Routes of drug administration

Variety of routes of drug administration

Local routes
Used for localized lesions at accessible sites.
  • Higher conc. Is attained at desired site

1. Topical
  • External application of drug to the surface
  • Ex. Lotion, ointment, powder, cream

2. Deeper tissue
  • It is given directly into tissue by syringe or needle
  • Ex. Intraarticular injections into joint, Retrobulbar in eye ball

3. Arterial supply
  • In artery drug is injected so it reach directly to site of action
  • Ex. Angiography contrast material injected through artery

Systemic routes
Drugs are administered through systemic routes and they are absorbed into bloodstream

1. Oral
  • Oldest and commonest mode which is used
  • Safer, more convenient
  • Do not need any assistance, non invasive
  • Painless mode
  • It is cheap
  • Ex. Tablets, capsules

2. Sublingual
  • Drug is placed under the tongue or crushed in the mouth
Pharmacology

- So it will be spread over mucosa and then systemically absorbed
- Only lipid soluble drugs can be administered through this route
- Absorption is rapid
- Liver is bypassed
- Ex. Glyseryl trinitrate

3. Rectal
- Drugs are given through rectum
- Irritant and unpleasant drugs can be given through this route
- Used in patients having recurrent vomiting or unconscious patient
- Bypass liver metabolism
- Rectal inflammation results sometimes
- Ex. Diazepam in children

4. Cutaneous
- Highly lipid soluble drugs can reach systemic circulation through skin
- Absorption can be enhanced by rubbing and using oily base

Transdermal Therapeutic system
- These are devices in the form of adhesive patch which deliver drugs
- It deliver the drug at constant rate into systemic circulation
- Drug is held in the patch
- It is delivered on skin through microspore membrane
- Drug is diffused from skin to systemic circulation
- Rate of delivery is slower than absorption rate

Benefit
- Through this method constant level of drug in systemic circulation can be maintained

Application of patch on chest, abdomen, back, mastoid region
- Drugs given through this route are GTn, nicotine, estradiol
- They are designed for several days

Disadvantage
- Local irritation, erythma at application site
- It can be decreased by applying at different sites
5. Inhalation
- Volatile liquids and gases given by this route
- Absorption take place through the alveoli
- Ex. General anesthetic can be administered through this route

6. Nasal
- Mucous membrane of nose can absorb many drugs
- Liver is bypassed
- Ex. GnRH antagonist, desmopressin

7. Parenteral
- Administration of drug by injection directly into tissue fluid or blood

Benefits
- No crossing from intestinal mucosa
- Drug acts faster through this route
- Gastric irritation and vomiting are not increased
- No interference by food
- Liver is bypassed

Disadvantages
- Preparations which are given should be sterilised
- It's costly
- Technique is invasive and painful
- Assistance is required
- Chances of tissue injury is higher

Different routes for parenteral drug administration
1) Subcutaneous –
- drug is deposited in subcutaneous tissue
- Irritant drugs can not be injected

A) dermojet - needle is not used
- High velocity jet of drug solution is projected at subcutaneous site

B) pellet implantation
- Drug in the form of solid pellet is introduced with trochar and canula
- It provides long term release of drug over weeks and months
C) sialistic and biodegradable implants
- Crysteline drug is packed in tubes or capsule
- It is implanted under skin
- **Uniform amount of drug is released**

Non biodegradable implant should be removed later
- Ex. Hormones for contraceptive

2) intramuscular
- Drug is injected in skeletal muscle
- Muscle is vascular so absorption occurs from the site of administration

It is given in deltoid, triceps, gluteus maximus
- It should be avoided in patients on anticoagulant therapy because it can produce hematoma

3) Intravenous
- Drug is injected directly into one of the superficial veins
- Drug directly reach into blood circulation
- **Effects are produced immediately**
- Drugs are diluted in blood so highly irritent drugs can also be given through this route

Disadvantage
- Thrombophlebitis
- Necrosis of adjoining tissue
- Vital organs like heart, brain get directly exposed to high concentration of drug

Advantage
- Bioavailability is 100%
- Large volumes can be infused
- Response is accurately measured

4) Intradermal injection
- The drug is injected into skin
- Ex. Bcg vaccination
- It is used for specific purpose only.
Absorption is movement of the drug from its site of administration into the circulation

Factors affecting absorption are…

1. Solubility
   - Soluble drugs are absorbed faster.
   - If the drug is in solid form then it must dissolve first and then absorbed.
   - Rate of dissolution regulates the rate of absorption

2. Concentration
   - Passive diffusion of drug depends on concentration gradient
   - As the drug given in higher concentration, the absorption becomes fast.

3. Area of absorbing surface
   - As the area of absorbing surface increase, absorption of drug increase

4. Vascularity of absorbing surface
   - If the blood flow is increased absorption from the site is increased

5. Route of administration
   - Each route having different type of absorption characteristic
     - Oral
       - Nonionized and lipid soluble drugs absorbed faster and more
       - Ionised drug are less absorbed
       - Absorption area is more of small intestine so more absorption occurs from here
       - Presence of food decrease absorption
       - Small particle sized drugs absorbed more

Subcutaneous and intramuscular route
   - Drugs are deposited at site and then absorbed in to circulation
   - Lipid soluble drugs absorbed faster
   - Vary large sized particles absorbed into lymphatic
   - Absorption is faster from intramuscular site than subcutaneous
   - Heat and muscular exercises increase drug absorption
Topical site
- Absorption from this site depends on lipid solubility of drug
- Lipid solubility increase, absorption increase
- Absorption can be increased by rubbing the drug.

Que. Bioavailability

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

Factors affecting bioavailability of drug are...

1. Route of administration of drug
   - Bioavailability of drug injected intravenously is 100%
   - In oral route, it is less because
     - It is incompletely absorbed
     - Absorbed drug undergo first pass metabolism
   - In subcutaneous and intramuscular route it is less due to
     - Local binding of drug to the tissue

2. Manufacturing
   - Different manufacturers or different batches of same drug have different bioavailability

3. Presence of other substance
   - Diluents, stabilizing agents, binders affect bioavailability

4. Particle size
   - Rate of absorption and bioavailability is more for small particle sized drug

5. Physical property
   - Solid, liquid or gas form of drug affect bioavailability of drug

6. Solubility and rate of absorption
   - Difference in bioavailability is seen in poorly soluble and slowly absorbed drugs
Que. Redistribution

Highly lipid soluble drugs are distributed first to organs with high blood flow [ex. Brain, heart, kidney etc.] Later more bulky tissue [Ex. Muscle, fat] take up the drug so, plasma concentration of drug falls down
This is known as redistribution.

- Drug action is terminated by redistribution
- Highly Lipid soluble drugs having faster redistribution
  Ex. Thiopentone sodium
  - Its action starts within few seconds and terminated in few minutes due to redistribution

What is blood brain barrier?

Capillary endothelial cells in brain have tight junctions and no intracellular pores. And neural tissue covers the capillaries. Together they known as blood brain barrier

- lipid soluble drugs and specific molecules can cross blood brain barrier
- In addition efflux transporters are also present which removes drugs entering into brain.

Que. Plasma protein binding

Most drugs have affinity for plasma proteins. They bind with plasma protein

Acidic drugs generally binds to plasma albumin
  - Ex. Barbiturates, benzodiazepines, NSAIDS
Basic drugs generally bind to alpha glycoprotein
  - Ex. Beta blockers, lidocaine

Amount of binding depends on individual compound

The significance of plasma protein binding are:
1. Highly plasma protein bound drugs are restricted to vascular compartment because plasma protein bound drug cannot cross membranes. So volume of distribution becomes less

2. Bound fraction of drug is not available for action

3. It is the temporary storage of drugs

4. Drug becomes longer acting because bound fraction is not available for metabolism or excretion
   - Liver metabolism and glomerular filtration is decreased due to plasma protein binding

5. In plasma concentration bound+ free drug concentration is taken.

6. One drug can bind to many sites of albumin molecule
   - More than one drug can bind to the same site
   - This give rise to interactions among drugs
     - One drug can displace other drug so displaced drug get metabolized or excreted. Ex. Salicylates displace sulfonylureas

7. In hypoproteinemia binding is reduced so high concentration of free drug is available.
Que. Bio-transformation

- Bio transformation means chemical alteration of drug in the body
- Most of the drugs are treated as foreign substance by body.

- The primary site for drug metabolism is liver others are kidney, intestine, lungs, and plasma

Bio transformation leads to following
1. Inactivation -
   - Drugs are converted into inactive form

2. Active metabolite from an active drug
   - Many drugs are converted into more active metabolite

3. Activation of inactive drug
   - Few drugs are inactive on administration. Such drugs are called as prodrug
   - They are converted into active form
   - Prodrug having advantage of stability, better bioavailability and less toxicity

Biotransformation can be classified into
Non synthetic reaction
1. Oxidation
   - It involves oxidation of drug particle
   - Initial insertion of oxygen atom into drug particle produce highly reactive intermediates
   - It is carried by a group of mono-oxygenase enzymes into liver
   - Ex. Barbiturates and paracetamol are oxidised

2. Reduction
   - drugs are converted into reduced form
   - Ex. Alcohol and quinones are reduced

3. Hydrolysis
   - Cleavage of drug particle by combining with water molecule. Ex. Aspirin

4. Cyclistion
   - Formation of ring structure from a straight chain compound. Ex. Proguanil

5. Decyclisation
   - Opening of ring and conversion into straight ring Ex.
Barbiturates, phenytoin

**Synthetic reaction**
These involves conjugation of the drug with endogenous substrate

1. **Glucuronide conjugation**
   - Drugs are conjugated with glucuronide. Ex. Aspirin, paracetamol
2. Acetylation
3. Methylation
4. Sulfate conjugation
5. Glycine conjugation

**Que. Microsomal enzyme induction**

- Microsomal enzymes are located on smooth endoplasmic reticulum in liver mainly. Also in kidney, intestinal mucosa and lungs
- **Many drugs interact with DNA and increase** the synthesis of Microsomal enzyme protein **So metabolism increase**

They mainly affect cytochrome P-450 and glucoronyl transferase
Ex
- Phenobarbitone, rifampin, glucocorticoids induce cyp3a
- Phenobarbital be also induce cyp2b1

**Different CYP** are involved in the metabolism of different drugs, **So they are involved with biotransformation of different drugs**

**Consequence of Microsomal enzyme induction**

1. **Decrease duration of action of drugs**
   - If enzyme induction increase metabolism of drugs, then duration and intensity of drug action is reduced

2. **Increased intensity of action of drugs**
   - If microsomal enzyme is converting drug into active metabolite
   - and some enzyme inducers are present than intensity of drug action is increased

3. **Tolerance**
   - If the drug induce its own metabolism then tolerance developed
Ex. Carbamazepine

4. Some endogenous substances are metabolized faster
5. Dose adjustment of drugs are needed

Uses of enzyme induction
1. Congenital nonhemolytic jaundice
   • Jaundice occurs due to deficient conjugation of bilirubin.
   • Phenobarbitone induce clearance of bilirubin
2. Cushing syndrome
   • Phenytoin enhance the degradation of steroids
3. Liver disease
4. Chronic poisoning

Que. first pass (pre systemic ) metabolism

Metabolism of drug during its passage from the site of absorption into the systemic circulation known as first pass metabolism
• It's mainly occurs in liver or intestinal wall

Due to first pass metabolism...
• Oral dose is mostly higher than parental route
• Individual variation of dose of drug
• In liver disease bioavailability is increased

Que. Excretion of drug

The drugs and their metabolites are excreted in
1. Urine [ Renal Excretion ]
   • The major route for excretion of drugs is through kidney in urine
   • Net renal excretion is:
     glomerular filtration + tubular secretion - tubular reabsorption

Glomerular Filtration
• Glomerular capillaries having pores
• Non protein bound drug [ lipid soluble or insoluble] is filtered
Glomerular filtration of drug depends on plasma protein binding and renal blood flow

Tubular reabsorption

- It depends on lipid solubility, more lipid soluble drugs are absorbed more and less excreted
- Ionized drugs being less lipid soluble and more excreted
- Acidic drugs [salicylates, barbiturates] are more ionized at alkaline ph. So urine should be alkalinized in poisoning of these drugs
- Urine should be acidified in poisoning of basic drugs
- Alkalization of urine is done by iv infusion of sodium bicarbonate and acidification is done by iv infusion of arginine hydrochloride followed by ammonium chloride

Tubular secretion

- Active transfer of substances into tubules is known as tubular secretion
- It does not depend on plasma protein binding or lipid solubility

2. Faeces

- Unabsorbed fraction of drug is present in faeces.
- The drug excreted in bile is also present in faeces

3. Exhaled air

- Gases and volatile liquids are eliminated by lungs
- Transfer of gases depends on partial pressure of drug in blood

4. Saliva and Sweat

- Minor route for excretion of drug
- Lithium, Potassium iodide, and rifampin are present in these secretion.

5. Breast Milk

- Lipid soluble and less protein bound drugs can enter breast milk by passive diffusion.
Que. Combined effect of drug

When two or more drugs are combined with each other Two types of effects are possible

- **Synergism**
- **Antagonism**

### Synergism

*When the action of one drug is increased by other, it is known as synergism.*

Drugs are known as synergistic.

**Synergism can be two types**

- **Additive**
  - When the drugs are acting in same direction and their effect simply adds up
  - **Effect of drug a + b = effect of drug a + effect of drug b**
  - Ex. Aspirin + paracetamol. As analgesic and antipyretic

- **Supra additive**
  - The effect of combination is greater than the individual effects of components
  - **Effect of drug A + B > effect of A + effect of B**
  - Ex. Acetylcholine + physostigmine

### Antagonism

*When one drug decrease the action of other they are called as antagonist*

**Effect of drug A + B < effect of drug A + effect of B**

1. **Physical antagonism**
   - Based on **physical property of drug**
   - Ex. Charcoal adsorbs alkaloids and prevent their absorption
   - That's how charcoal decrease the effect of alkaloids and used in alkaloid poisoning

2. **Chemical antagonism**
   - Two drugs react chemically and form an **inactive product**
Pharmacology

- Ex. Chelating agents combines with metal ions and helps in removal of toxic metals
- Drugs react with each other when combined in same infusion bottle
  Thiopentone sodium with succinylcholine

3. Physiological antagonism
- When two drugs act on different receptors by different mechanism
  But having opposite effects
- Ex. glucagon and insulin on blood sugar level
- Histamine and adrenaline on bronchial muscles and blood pressure

4. Receptor antagonism
- One drug blocks the receptor action of other
- This antagonism is selective
  a. Competitive antagonism
    - Antagonist is chemically similar to the agonist So it competes with it
    - Antagonist binds with receptor site and prevents the action of agonist
    - Here antagonist binding is reversible so the response is dependent on relative concentration of agonist and antagonist
    - DRC is shifted to right side
  b. Non competitive antagonism
    - Antagonist is chemically unrelated to the agonist
    - It binds with different site
    - It change receptor in such a way that agonist is unable to bind.
    - Response mainly dependent on concentration of antagonist
    - Agonist concentration cannot revert the block
  c. Nonequilibrium antagonism
    - Some antagonist binds with receptors with strong bond So irreversible type of antagonism is produced
    - Flattening of dose response curve
    - Maximal response is suppressed
    - It is mainly dependent on concentration of antagonist
Que. factors modifying drug action

Variation in response is seen with the same dose of drug.
Response is different in different patients and also in same patient on different occasions

Various factors are discussed below

1. Body size-
   - Concentration of drug at site of action depends on body size
     - Average adult dose refers to individual of medium built
     - Obese or lean individuals dose calculated from their body weight
     - It can be calculated from body surface area also

2. Age
   Dose of drug depends on age of patient

Dose for child can be calculated from adult dose
   - Children are not small adult
   - New born child Gfr is different
   - Hepatic metabolism is inadequate
   - Transdermal absorption is faster

After first year of life
   - Drug metabolism is faster than adults
   - They are susceptible to special adverse reactions

Elder
   - Renal function and hepatic function reduced
   - Adverse drug reactions are higher

3. Sex
   - Females have smaller body size and different mental setup.
   - Drugs during pregnancy can affect foetus
   - Some drugs create adverse reaction only in male Ex. Gynecomastia
4. Species and race
Rabbits are resistant to atropine
In human
  • Blacks require higher and Mongols require lower dose of atropine for its action
  • Indians tolerate thiacetazone better than whites

5. Genetics
Drugs act by receptors and transporter help for mobility and enzymes do their metabolism
  • Receptor, transporter and enzymes production depends on gene
  • So drug effect is changed individually

6. Route of administration
It controls the speed and intensity of drug action
  • Drug having different use through different routes

7. Environmental factors and time of administration
Environmental factors modify drug action
  • Exposures to insecticides, carcinogens, smoke change drug metabolism
  • Hypnotics taken at night and in quite familiar surroundings work more easily

8. Psychological factors
Efficacy of drug can be affected by patient’s beliefs, attitudes and expectations

9. Placebo
This is an inert substance which work by psychological phenomenon
It's having no pharmacological action
  • It produce action equivalent to the active drug

They are used in
  • As a control devise in clinical trials of drugs
  • To treat patients who is in the opinion of the physician does not require an active drug
It mainly depends on the Doctor patient relationship
- Placebo induce psychological response by Releasing endorphins in brain Causing analgesia
- Their actions different in the same individuals

Substances commonly used as placebo are
- Lactose tabulates
- Distilled water injection

Nocebo
Negative psychodynamic effects evoked by loss of faith in the medication or in physician
- It oppose the therapeutic effect of active medication

9. Pathological states
a. Gastrointestinal disease
   - They affect the action of drug taken orally
   - It affects absorption of drugs
b. Liver disease
   - It affect bioavailability, metabolism, activity and elimination of drug
c. Kidney disease
   - Affect elimination of drug
   - Dose of drug which are excreted by kidney should be modified in renal failure

10. Other drug
- Other drug can affect the drug action
- It can produce synergism or antagonism

11. Cumulation
   - Drug will cumulate when rate of administration is more than rate of elimination Ex. Digoxin, chloroquine
12. Tolerance

It refers to the requirement of higher dose to produce given response

- It is a biological phenomenon

Drug tolerance may be

- Natural
  - Individual is less responsive to certain drugs
  - Some people are less responsive to Beta blockers or alcohol

- Acquired
  - This occurs due to repeated use of drug
  - Initially person is responsive
  - Continuous presence of drug in the body favors development of tolerance

Ex. Tolerance develops to analgesic action of morphine but not for its constipation and Miotic action

- Cross tolerance
  - It is the development of tolerance to pharmacologically related drugs
  - Alcoholic persons are tolerant to barbiturates and general anesthetics
  - Cross tolerance is more between two closer compounds

Mechanism

- Incompletely understood
- Due to drug deposition and increased excretion
- Cellular tolerance
  - Target receptors become less responsive and their down regulation occurs

Tachyphylaxis

- It is rapid development of tolerance when dose of drug repeated quickly results in reduction in response

Drug resistance

- It refers to tolerance of micro organism to inhibitory action of antimicrobials
Que. Teratogenicity

It refers to capacity of drug to cause foetal abnormalities when administered to the pregnant mother

- Placenta does not work as a strict barrier so drug can cross it at greater or lesser extent

Drugs can affect the foetus at 3 stages

1. Fertilization and implantation
   - Conception to 17 days
   - Failure of pregnancy can result

2. Organogenesis
   - 18 to 55 days
   - Deformities are produced

3. Growth and development
   - 56 days onwards development and functional abnormalities can occur

Ex. Ace inhibitors can cause hypoplasia of organs especially lungs and kidneys
   - Thalidomide cause phocomelia and multiple defects

Teratogenicity depends on blood level and duration for which it remains in the maternal circulation

Majority of drugs are low grade teratogens

- Therefore, wise to avoid all drugs during pregnancy except for some serious conditions

Drug induced malformations especially neural tube defect may be reduced by folate therapy during pregnancy.