug**
intra-articular injection	hydrocortisone acetate in knee joint, infiltration around a nerve
intrathecal injection	Lidocaine
retrobulbar injection	hydrocortisone acetate behind the eyeball

1.3 Arterial supply

Close intra-arterial injection is used for contrast media in angiography; anticancer drugs can be infused in femoral or brachial artery (to localise the effect for limb malignancies)

2 Systemic routes

2.1 Oral

Oral ingestion is the oldest and commonest mode of drug administration. It is safer, more convenient, does not need assistance, noninvasive, often painless, the medicament need not be sterile and so is cheaper. Both solid dosage forms (powders, tablets, capsules, **spansules**, **dragees**, moulded tablets, **gastrointestinal therapeutic systems— GITS**) and liquid dosage forms (elixirs, syrups, emulsions, mixtures) can be given orally.

Condition	Drugs
Antihypertensive	Prazosin GITS
Blood forming agent	Folic acid sapnsules
Diarrhea	Casanthrol dragees
Tablet	Ibuprofen Nimusilide Diclofenac Acceclofenac Paracetamol

GITS

SPANSULES

DRAGEES

Limitations of oral routes

- Action of drugs is slower and thus not suitable for emergencies.
- Unpalatable drugs (chloramphenicol) are difficult to administer; drug may be filled in capsules to circumvent this.
- May cause nausea and vomiting (emetine).
- Cannot be used for uncooperative/unconscious/ vomiting patient.
- Absorption of drugs may be variable and erratic; certain drugs are not absorbed (streptomycin).
- Others are destroyed by digestive juices (penicillin G, insulin) or in liver (GTN, testosterone, lidocaine)

2.2 Sublingual (S.l.) or buccal

The tablet or pellet containing the drug is placed under the tongue or crushed in the mouth and spread over the buccal mucosa.

Only lipid soluble and non-irritating drugs can be so administered.

Absorption is relatively rapid—action can be produced in minutes. Though it is somewhat inconvenient, one can spit the drug after the desired effect has been obtained.

The chief advantage is that liver is bypassed and drugs with high first pass metabolism can be absorbed directly into systemic circulation.

Drugs given sublingually are—GTN, buprenorphine, desamino-oxytocin.

2.3 Rectal

Certain irritant and unpleasant drugs can be put into rectum as suppositories or retention enema for systemic effect. This route can also be used when the patient is having recurrent vomiting or is unconscious.

However, it is rather inconvenient and embarrassing; absorption is slower, irregular and often unpredictable, though **diazepam solution and paracetamol suppository** are rapidly and dependably absorbed from the rectum in children.

Drug absorbed into external **haemorrhoidal veins** (about 50%) bypasses liver, but not that absorbed into **internal haemorrhoidal veins**. Rectal inflammation can result from irritant drugs.

Diazepam, indomethacin, paracetamol, ergotamine and few other drugs are sometimes given rectally.

2.4 Cutaneous

Highly lipid soluble drugs can be applied over the skin for slow and prolonged absorption. The liver is also bypassed.

The drug can be incorporated in an ointment and applied over specified area of skin. Absorption of the drug can be enhanced by rubbing the preparation, by using an oily base and by an occlusive dressing.

Transdermal patches of GTN, fentanyl, nicotine and estradiol are available in India, while those of isosorbide dinitrate, hyoscine, and clonidine are marketed elsewhere.

For different drugs, TTS have been designed to last for 1–3 days. Though more expensive, they provide smooth plasma concentrations of the drug without fluctuations; minimize inter individual variations (drug is subjected to little first pass metabolism) and side effects.

They are also more convenient— many patients prefer transdermal patches to oral tablets of the same drug; patient compliance is better. Local irritation and erythema occurs in some, but is generally mild; can be minimized by changing the site of application each time by rotation. Discontinuation has been necessary in 2–7% cases.

2.5 Inhalation

Volatile liquids and gases are given by inhalation for systemic action, e.g. general anaesthetics. Absorption takes place from the vast surface of alveoli—action is very rapid.

When administration is discontinued the drug diffuses back and is rapidly eliminated in expired air. Thus, controlled administration is possible with moment to moment adjustment.

Irritant vapours (ether) cause inflammation of respiratory tract and increase secretion.

Drugs	Method	Condition
Ipratropium , tiotropium	Given by inhalation in **nebulized form**	for COPD and rhinorhhea
Salbutamol and terbutaline, Salemterol Formoterol	delivered mostly from pressurized metered dose inhaler **(pMDI)**	bronchodilatation within 5 min and the action lasts for 2–4 hours in asthma and COPD
	Spinhalers for powdered drugs	
Budesonide (inhaled corticoids)	Rotahalers for powdered drugs	Only non halogenated corticoid in this category for **rhinitis**

2.6 Nasal

The mucous membrane of the nose can readily absorb many drugs; **digestive juices and liver are bypassed.**

However, only certain drugs like **GnRH agonists and desmopressin** applied as a spray or nebulized solution have been used by this route.

This route is being tried for some other peptide drugs like insulin, as well as to bypass the blood brain barrier.

Use	Drugs	Pka
Nasal decongestant	naphazoline xylometazoline, oxymetazoline (**α2 agonist**)	9 to 10
Intra-nasal spray	**Flunisolid, Beclomethasone dipropionate** **(inhaled corticosteroidal drug for asthama)**	-

3 Parenteral

Conventionally, parenteral refers to administration by injection which takes the drug directly into the tissue fluid or blood without having to cross the enteral mucosa. The limitations of oral administration are circumvented. Drug action is faster and surer (valuable in emergencies).

- ✓ Gastric irritation and vomiting are not provoked.
- ✓ can be employed even in unconscious, uncooperative or vomiting patient.
- ✓ no chances of interference by food or digestive juices.
- ✓ Liver is bypassed.

Disadvantages of parenteral routes are—

- ✓ the preparation has to be sterilized and is costlier
- ✓ the technique is invasive and painful,
- ✓ assistance of another person is mostly needed (though self-injection is possible, e.g. insulin by diabetics),
- ✓ there are chances of local tissue injury and,
- ✓ in general parenteral route is more risky than oral.

3.1 Subcutaneous (s.c.)

The drug is deposited in the **loose subcutaneous tissue** which is richly supplied by **nerves** (irritant drugs cannot be injected) but is less **vascular** (absorption is slower than intramuscular).

Only small volumes can be injected s.c. Self-injection is possible because deep penetration is not needed.

This route should be avoided in shock patients who are **vasoconstricted**— absorption will be delayed.

Repository (depot) preparations that are aqueous suspensions can be injected for prolonged action.

Insulin analouges : I-LISPRO, I-APSPART, I-GLULYSINE, I-GLARGINE, I-DETEMIR.

Some special forms of this route are:

(a) **Dermojet**

In this method needle is not used; a high velocity jet of drug solution is projected from a microfine orifice using a gun like implement. The solution passes through the superficial layers and gets deposited in the subcutaneous tissue. It is essentially painless and suited for **mass inoculations**.

(b) **Pellet implantation**

The drug in the form of a solid pellet is introduced with a **trochar and cannula**. This provides sustained release of the drug over weeks and months, e.g. **DOCA, testosterone**.

(c) **Sialistic (nonbiodegradable) and biodegradable implants**

Crystalline drug is packed in tubes or capsules made of suitable materials and implanted under the skin. Slow and uniform leaching of the drug occurs over months providing constant blood levels. The nonbiodegradable implant has to be removed later on but not the biodegradable one. This has been tried for hormones and contraceptives (e.g. NORPLANT).

3.2 Intramuscular (i.m.)

The drug is injected in one of the large **skeletal muscles—deltoid, triceps, gluteus maximus, rectus femoris**, etc.

Muscle is less richly supplied with sensory **nerves** (mild irritants can be injected) and is more **vascular** (absorption of drugs in aqueous solution is faster).

It is less painful, but self injection is often impracticable because deep penetration is needed. Depot preparations (oily solutions, aqueous suspensions) can be injected by this route.

Intramuscular injections should be avoided in anticoagulant treated patients, because it can produce local haematoma.

Drugs	Condition
Nandronolone, stanazole, oxymetholone	**Suboptimal growth**

(17-alkyl substituted dvt)	**Catabolic states** **Osteoporosis**

3.3 Intravenous (i.v.)

The drug is injected as a bolus (Greek: bolos–lump) or infused slowly over hours in one of the superficial veins.

The drug reaches directly into the blood stream and effects are produced immediately (great value in emergency).

The intima of veins is insensitive and drug gets diluted with blood, therefore, even highly irritant drugs can be injected i.v., but hazards are—**thrombophlebitis** of the injected vein and **necrosis** of adjoining tissues **if extravasation occurs**. These complications can be minimized by diluting the drug or injecting it into a running i.v. line.

Only aqueous solutions (not suspensions, because drug particles can cause embolism) are to be injected i.v. and there are no depot preparations for this route.

Chances of causing air embolism is another risk

The dose of the drug required is smallest (bioavailability is 100%) and even large volumes can be infused.

One big advantage with this route is—in case response is accurately measurable (e.g. BP) and the drug short acting (e.g. sodium nitroprusside), titration of the dose with the response is possible. However, this is the most risky route—vital organs like heart, brain, etc. get exposed to high concentrations of the drug.

Category	**Drugs**	**Conditions**
Peripheral skeletal muscle relaxant (somatic)	Succinylcholine, vecuronium , rocuronium, rapacuronium, pancuronium	To adjuvant general anaesthesis, surgical and intubation procedures
General anaesthics	Thiopentane sod	For inducing anaesthesia

	(ultrashort acting thiobarbi) Propofol	 DOC- ICU
Dissocative anaesthesia	Ketamine	bleed much, in cases where consciousness is to be retained.

3.4 Intradermal injection

The drug is injected into the skin raising a bleb (e.g. BCG vaccine, sensitivity testing) or scarring/multiple puncture of the epidermis through a drop of the drug is done. This route is employed for specific purposes only.

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ABSORPTION

Absorption is movement of the drug from its site of administration into the circulation.

- fraction of the administered available for absorption
- rate of absorption

Other factors affecting absorption are: Aqueous solubility Drugs given in solid form must dissolve in the aqueous biophase before they are absorbed.

4 Factors

✓ **Aqueous solubility**

Water soluble- rate of transport across membrane governs rate of absorption

Poorly water-soluble drugs (aspirin, griseofulvin) rate of dissolution governs rate of absorption

✓ **Dosage form**

Obviously, a drug given as watery solution is absorbed faster than when the same is given in solid form or as oily solution.

✓ **Area of absorbing surface**

Larger is the surface area, faster is the absorption

✓ **Vascularity of the absorbing surface**

Blood circulation removes the drug from the site of absorption and maintains the concentration gradient across the absorbing surface. (**sink conditions**)

✓ **Route of administration**

This affects drug absorption, because each route has its own peculiarities.

5 Oral Route

The effective barrier to orally administered drugs is the epithelial lining of the gastrointestinal tract, which is lipoidal in nature. Because of this lipoidal nature lipophilic drugs are readily absorbed.

Acidic drugs, e.g. salicylates, barbiturates, etc. are predominantly unionized in the acid gastric juice and are absorbed from stomach

basic drugs, e.g. morphine, quinine, etc. are largely ionized and are absorbed only on reaching the duodenum.

Factors to be considered in drug absorption are:

- ✓ However, even for acidic drugs absorption from stomach is slower, because the mucosa is thick, covered with mucus and the surface area is small.
- ✓ Absorbing surface area is much larger in the small intestine due to villi. Thus, faster gastric emptying accelerates drug absorption in general.
- ✓ Presence of food dilutes the drug and retards absorption. Further, certain drugs form poorly absorbed complexes with food constituents, e.g. tetracyclines with calcium present in milk; moreover food delays gastric emptying. Thus, most drugs are absorbed better if taken in empty stomach. However, there are some exceptions, e.g. fatty food greatly enhances lumefantrine absorption.
- ✓ Highly ionized drugs, e.g. gentamicin, neostigmine are poorly absorbed when given orally.
- ✓ Certain drugs are degraded in the gastrointestinal tract, e.g. penicillin G by acid, insulin by peptidases, and are ineffective orally.
- ✓ Enteric coated tablets (having acid resistant coating) and sustained release preparations (drug particles coated with slowly dissolving material) can be used to overcome acid lability, gastric irritancy and brief duration of action.
- ✓ The oral absorption of certain drugs is low because a fraction of the absorbed drug is extruded back into the intestinal lumen by the efflux transporter P-gp located in the gut epithelium. The low oral bioavailability of digoxin and cyclosporine is partly accounted by this mechanism.

Inhibitors of P-gp	inducers of P-gp
quinidine, verapamil, erythromycin	rifampin and phenobarbitone

Absorption of a drug can be affected by other concurrently ingested drugs.

This may be a luminal effect: formation of insoluble complexes, e.g. tetracyclines and iron preparations with calcium salts and antacids, phenytoin with sucralfate. Such interaction can be minimized by administering the two drugs at 2–3 hr intervals.

Intestinal part	Drugs affecting	Consequence
Alteration of gut flora	Antibiotics	enterohepatic cycling of oral contraceptives and digoxin

gut wall effects: altering **motility**	anticholinergics, tricyclic antidepressants, opioids, metoclopramide	-
gut wall effects: mucosal damage	neomycin, methotrexate, vinblastine	-

6 Subcutaneous and Intramuscular

Drug is deposited directly in the vicinity of the capillaries. Lipid soluble drugs pass readily across the whole surface of the capillary endothelium.

Capillaries having large paracellular spaces do not obstruct absorption of even large lipid insoluble molecules or ions.

Absorption from s.c. site is slower than that from i.m. site, but both are generally faster and more consistent/ predictable than oral absorption.

Application of heat and muscular exercise accelerate drug absorption by increasing blood flow (vasodilation), while vasoconstrictors, e.g. adrenaline injected with the drug (local anaesthetic) retard absorption.

7 Topical sites (skin, cornea, mucous membranes)

Systemic absorption after topical application depends primarily on **lipid solubility of drugs**. However, only few drugs significantly penetrate intact skin.

Eg- Hyoscine, fentanyl, GTN, nicotine, testosterone, and estradiol

Corticosteroids applied over extensive areas can produce systemic effects and pituitary-adrenal suppression.

Absorption can be promoted by rubbing the drug incorporated in an olegenous base or by use of occlusive dressing which increases hydration of the skin.

Organophosphate insecticides coming in contact with skin can produce systemic toxicity.

Abraded surfaces readily absorb drugs, e.g. **tannic acid** applied over burnt skin has produced hepatic necrosis.

Cornea is permeable to lipid soluble, unionized **physostigmine** but not to highly ionized **neostigmine**.

Mucous membranes of mouth, rectum, vagina absorb lipophilic drugs

8 Bioavailability

Bioavailability refers to the rate and extent of absorption of a drug from a dosage form as determined by its concentration-time curve in blood or by its excretion in urine.

It is a measure of the fraction (F) of administered dose of a drug that reaches the systemic circulation in the unchanged form.

Bioavailability of drug injected i.v. is 100%, but is frequently lower after oral ingestion because—

(a) The drug may be incompletely absorbed.

(b) The absorbed drug may undergo first pass metabolism in the intestinal wall/liver or be excreted in bile.

Incomplete bioavailability after s.c. or i.m. injection is less common, but may occur due to local binding of the drug.

9 Bioequivalence

Oral formulations of a drug from different manufacturers or different batches from the same manufacturer may have the same amount of the drug (chemically equivalent) but may not yield the same blood levels—**biologically in equivalent.** Two preparations of a drug are considered bioequivalent when the rate and extent of bioavailability of the active drug from them is not significantly different under suitable test conditions.

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DISTRIBUTION

Once a drug has gained access to the blood stream, it gets distributed to other tissues that initially had no drug, concentration gradient being in the direction of plasma to tissues.

The extent and pattern of distribution of a drug depends on its:

- lipid solubility
- ionization status at physiological pH (a function of its pKa)
- extent of binding to plasma and tissue proteins
- presence of tissue-specific transporters
- differences in regional blood flow

Movement of drug proceeds until an equilibrium is established between unbound drug in the plasma and the tissue fluids. Subsequently, there is a parallel decline in both due to elimination.

1 Apparent volume of distribution (V)

V = Dose administered IV / plasma conc

Distribution is not only a matter of dilution, but also **binding and sequestration**.

Binding - Drugs extensively bound to plasma proteins are largely restricted to the vascular compartment and have low values, e.g. diclofenac and warfarin (99% bound) V = 0.15 L/kg.

Sequestration - Drugs sequestrated in other tissues may have, V much more than total body water or even body mass, e.g. digoxin 6 L/kg, propranolol 4 L/kg, morphine 3.5 L/kg, because most of the drug is present in other tissues, and plasma concentration is low.

A large value of V indicates that larger quantity of drug is present in extravascular tissue.

A smaller value of V indicates that larger quantity of drug is present in vascular tissue.

Therefore, in case of poisoning, drugs with large volumes of distribution are not easily removed by haemodialysis.

2 Factors governing volume of drug distribution

- Lipid: water partition coefficient of the drug
- pKa value of the drug
- Degree of plasma protein binding
- Affinity for different tissues
- Fat: lean body mass ratio, which can vary with age, sex, obesity, etc.
- Diseases like CHF, uremia, cirrhosis

3 Pathological states alter the V of many drugs by altering

- distribution of body water
- permeability of membrane
- binding proteins
- by accumulation of metabolites that displace the drug from binding sites

Compounds with higher lipophilicity tend to have higher values of V_d.

More importantly, binding to blood plasma proteins has a significant effect on the volume of distribution. Human plasma contains over 60 proteins, however only three of these account for the majority of drug binding:

- ✓ albumin (carries mostly anionic drugs, some cationic and neutral drugs)
- ✓ α_1-acid glycoprotein (AAG) (cationic and neutral drugs)
- ✓ lipoproteins (cationic and neutral drugs)

Most computational studies that link plasma protein binding and acid/base characteristics have been limited to modelling the compounds using the following broad categories at physiological pH: acidic, basic, neutral or zwitterionic. In general, basic compounds have large values of V_d while acidic compounds exhibit smaller values.

The amount of drug exposed to the liver and the kidney thus varies considerably between acids and bases. Tissue bound compounds such as bases, tend to form interactions with the acidic head groups of (phospho)lipids whereas acids will readily bind to lysine residues in blood plasma proteins.

A recent study at GlaxoSmithKline concurred with these established findings, demonstrating that basic compounds are more widely distributed throughout the body.

Acids had lower values of V_d than either neutral or zwitter ionic compounds. Once again, other factors play a role to the extent of protein binding of drugs, particularly, lipophilicity and together with acid/base properties they greatly affect clearance and target organ exposure.

4 Redistribution

Highly lipid-soluble drugs get initially distributed to organs with high blood flow, i.e. brain, heart, kidney, etc. Later, less vascular but more bulky tissues (muscle, fat) take up the drug—plasma concentration falls and the drug is withdrawn from the highly perfused sites.

Greater the lipid solubility of the drug, faster is its redistribution.

If the site of action of the drug was in one of the highly perfused organs, redistribution results in termination of drug action.

Hypnotic drugs and redistribution

Anaesthetic action of **thiopentone sod. i.v**. is terminated in few minutes due to redistribution.

A relatively short hypnotic action lasting **6–8 hours** is exerted by **oral diazepam or nitrazepam** due to redistribution despite their elimination t **½ of > 30 hr**.

However, when the same drug is given repeatedly or continuously over long periods, the low perfusion high capacity sites get progressively filled up and the drug becomes longer acting.

5 Penetration into brain and CSF

The capillary endothelial cells in brain have tight junctions and lack large paracellular spaces. Further, an investment of neural tissue covers the capillaries. Together they constitute the so called blood-brain barrier (BBB).

A similar blood-CSF barrier is located in the **choroid plexus**: capillaries are lined by **choroidal epithelium** having tight junctions. Both these barriers are **lipoidal**

limit the entry of non-lipidsoluble drugs, e.g. streptomycin, neostigmine

Only lipid-soluble drugs, therefore, are able to penetrate and have action on the central nervous system.

Dopamine does not enter brain but its precursor levodopa does; as such, the latter is used in parkinsonism.

Inflammation of meninges or brain increases permeability of these barriers.

It has been proposed that some drugs accumulate in the brain by utilizing the transporters for endogenous substances.

In addition, **efflux transporters like P-gp and OATP** present in brain and choroidal vessels extrude many drugs that enter brain by other processes and serve to augment the protective barrier against potentially harmful xenobiotics.

There is also an **enzymatic BBB: Monoamine oxidase (MAO), cholinesterase** and some other enzymes are present in the capillary walls or in the cells lining them. They do not allow catecholamines, 5-HT, acetylcholine, etc. to enter brain in the active form.

The BBB is deficient at the CTZ in the medulla oblongata (even lipid-insoluble drugs are emetic) and at certain periventricular sites—(anterior hypothalamus). Exit of drugs from the CSF and brain, however, is not dependent on lipid-solubility and is rather unrestricted. Bulk flow of CSF (along with the drug dissolved in it) occurs through the arachnoid villi. Further, nonspecific organic anion and cation transport processes (similar to those in renal tubule) operate at the choroid plexus.

6 Passage across placenta

Placental membranes are lipoidal and allow free passage of lipophilic drugs, while restricting hydrophilic drugs.

The placental efflux P-gp and other transporters like BCRP, MRP3 also serve to limit foetal exposure to maternally administered drugs.

Placenta is a site for drug metabolism as well, which may lower/modify exposure of the foetus to the administered drug.

However, restricted amounts of nonlipid-soluble drugs, when present in high concentration or for long periods in maternal circulation, gain access to the foetus.

Some influx transporters also operate at the placenta. Thus, it is an incomplete barrier and almost any drug taken by the mother can affect the foetus or the newborn (drug taken just before delivery, e.g. morphine).

7 Plasma protein binding

Most drugs possess physicochemical affinity for plasma proteins and get reversibly bound to these.

Acidic drugs generally bind to plasma albumin and basic drugs to α1 acid glycoprotein.

Extent of binding depends on the individual compound; no generalization for a pharmacological or chemical class can be made (even small chemical change can markedly alter protein binding)

for example the binding percentage of some benzodiazepines is: Flurazepam 10% Alprazolam 70% Lorazepam 90% Diazepam 99%

Increasing concentrations of the drug can progressively saturate the binding sites: fractional binding may be lower when large amounts of the drug are given. The generally expressed percentage binding refers to the usual therapeutic plasma concentrations of a drug.

The clinically significant implications of plasma protein binding are:

(i) **Highly plasma protein bound drugs** are largely restricted to the **vascular** compartment because protein bound drug does not cross membranes (except through large paracellular spaces, such as in capillaries). **They tend to have smaller volumes of distribution.**

(ii) **The bound fraction is not available for action**. However, it is in equilibrium with the free drug in plasma and dissociates when the concentration of the latter is reduced due to elimination. Plasma protein binding thus tantamounts to temporary storage of the drug.

(iii) High degree of protein binding generally **makes the drug long acting**, because bound fraction is **not available for metabolism or excretion**, unless it is actively extracted by liver or by kidney tubules.

Glomerular filtration does not reduce the concentration of the free form in the efferent vessels, because water is also filtered. **Active tubular secretion**, however, removes the drug without the attendant solvent → concentration of free drug falls → bound drug dissociates and is eliminated resulting in a higher renal clearance value of the drug than the total renal blood flow.

The same is true of active transport of highly extracted drugs in liver. **Plasma protein binding in this situation acts as a carrier mechanism and hastens drug elimination**, e.g. excretion of penicillin (elimination t½ is 30 min); metabolism of lidocaine.

Highly protein bound drugs are not removed by haemodialysis and need special techniques for treatment of poisoning.

(iv) **The generally expressed plasma concentrations of the drug refer to bound as well as free drug.** Degree of protein binding should be taken into account while relating these to concentrations of the drug that are active in vitro, e.g. MIC of an antimicrobial.

(v) One drug can bind to many sites on the albumin molecule. Conversely, more than one drug can bind to the same site. This can give rise to displacement interactions among drugs bound to the same site(s).

The drug bound with higher affinity will displace that bound with lower affinity. If just 1% of a drug that is 99% bound is displaced, the concentration of free form will be doubled. This, however, is often transient because the displaced drug will diffuse into the tissues as well as get metabolized or excreted: the new steady state free drug concentration is only marginally higher unless the displacement extends to tissue binding or there is concurrent inhibition of metabolism and/or excretion.

The overall impact of many displacement interactions is minimal; clinical significance being attained only in case of highly bound drugs with limited volume of distribution (many acidic drugs bound to albumin) and where interaction is more complex. Moreover, two highly bound drugs do not necessarily displace each other—their binding sites may not overlap, e.g. probenecid and indomethacin are highly bound to albumin but do not displace each other. Similarly, acidic drugs do not generally displace basic drugs and vice versa.

Some clinically important displacement interactions are:

• Aspirin displaces sulfonylureas.

• Indomethacin, phenytoin displace warfarin.

• Sulfonamides and vit K displace bilirubin (kernicterus in neonates).

• Aspirin displaces methotrexate.

(vi) In hypoalbuminemia, binding may be reduced and high concentrations of free drug may be attained, e.g. phenytoin and furosemide. Other diseases may also alter drug binding, e.g. phenytoin and pethidine binding is reduced in uraemia; propranolol binding is increased in pregnant women and in patients with inflammatory disease (acute phase reactant α1 acid-glycoprotein increases).

8 Tissue storage

Drugs may also accumulate in specific organs by active transport or get bound to specific tissue constituents. Drugs sequestrated in various tissues are unequally distributed, tend to have larger volume of distribution and longer duration of action.

Some may exert local toxicity due to high concentration,

Drug	Organ
Tetracyclines	bone and teeth
Chloroquine	Retina
Streptomycin	vestibular apparatus
Emetine	heart and skeletal muscle

Drugs may also selectively bind to specific intracellular organelle,

e.g**. tetracycline to mitochondria, chloroquine to nuclei.**

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Metabolism

Metabolism leads to

- ✓ Inactivation of drug
- ✓ Activation of drug
- ✓ Generation of active metabolite
- ✓ Generation of active metabolite having toxic effect

Active drug - Active metabolite	*Prodrug - Active form*
Chloral hydrate — Trichloroethanol	**Levodopa — Dopamine**
Morphine — Morphine-6-glucuronide	**Enalapril — Enalaprilat**
Cefotaxime — Desacetyl cefotaxime	**a-Methyldopa — a-methylnorepinephrine**
Allopurinol — Alloxanthine	**Dipivefrine — Epinephrine**
Procainamide — N-acetyl procainamide	**Sulindac — Sulfide metabolite**
Primidone — Phenobarbitone, phenylethylmalonamide	**Proguanil — Cycloguanil**
Diazepam — Desmethyl-diazepam, oxazepam	**Prednisone — Prednisolone**
Digitoxin — Digoxin	**Bacampicillin — Ampicillin**
Imipramine — Desipramine	**Sulfasalazine — 5-Aminosalicylic acid**
Amitriptyline — Nortriptyline	**Cyclophos- — Aldophosphamide, phamide phosphoramide mustard, acrolein**
Codeine — Morphine	**Fluorouracil — Fluorouridine monophosphate**
Spironolactone — Canrenone	**Mercaptopurine — Methylmercaptopurine ribonucleotide**
Losartan — E 3174	**Acyclovir — Acyclovir triphosphate**

1 Sites of drug metabolism

1.1 At the organ level

The **liver** is the **primary organ** of drug metabolism.

The **gastrointestinal tract** is the most important **extrahepatic site**. Some orally administered drugs (e.g., isoproterenol) are conjugated extensively in the intestinal epithelium, resulting in decreased bioavailability.

The **lung, kidney, intestine, skin and placenta** can also carry out drug metabolizing reactions.

1.2 Cellular level

Most enzymes involved in drug metabolism are located within the lipophilic membranes of the **smooth endoplasmic reticulum (SER).**

When the SER is isolated in the laboratory by tissue homogenation and centrifugation, the SER membranes re-form into vesicles called microsomes. Since most of the enzymes carry out oxidation reactions, this SER complex is referred to as the microsomal mixed function oxidase (MFO) system.

1.3 At the biochemical level

Few metabolic reactions occur at biochemical levels.

2 Classification of metabolism phases

Phase I	Phase II
convert a drug to a more polar compound	Some Phase I products are still not eliminated rapidly, and hence undergo Phase II reactions
introduces or unmasks polar functional groups such as - OH, -NH2, or –SH	involve conjugation of the newly established polar group with endogenous compounds such as glucuronic acid, sulfuric acid, acetic acid, or amino acids (typically glycine).

Phase II reactions: Glucuronide formation is the most common phase II reaction.

Active metabolites generated phase wise

(a) Nonsynthetic / Phase I / Functionalization reactions a functional group is generated or exposed— metabolite may be active or inactive.

(b) Synthetic/Conjugation/ Phase II reactions
an endogenous radical is conjugated to the drug— metabolite is mostly inactive; except few drugs,

e.g. glucuronide conjugate of **morphine** and sulfate conjugate of **minoxidil** are active.

2.1 Nonsynthetic reactions or Phase 1 reaction

2.1.1 Oxidation

- **reaction involves** - addition of oxygen/negatively charged radical or removal of hydrogen/positively charged radical.
- **oxidation reactions are** - hydroxylation; oxygenation at C, N or S atoms; N or O-dealkylation, oxidative deamination
- **Functional groups altered are** - Alcohols, aldehydes, quinones

In many cases the initial insertion of oxygen atom into the drug molecule produces short lived highly reactive quinone/epoxide/superoxide intermediates which then convert to more stable compounds.

Oxidative reactions are mostly carried out by a group of monooxygenases in the liver, which in the final step involve a cytochrome P-450 haemoprotein, NADPH, cytochrome P-450 reductase and molecular O2.

Depending upon the extent of amino acid sequence homology, the cytochrome P-450 (CYP) isoenzymes are grouped into families designated by numerals (1, 2, 3.....), each having several sub-families designated by capital letters (A, B, C.....), while individual isoenzymes are again allotted numerals (1, 2, 3....). In human beings, only a few members of three isoenzyme families (CYP 1, 2 and 3) carryout metabolism of most of the drugs, and many drugs such as tolbutamide, barbiturates, nifedipine are substrates for more than one isoform.

P450 Gene Family/Subfamily	Characteristic Substrates	Characteristic Inducers	Characteristic Inhibitor
CYP 3A4, 5, 7	Cyclosporin Clarithromycin Hydrocortisone Vincristine Many, many others	Barbiturates Glucocorticoids Carbamazepine St. John's Wort	Cimetidine Clarithromycin Ketoconazole Grapefruit Juice Many others
CYP 2E1	Ethanol Benzene Halothane	Ethanol Isoniazid	Disulfiram
CYP 2D6	Debrisoquine Ondansetron Amphetamine	Dexamethasone? Rifampin	Cimetidine Fluoxetine Methadone
CYP 2C9	Tamoxifen Ibuprofen Fluoxetine	Rifampin Secobarbital	Fluvastatin Lovastatin Isoniazid
CYP 2C19	Diazepam, Omeprazole Progesterone	Prednisone Rifampin	Cimetidine Ketoconazole Omeprazole
CYP 1A2	Acetominophen Estradiol Caffeine	Tobacco Char-Grilled Meats Insulin	Cimetidine Amiodarone Ticlopidine

CYP3A4/5

Carryout biotransformation of large number (nearly 50%) of drugs. In addition to liver, these isoforms are expressed in intestine (responsible for first pass metabolism at this site) and kidney as well.

Inhibition of this isoenzyme by erythromycin, clarithromycin, ketoconazole, itraconazole is responsible for the important drug interaction with terfenadine, astemizole and cisapride which are its substrates.

Losartan, nifedipine hydrocortisone, mifepristone, simvastatin, ritonavir, carbamazepine and cyclosporine are also metabolized by CYP3A4/5.

Verapamil, diltiazem, ritonavir and a constituent of grape fruit juice are other important inhibitors, while rifampicin, barbiturates and other anticonvulsants are the important inducers.

CYP2D6

This is the next most important CYP isoform which metabolizes nearly 20% drugs including tricyclic antidepressants, selective serotonin reuptake inhibitors, many neuroleptics, antiarrhythmics, β-blockers and opiates.

Inhibition of this enzyme by quinidine results in failure of conversion of codeine to morphine > analgesic effect of codeine is lost.

Human subjects can be grouped into 'extensive' or 'poor' metabolizers of metoprolol and debrisoquin. The poor metabolizers have an altered CYP2D6 enzyme and exhibit low capacity to hydroxylate many drugs.

CYP2C8/9

phenytoin, carbamazepine, warfarin (narrow safety margin drugs) and ibuprofen, tolbutamide, repaglinide, celecoxib and losartan.

CYP2C19

Metabolizes > 12 frequently used drugs including omeprazole, lansoprazole, phenytoin, diazepam, propranolol.

Rifampicin and carbamazepine are potent inducers of the CYP2C subfamily, while omeprazole is an inhibitor.

CYP1A1/2

Though this subfamily participates in the metabolism of only few drugs like theophylline, caffeine,paracetamol, carbamazepine, it is more important for activation of procarcinogens.

Apart from rifampicin and carbamazepine, polycyclic hydrocarbons, cigarette smoke and charbroiled meat are its potent inducers.

CYP2E1

It catalyses oxidation of alcohol, holothane, and formation of minor metabolites of few drugs, notably the hepatotoxic N-acetyl benzoquinoneimine from paracetamol; chronic alcoholism induces this isoenzyme.

relative amount of different cytochrome P-450s varies depending on

- ✓ individual basis
- ✓ gender
- ✓ interspecies

drugs which metabolized by oxidation but not by these CYP 450 systems

- flavin-monooxygenases (hepatic endoplasmic reticulum)
  - cimetidine, ranitidine, clozapine are oxidized at their N, P or S atoms

- They are not susceptible to induction or inhibition by other drugs, and thus are not involved in drug interactions.

- mitochondrial or cytoplasmic enzymes
  - adrenaline, alcohol, mercaptopurine

2.1.2 Reduction

Functional groups altered are - Alcohols, aldehydes, quinones are reduced.

Drugs primarily reduced are chloralhydrate, chloramphenicol, halothane, warfarin.

2.1.3 Hydrolysis

This is cleavage of drug molecule by taking up a molecule of water.

2.1.4 Esterases

esterase

Ester + H2O ---------->>>>Acid + Alcohol

2.1.5 Amidase and polypeptidase

Similarly, amides and polypeptides are hydrolysed by amidases and peptidases.

2.1.6 epoxide hydrolases

In addition, there are epoxide hydrolases which detoxify epoxide metabolites of some drugs generated by CYP oxygenases.

Hydrolysis occurs in liver, intestines, plasma and other tissues. Examples of hydrolysed drugs are choline esters, procaine, lidocaine, procainamide, aspirin, carbamazepine-epoxide, pethidine, oxytocin.

2.1.7 Cyclization - proguanil

2.1.8 Decyclization-barbiturates, phenytoin

2.2 Synthetic reactions

- ✓ form a polar highly ionized molecules
- ✓ easily excreted in urine or bile.

Conjugation reactions have high energy requirement.

Metabolic reaction	Enzymes	Endogenous subtstrate	Drug metabolized	Structural requirement
Glucuronide conjugation	UDP-glucuronosyl transferases (UGTs)	glucuronic acid	chloramphenicol, aspirin, paracetamol, diazepam, lorazepam, morphine, metronidazole bilirubin, steroidal hormones and thyroxine	Nucleophilic groups such as COOH, SH or NH2 and OH
Acetylation	N-acetyl transferases (NATs)	acetyl coenzyme-A	sulfonamides, isoniazid, PAS, dapsone, hydralazine, clonazepam, procainamide	hydrazine and aromatic amines
Methylation	methyl transferases (MT)	methionine and cysteine	adrenaline, histamine, nicotinic acid, methyldopa, captopril, mercaptopurine.	amines and phenols
Sulfate conjugation	Sulfotransferases (SULTs)		chloramphenicol, methyldopa, adrenal and sex steroids	Phenolic compounds and steroids
Glycine conjugation		glycine		
Glutathione conjugation	glutathione-S transferase (GST)		Paracetamol	quinone or epoxide intermediates

List of drugs with their active metabolites and respective toxic effects

Drug	Metabolite	Toxic effect
Diazepam	Nor-Diazepam	sedative hypnotic properties.
Meperidine	Nor-meperidine	Serotonin synd
Morphine	Morphine 6 glucoronide	renal toxic
Ethanol	Acetaldehyde	folate inactivation & thimine, disulfiram like reaction
Acetaminophen	N-acetyl benzoquinonamine	hepatic necrosis & failure
Atracurium	Laudanosine	can cause seizures

Generation of active metabolites by Aliphatic Hydroxylation mediated biotransformation

Drug	**Active Metabolites**	**Therapeutic Action**
Atomoxetine	4-Hydroxyatomoxetine	Treatment of attention-deficit hyperactivity disorder
Atorvastatin	2- or 4-Hydroxyatorvastatin	Anti-hyperchloesterolemia
Chlorpromazine	7-Hydroxychlorpromazine	Anti-depressive
Clomiphene	4-Hydroxyclomiphene	Anti-uterotrophic
Granisetron	7-Hydroxyfranisteron	Anti-nausea
Indapamide	4-Hydroxyindapamide	Anti-hypertensive
Levamisole	4-Hydroxylevamisole	Anthelmintic
Propafenone	5-Hydroxypropafenone	Anti-arrhythmic
Propranolol	4-HydroxyPropanolol	Anti-arrhythmic

Generation of active metabolites by Aromatic Hydroxylation mediated biotransformation

Drug	**Active Metabolites**	**Therapeutic Action**
Alprazolam	4-Hydroxyalprazolam	Anti-depressant
Bupropion	Hydroxybupropion	Anti-mental depression
Clarithromycin	14- Hydroxyclarithromycin	Anti-biotic
Cyclosporin A	Hydroxycyclosporin A	Immunosuppresive
Ibuprofen	Hydroxyibuprofen	Anti-inflammatory
Itraconazole	Hydroxyitraconazole	Anti-mycotic
Metronidazole	Hydroxymetronidazole	Anti-biotic
Midazolam	1`-Hydroxymidazolam	Anxiolytic Effects
Nebivolol	4-4` Hydroxynebivolol	Vasodilation
Nefazodone	Hydroxynefazodone	Anti-depressant
Praziquantel	4-Hydroxypraziquqntel	Anti-neurocysticercerosis
Quinidine	3- Hydroxyquinidine	Anti-arrhythmic
Risperidone	9- Hydroxyrisperidone	Anti-psychotic
Simavastatin	Simavastin hydroxylic acid	Anti-hypercholesterolmia

Generation of active metabolites by *N*- Dealkylation mediated biotransformation

Drug	Active Metabolites	Therapeutic Action
Amiodarone	Desethylamiodarone	Anti-arrhythmic
Azonafide	N-Desmethylazonafide	Anti- tumoral
Chlordiazepoxide	Desmethylchlordiazepoxide	Anxiolytic
Clomipramine	N-Desmethylclomipramine	Anti-depressant
Clozapine	Norclozapine	Anti-psychotic
Fluoxetine	Norfluoxetine	Anti-depressant
Verapamil	Norverapmil	Anti-arrhythmic
Sertraline	N-Desmethylsertraline	Anti-hypercholesterolemia
Zopiclone	(s)- Desmethylzopiclone	Z class drug

Generation of active metabolites by O- Dealkylation mediated biotransformation

Drug	Active Metabolites	Therapeutic Action
Artemether	Dihydroartemisinin	Anti-malerial
Tramadol	O-Demethyltramadol	Centrally acting analgesic

Miscellaneous

Drug	Active Metabolites	Biotrasnformation process	Therapeutic Action
Albendazole	Albendazole sulfoxide	Sulfoxidation	Anti-Parasitic
Carbamazepine	Carbamazepine-10, 11-dihydroCBZ	Epoxidation	Anti-epilepsy
Losartan	Carboxylosartan	Carboxylation	Anti-hypertensive
Minoxidil	Minoxidil Sulfate	Sulfonation	Hair Growth
Rifampicin	25-Desacetylrifampicin	Deacetylation	Anti-TB

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EXCRETION

RENAL EXCRETION

The kidney is responsible for excreting all water soluble substances. The amount of drug or its metabolites ultimately present in urine is the sum total of glomerular filtration, tubular reabsorption and tubular secretion

Glomerular filtration

Glomerular capillaries have pores larger than usual; all non-protein bound drug (whether lipid-soluble or insoluble) presented to the glomerulus is filtered.

Thus, glomerular filtration of a drug depends on its plasma protein binding and renal blood flow.

Glomerular filtration rate (g.f.r.), normally ~ **120 ml/min**, declines progressively after the age of 50, and is low in renal failure.

Angiotensin II reduces GFR, opposite happens in case of renal disease patients.

Tubular reabsorption

This occurs by **passive diffusion** and depends on **lipid solubility and ionization of the drug** at the **existing urinary pH.**

Lipid-soluble drugs filtered at the glomerulus back diffuse in the tubules because 99% of glomerular filtrate is reabsorbed, but nonlipid-soluble and highly ionized drugs are unable to do so. e.g. aminoglycoside antibiotics, quaternary ammonium compounds parallels **g.f.r. (or creatinine clearance**).

Changes in urinary pH affect tubular reabsorption of drugs that are partially ionized, The effect is greatest for those having **pKa values between 5 to 8**, because only in their case pH dependent passive reabsorption is significant —

• acidic urine **- Weak bases ionize more** and are **less reabsorbed**.

• alkaline urine - **Weak acids ionize more** and are **less reabsorbed**.

This principle is utilized for facilitating elimination of the drug in poisoning, i.e. urine is alkalinized in **barbiturate and salicylate poisoning**.

Though elimination of weak bases (morphine, amphetamine) can be enhanced by acidifying urine, this is not practiced clinically, because acidosis can induce rhabdomyolysis, cardiotoxicity and actually worsen outcome.

Tubular secretion This is the **active transfer of organic acids and bases** by two separate classes of **relatively nonspecific transporters (OAT and OCT)** which operate in the proximal tubules. In addition, **efflux transporters P-gp and MRP2** are located in the luminal membrane of proximal tubular cells.

If renal clearance of a drug is greater than 120 mL/min (g.f.r.), additional tubular secretion can be assumed to be occurring.

Active transport of the drug across tubules reduces concentration of its free form in the tubular vessels and promotes dissociation of protein bound drug, which then becomes available for secretion.

Thus, protein binding, which is a hinderance for glomerular filtration of the drug, is not so (may even be facilitatory) to excretion by tubular secretion.

(a) Organic acid transport (through OATP) operates for penicillin, probenecid, uric acid, salicylates, indomethacin, sulfinpyrazone, nitrofurantoin, methotrexate, drug glucuronides and sulfates, etc.

(b) Organic base transport (through OCT) operates for thiazides, amiloride, triamterene, furosemide, quinine, procainamide, choline, cimetidine, etc.

Inherently both transport processes are bidirectional, i.e. they can transport their substrates from blood to tubular fluid and vice versa. However, for drugs and their metabolites (exogenous substances) secretion into the tubular lumen predominates, whereas an endogenous substrate like uric acid is predominantly reabsorbed.

Drugs utilizing the same active transport compete with each other.

Probenecid is an organic acid which has high affinity for the tubular OATP. It blocks the active transport of both penicillin and uric acid, but whereas the net excretion of the former is decreased, that of the latter is increased. This is because penicillin is primarily secreted while uric acid is primarily reabsorbed.

Many drug interactions occur due to competition for tubular secretion, e.g.

(i) Salicylates block uricosuric action of probenecid and sulfinpyrazone and decrease tubular secretion of methotrexate.
(ii) Probenecid decreases the concentration of nitrofurantoin in urine, increases the duration of action of penicillin/ampicillin and impairs secretion of methotrexate.
(iii) Sulfinpyrazone inhibits excretion of tolbutamide.
(iv) Quinidine decreases renal and biliary clearance of digoxin by inhibiting efflux carrier P-gp. Tubular transport mechanisms are not well developed at birth. As a result, duration of action of many drugs, e.g. penicillin, cephalosporins, aspirin is longer in neonates. These systems mature during infancy. Renal function again progressively declines after the age of 50 years; renal clearance of most drugs is substantially lower in the elderly (>75 yr).

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