Routes of administration

- Most of drugs can be administered by a variety routes.
- The various routes are depends on the choice of drugs and patient conditions.

Factors governing the choice of routes are

- Physical and chemical properties of the drug (pH, solid, liquid, gas, solubility).
- Site of desired action
- Rate and extent of absorption of the drug from different routes.
- Effect of digestive juices and first pass metabolism of drug.
- Accuracy of desired dose.
- Condition of the patient.

The various routes can be divided into

1. Local routes
2. Systemic routes
Local routes

- can only be used for localized lesions at accessible sites and for drugs whose systemic absorption is minimal or absent.
- Toxicity also is less.
1) **Topical route**

- This refers to the external application of drugs to the surface for localized action.
- Administration of drug is convenient
- Used in areas like nasal mucosa, eyes, ear, skin etc.
- Given in the form of drops, spray, paints, cream, ointment etc.

2) **Deeper tissues**

- In certain areas drug can be approached by syringe and needle, but the drug should be such that systemic circulation is slow.
- Eg: intra-articular injection, infiltration around a nerve.

3) **Arterial Supply**

- Drug is infused in femoral or brachial artery.
- Mainly anticancer drugs are given.
Systemic routes

- Oral
- Inhalation
- Sublingual or buccal
- Nasal
- Rectal
- Cutaneous
- Parenteral
Systemic routes

Drug is absorbed into the blood stream and distributed all over, including the site of action through circulation.

1. **Oral:**

   - Oldest and commonest mode.
   - Safer, convenient, does not need any assistance.
   - Non-invasive, medicament need not be sterile and so is cheaper.
   - Both solid dosage forms (eg: powders, capsules, tablets etc) and liquid dosage forms like syrups, suspensions, emulsions can be given.
Disadvantages of oral route:

- Action of drug is slower and so not suitable for emergencies.
- Unpalatable drugs are difficult to give and may cause nausea or vomiting.
- Cannot use the route for unconscious, vomiting and uncooperative patient.
- Absorption of drug may be variable and erratic.
- Destroyed by digestive enzymes.

2. **Sub-lingual or Buccal:**

- The tablet or pellet containing the drug is placed under the tongue or crushed in the mouth.
- Only lipid soluble and non-irritating drugs can be administered.
- Drug can be rapidly absorbed.

**Advantage**

- Drugs with high first pass metabolism can be absorbed directly into systemic circulation.
3. **RECTAL**

- Certain irritant and unpleasant drugs can be given into rectum as suppositories or retention enema for systemic effect.
- Can be used when the patient is having recurrent vomiting or when unconscious.

**Disadvantages**

- Inconvenient and embarrassing.
- Absorption is slower, irregular and often unpredictable.
- Rectal inflammation can occur from irritant drugs.

4. **CUTANEOUS**

- Highly lipid soluble can be applied over the skin for slow and prolonged absorption.
- Drug is applied by rubbing the preparation on the skin.
Trans-dermal therapeutic system

- These are devices in the form of adhesive patches of various shapes and sizes (5-20cm²), deliver the contained drug at a constant rate into the systemic circulation via the stratum corneum.
- The drug is delivered to skin by diffusion and absorption into circulation.
- Drug is available at constant rate, applied usually at chest, abdomen, upper arm, lower back etc.
- These are designed to last for 1-7 days, are increasingly popular, they provide drug without fluctuations.
- Drug are subjected little first pass metabolism and side effects.
- Local irritation and erythema occur in some cases.
5. **INHALATION**

- Volatile liquids and gases are given by inhalation for systemic action.
- Absorption takes place from the vast surface of alveoli and action is rapid.
- Drug is discontinued the drug diffuses back and is rapidly eliminated in expired air.

**Disadvantage**

- Irritant vapour cause inflammation of the respiratory tract.

6. **NASAL**

- The mucous membrane of the nose can readily absorb many drugs like peptide drugs like insulin, GnRh agonists.
- Digestion and liver metabolism of the drug is bypassed.
Par enteral

- Sub cutaneous
- Intra- muscular (i.m.)
- Intra-venous (i.v.)
- Intra-dermal
7. **PAR ENTERAL (Par – beyond, enteral – intestine)**

- Administration of drug by injection which takes the drug directly into the tissue fluid or blood without entering the intestine.
- Action of drug is rapid, sure and used highly in emergencies.
- Gastric irritation and vomiting are not provoked.
- Can be given for patients who are unconscious, uncooperative.

**Disadvantages**

- The preparation has to be sterilized and so costlier.
- Invasion is painful.
- Assistance is required.
- Local tissue injury may occur.
- Risky than oral route.
A. Subcutaneous

- Administration of drug is at the loose subcutaneous tissue which is richly supplied by nerves.
- Absorption is slower than intra-muscular.
- Irritant drugs cannot be given.
- Self injection is possible because deep penetration is not required.
- The injection should be avoided for patients with shock, because of vasoconstriction and so absorption is delayed.

1. Dermojet:
   - In this needle is not used, a high velocity jet of drug solution is projected from a microfine orifice using gun like instrument.
   - Painless and suited for mass inoculation.

2. Pellet implementation:

Drug in the form of pellets is introduced with a trochar or canula.
3. Sialistic and biodegradable implants:
   - crystalline drugs are placed in tubes or capsules and implanted under the skin.
   - Slow and uniform absorption of drugs.

B. Intra-muscular (i.m.)
- Drug is injected at large skeletal muscles like triceps, rectus femoris, deltoid etc.
- Mild irritant drugs can be delivered.
- Both oily and aqueous suspensions can be injected by this route.
- Should be avoided in patients with anti-coagulant drugs since it may cause local haematoma.
- Less painful, assistance is required since deeper penetration is required.
C. Intra-venous (i.v.)
- Drug is injected as bolus in the superficial veins.
- Enters the blood immediately and action is rapid.
- Only aqueous suspensions can be injected by this route.
- Drug is completely absorbed, little quantity of drug is required and so dose response can be easily measured.
- Irritant drug is diluted and given.
- Assistance is required since deeper penetration is required.

D. Intra-dermal
- The drug is injected into the skin raising a bleb (eg: BCG vaccine, sensitivity testing) by puncturing the epidermis.
- This route is for specific purpose only.
Pharmacotherapy, Clinical Pharmacology and Drug Development

Pharmaco- drug therapy is ever evolving science, dealing with various factors like patients, the drug, understanding the disease etc.

Drug Dosage

Dose – is amount of drug required produce a certain degree of response in a patient.

Prophylactic dose - it is defined as dose given prior to infection or preventive dose. Eg. Drugs that are given to prevent supra – infection.
- **Therapeutic dose** – it is defined as amount of drug required to produce a desirable / favorable effect in a patient.

- **Toxic dose** – it is the amount of drug required to produce toxic or adverse effect in a patient.

- **Lethal dose** – it is the amount of drug required to produce death or lethality in a patient.

The dose a drug is in turn governed by its potency, i.e. the concentration in the target site and its pharmacokinetics properties.

**Standard dose**

it is same dose appropriate for most patients.

**Regulated dose**

the drug modifies finely the body functions which can be easily measured. Eg. Antihypertensives, hypoglycemics etc.
Target level dose
The response is not easily measurable, crude adjustments are made by observing the patients at relatively long intervals.
Eg. Anti-depressants, antiepileptics etc.

Titrated dose
The dose needed to produce maximal therapeutic effect cannot be given because of intolerable adverse effects.
e.g. anticancer drugs, corticosteroids etc.

Fixed dose ratio combination preparations

<table>
<thead>
<tr>
<th>Advantages</th>
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<tbody>
<tr>
<td>Convenience</td>
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<td>Certain drug preparations are synergistic.</td>
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Disadvantages

- The patient may not actually need all the drugs present in the combination.
- The dose needs to be adjusted.
- Time course of action may be different.
- There might be altered renal and kidney functions.
- Contraindication to one drug may contraindicate the whole preparation.
- Adverse effect, when it occurs cannot be easily attributed to the particular drug causing it.
- Confusion of therapeutic aims.

Factors modifying the drug action

Variation in response to same dose of drug between different patients or even with the same patients on different occasions is rule rather than the exception.

Reasons in variation may be due to

1. Individual differ in pharmacokinetic handling of drugs.
2. Variation in neurogenic / hormonal tone or concentrations of specific constituents.
3. Variation in number or state of receptors, coupling proteins.
Large number of host and external factors influence a drug response.

**Factors affecting drug action**

- **Genetic**
- **Non-genetic**

**Factor modify drug action either**

- **Quantitatively** - the plasma concentration/action of drug is increased or decreased. It can be dealt with drug dosage. Most of the factors induce this type of change.

- **Qualitatively** - the type of response is altered. Eg. Drug allergy/idiosyncrasy.
Factors modifying drug action

- Body size
- Age
- Sex
- Species & race
- Genetics
- Routes of administration
- Environmental factors & time of administration
- Psychological factor
- Pathological states
- Other drugs
- Cumulation
- Tolerance
BODY SIZE
- It influences the concentration of the drug at the target area.
- The average adult dose refers to individuals of medium built.
- For obese, lean and children dose is calculated on body weight.

AGE
- The dose of drug of children is often calculated from adult dose.

The important physiological differences of infants and children are:
1. The newborn have low g.f.r. and their tubular transport is immature.
2. Their g.f.r reaches adult rates by 5 months of age and tubular secretion by 7 months to mature.
3. Similarly hepatic system is inadequate in newborns.
4. Blood brain barrier is more permeable.
5. These effects are exaggerated in premature infants.
6. Drug absorption is altered because low acidity and slower intestinal transit.
7. Transdermal absorption is faster since their skin is thin and so permeable.

And so infant dose should be learned as such and not derived from formula.

After 1st year of life drug metabolism is faster than adults.
Solid dosage forms are difficult to administer and are susceptible to adverse effects.
Elderly
- The renal function declines so that g.f.r. is reduced.
- There is also reduction in hepatic enzyme and liver blood flow.
- Absorption of drug is reduced due to slower motility of and blood flow to intestines, lesser plasma protein binding.
- May develop adverse effect because of multiple drugs.

SEX
- Females have lesser body size and so dose according to it is required.
- Because of their mental make up, subjective effect vary.
- In women, pregnancy, lactation and menstruation is to considered.
  - Drugs given during pregnancy affect the foetus esp. 3rd trimester.
  - Gastrointestinal motility is reduced.
  - Plasma and fluid volume increses.
  - Plasma albumin levels falls.
  - Renal blood flow increases.
  - Drugs may be metabolized faster.
- Thus overall drug action is complex and difficult to predict.
SPECIES AND RACE

- There is a wide range of differences are seen in drug response.
- For instance, Blacks require higher concentration of drug and Mongols require lower concentrations of atropine and ephedrine to dilate their pupil.
- Indians tolerate thiacetazone better than Whites.

GENETICS

- The dose of drug to produce a response will vary 6-7 folds with each individual.
- Key determinants in drug response are transporters, ion channels, metabolizing enzymes etc are genetically controlled.
- The study of genetic basis for variability in drug response is called as “Pharmacogenetics”.
- Pharmacogenomics is the use of genetic information to guide the choice of drug and dose on an individual basis.
- It helps in identifying individuals who more likely or less likely respond to a drug.
- There are still some specific genetic variation in drug responses
- Eg.
It helps in identifying individuals who more likely or less likely respond to a drug.

There are still some specific genetic variation in drug responses

Eg. G-6P deficiency is responsible for hemolysis with Primaquine and other oxidising drugs like sulphonamides, menadione etc.

Inability to hydroxylate phenytoin results in toxicity at usual doses etc.

**Routes of administration**

Various routes direct the speed and intensity of drug response.

- e.g.
  - Magnesium Sulphate
  - Oral
  - Topical
  - i.v.
  - Purgation
  - Decreases swelling
  - Depression & hypotension
Environmental factors

- Various environmental factors affects drug response.
- e.g. Exposure to insecticides, carcinogens, passive smoking, consumption of charcoal broiled meat etc.
- Type of foods we consume can greatly alter its absorption.
- Eg. Food interferes with ampicillin, fatty meal increases the absorption of griseofulvin.

Psychological factors

- The efficacy of drugs can greatly vary by patients beliefs, attitudes and expectations, particularly to CNS acting drugs.
- Placebo – is inert substance given as medicine, works psychological than pharmacological means, gives response to the active drugs.
- Placebo is given in 2 situations like
  - As control device in clinical trial.
  - When doctor feels that patient doesn’t need any medication.
Nocebo

Is completely opposite of Placebo, where the patient thinks that the drug is not going to work within him.

PATHOLOGICAL STATES

It is not only the drug modify the disease, but disease of person can also change the drug action.

E.g. GIT diseases, Liver diseases, Kidney diseases, Thyroid diseases etc.

OTHER DRUGS

Drug itself can modify the response with other drugs by altering its kinetic and dynamic properties.

CUMULATION

The prolonged accumulation of drug can alter the kinetic and dynamic rates of the other drugs in the body.
TOLERANCE

- Is defined as the requirement of higher dose of drug to produce a given response.
- Tolerance is generally a mere adaptive mechanism of drugs.
- Tolerance is classified as Natural, Acquired and cross Tolerance.
- Loss therapeutic efficacy which is a form of tolerance is called as refractoriness.

Natural

For instance, Blacks require higher concentration of drug and Mongols require lower concentrations of atropine and ephedrine to dilate their pupil.

Acquired

This occurs by repeated use of drugs, where the individual initially responded.

Cross Tolerance

Development of tolerance due to action of related drugs.

Eg. Morphine and pethidine.
Tachyphylaxis - is the fast development of tolerance when the drug is given repeatedly.

Drug resistance - is the tolerance to micro-organisms.
**Enzymes**

- Almost all biological reactions are carried out under catalytic influence of enzymes.
- Catalyst is a substance which enhance or decrease the reaction without alteration in them.

\[
\text{A} + \text{B} \rightarrow \text{C} \rightarrow \text{P}
\]

- Hence enzymes are important target in drug action.
enzyme + substrate entering active site

enzyme/substrate complex
enzyme changes shape slightly as substrate enters active site, making the fit more precise

enzyme/products complex

enzyme + products leaving active site
- A drug can either increase or decrease the enzymatically mediated reaction.
  - E.g. Pyridoxine acts as a co-factor and increase the decarboxylase activity

- Several enzymes are stimulated through receptors and secondary messengers.
  - E.g. adrenaline stimulates hepatic glycogen phosphorylase through β receptors and cyclic AMP.

- Increase of enzyme activity is also done by induction.
  - i.e synthesis of enzyme protein. It can’t be called as stimulation because the kM does not change.

- Example
  - induction of cyt P450 isoenzymes in liver.
  - Inducers are chloral hydrate, DDT, griseofluvin etc.
(a) Reaction

- Substrate molecule binds with the active site of enzyme molecule.
- Reaction occurs and product molecules are generated.

(b) Inhibition

- Inhibitor molecule binds with the inhibitor site of enzyme molecule and alters the structure of the active site.
- Substrate molecule may still bind with the enzyme molecule, but the reaction is hindered.
Inhibition of enzymes

Non-specific inhibition

Many drugs denature the proteins thus alter the structure of protein, thus inhibit the enzyme.

E.g. heavy metals, strong acids, alcohol inhibit enzymes.

Specific inhibition

Many drugs specifically go and bind to enzyme thus inhibit it.
Specific inhibition

- Competitive
- Non-competitive
- Allosteric
Competitive inhibition

- Drug is similar in structure to the substrate competes with substrate for the catalytic site and binds to it.
- Thus here a non-functional product is formed or product is not formed.
- Such inhibitors increase the $k_M$ but the $V_{max}$ remains unchanged (equilibrium type).
  - Eg. Physostigmine and neostigmine compete with acetylcholine for choline esterase.
  - Carbidopa and methyldopa compete with levodopa for dopa carboxylase.
Competitive Inhibitor

- Substrate
- Inhibitor
- Products

Competition depends upon concentration.
Non-Competitive inhibition

- The drug reacts with the enzyme in an adjacent site and not with catalytic site.
- But alters the enzyme in such a way enzyme does not react with substrate.
- Here, the $kM$ is unchanged but $V_{max}$ is reduced.

Examples

- Aspirin, indomethacin ------ cyclooxygenase
- Theophylline ------ Phosphodiesterase
- Omeprazole ---- H+K+ATPase
Allosteric inhibition

Enzyme reacts with substrate to form products.

\[ A + B \rightarrow C \rightarrow P \]

When product level is increased, the product goes and binds to the enzyme thus inhibiting it.
Active site

Substrate fits into the active site

Allosteric site empty

The inhibitor molecule is absent

Conformational change

Substrate cannot fit into the active site

Inhibitor molecule is present

Inhibitor fits into allosteric site