2 Routes of Drug Administration

Drugs can be administered by different routes for local and systemic effects.

Factors Deciding the Route of Choice

- **Physicochemical properties** of the drug, i.e. whether the drug is solid (tablet, capsule, powder, pessary and suppository), liquid (mixture, syrup, lotion, enema and injection) or gas, soluble or insoluble, irritant or nonirritant, etc.
- **Type** of desired effect, i.e. systemic or local effect for which the drug is used.
- **Rapidity** of desired effect, e.g. oral, IM, etc. for routine treatment, IV for emergency treatment.
- **Quality** of desired effect, e.g. magnesium sulphate given orally is a purgative, but when given rectally lowers intracranial tension.
- **Condition** of the patient, i.e. whether the patient is conscious or unconscious, vomiting or not vomiting, etc.

Local Routes

These are used for localized lesions at accessible sites. Systemic absorption of the drug from these sites is minimum or absent. Thus a high concentration of the drug is attained at the desired site without exposing the rest of the body. This minimizes systemic adverse effects or toxicity of the drug. The drug is applied on the skin and various mucous membranes as ointment, cream, lotion, drops, jelly, powder, tablet, suppository, or pessary. Injections in deeper tissues include intra-articular (in joint cavity), e.g. hydrocortisone hemisuccinate; intrathecal (into subarachnoid space of L 2–3 or L 3–4), e.g. lidocaine, isoniazid, amphotericin B, etc. intramedullary (into bone marrow), e.g. hematinics; intra-arterial (into artery of limbs), e.g. anticancer drugs in limb cancer; retrobulbar (behind the eyeball), e.g. hydrocortisone hemisuccinate/acetate; intrapleural (inside pleural cavity), e.g. antitubercular drugs, anticancer drugs and intraperitoneal (inside peritoneal cavity), e.g. antitubercular drugs, inhalation have been discussed later on anticancer drugs.

Systemic Routes

These are used for systemic effects of drugs. The drug is absorbed into blood and distributed all over the body including the site of action through circulation (Flow Chart 2.1). These routes are:

Enteral (GIT)

These are given as follows:

a. Oral (ingestion of drug): It is most convenient and economical. It is more safe than other routes. It requires patient's cooperation. The absorption of the drug may be variable and erratic. Drugs that are poorly soluble, slowly absorbed, unstable or extensively metabolized by the liver

ii. **Intramuscular (IM) injection:** It produces rapid effect from aqueous solution and slow and sustained effects from repository (depot) preparations. It is suitable for moderate volumes, oily vehicles and some irritant substances, e.g. penicillins, aminoglycosides, iron preparations, etc. It can produce pain (from irritant substances) and abscess formation (if not properly sterilized). It should be avoided during anticoagulant medication. It may damage a nerve if injected into it producing severe pain and paresis.

iii. **Subcutaneous (SC) injection:** It produces rapid effect from aqueous solution and slow and sustained effects from repository preparations as IM injection. It is suitable for some insoluble suspensions and for implantation of solid pallets. It is not suitable for large or moderate volumes of drugs. It can produce pain or necrosis of tissue from irritant substances. Drugs like insulin, adrenaline, heparin (low M.W.), tetanus toxoid, etc. are administered subcutaneously.

Pellet implantation: The drug as solid pellet is introduced into the subcutaneous tissue with the help of a trocar and cannula. It provides a sustained release of the drug for several weeks or months, e.g. testosterone, DOCA, etc.

iv. **Intradermal injection:** In it, the drug is injected into the layers of skin by raising a bleb or multiple puncture of epidermis (by a needle), e.g. BCG or smallpox vaccination. It is also used for testing of drug sensitivity, e.g. penicillin, ATS, etc.

v. **Controlled release drug delivery systems:** These are given as follows:

a. *Transdermal (transcutaneous) drug delivery system (TDS):* It is used for percutaneous absorption of some drugs, e.g. glyceryl trinitrate, isosorbide dinitrate, scopolamine, clonidine, insulin, verapamil, timolol, digoxin, fentanyl, nicotine, prostaglandin, oestradiol, testesterone, etc. The drug is held in a reservoir of suitable materials are applied on the surface of the skin in the form of adhesive patches of various shapes and sizes (5–20 cm sq.), which deliver the incorporated drug at a constant rate into the systemic circulation *via* the skin by diffusion. A single patch can ensure continuous low grade absorption for about 7 days. Common sites of application of adhesive patches are chest, abdomen, upper arm, lower back, buttock, mastoid region and behind the ear (pinna). Its advantages are longer duration of action, decreased frequency of administration, relatively stable plasma concentration, minimum adverse effects (local irritation and oedema) and better patient compliance. The patch can be removed if adverse effects (local inflammation and oedema) appear. Other types of transdermal drug delivery system are dermojet injection, iontophoresis, inunction and implantable miniature syringe pump. Iontophoresis provides penetration of drug into deeper tissues from surface of the skin by galvanic current, e.g. salicylates in arthritis. Inunction provides absorption of drugs into blood by rubbing the drug on the surface of the skin, e.g. nitroglycerine ointment in angina pectoris. Dermojet is a type of transdermal drug delivery system in which needle is not used. A high velocity jet of drug solution is projected from a microfine orifice using a gun-like implement. The drug passes through the layers of skin and gets deposited in the subcutaneous tissue. It is painless and suitable for mass inoculation of vaccines. Implantable computerized miniature syringe pump is used for adminiztration of drugs like insulin, glyceryl trinitrate, etc.

of transfer of the drug is proportional to lipid/water partition coefficient of the drug. Greater the coefficient of the drug, higher the concentration of the drug in the membrane and faster the diffusion of the drug through the membrane. Ionized drugs are not lipid-soluble and cannot easily cross cell membrane by diffusion.

ii. **Filtration:** It is the passage of the drug molecule through the aqueous pores in the cell membrane or through inter-epithelial gaps (paracellular spaces). Water-soluble drugs of low molecular weights whether ionized or unionized can easily pass through the membrane pores and enter intracellular or extracellular space or excreted in urine by glomerular filtration, e.g. atenolol, heparin, alcohol, mannitol, etc.

iii. **Active transport:** It is the movement of the drug molecule across the cell membrane against the concentration gradient (uphill movement) requiring expenditure of energy (ATP). It is carrier mediated, i.e. carried by a specific carrier called a transport protein. It can be inhibited by metabolic poisons (antimetabolites). Absorption of glucose, iron and amino acids from intestine occurs by active transport process.

iv. **Facilitated diffusion:** In it, the drug molecule crosses the cell membrane by the help of a carrier protein but the movement of the drug molecule is towards the concentration gradient (i.e. downhill movement) and so does not require expenditure of energy. Absorption of vitamin B_{12}, folic acid and pyrimidines from intestine occurs by facilitated diffusion. It is faster than passive (simple) diffusion.

v. **Exchange diffusion:** It is a bidirectional facilitated diffusion, e.g. Na^+ is reabsorbed in distal renal tubules in exchange of K^+ or H^+ (which are excreted in urine) to preserve important Na^+ in the body.

vi. **Pinocytosis:** It is vesicular uptake and transport. In it, the cell engulfs (swallows) a large size drug molecule (polypeptide, lipoprotein, etc.) by an infolding process of a small portion of a cell membrane forming a vesicle and transports it. It requires expenditure of energy like active transport. It occurs mainly in liver cells.

Factors influencing the rate of absorption of drugs from GIT are as follows:

i. ***Biological factors (intrinsic factors):*** These are gut (GIT) related factors.

   a. **Local pH of gut:** Most drugs are either weak acids or weak bases and exist in aqueous solution as a mixture of ionized and unionized forms. Ionized form is lipid-insoluble, whereas unionized form is lipid-soluble. Acidic drugs like salicylates, barbiturates and sulphonamides are rapidly absorbed from the stomach as they are poorly ionized in the acid pH (less than 5) of stomach and thus remain mostly in unionized form. Basic drugs like morphine, quinine, chloroquine, amphetamine and ephedrine are not absorbed from the stomach, but absorbed from the small intestine in the alkaline pH where they remain mostly in unionized form in the alkaline pH (more than 7) of small intestine.

   b. **Presence of food and other drugs in gut:** Most drugs are better absorbed in empty stomach. Presence of food in the stomach dilutes the drug and retards absorption of the drug, e.g. ampicillin, aspirin, isoniazid, rifampicin, tetracycline, etc. Presence of other drugs in the gut may increase or decrease the absorption of the drug by drug-drug interaction, e.g. presence of vitamin C increases the absorption of iron salt from the gut, presence of calcium, magnesium or iron salt decreases the absorption of tetracyclines by forming poorly absorbed chelate complexes.

   c. **Surface area of gut:** The greater the surface area of the absorbing surface

on which the drug is spread, the more rapid is the rate of absorption. Drugs are better absorbed from the small intestine than the stomach due to the greater surface area. Decrease in surface area due to gastrectomy or enterectomy reduces absorption of drugs.

d. **Motility of gut:** Increase in gut motility as in diarrhoea, decreases absorption of drugs due to rapid elimination in faeces. Decrease in gut motility as in shock or CCF slows absorption of drugs. Vomiting also decreases absorption of drugs.

e. **Local circulation (blood flow) in gut:** Increase of blood flow in gut due to vasodilation increases absorption of drugs. Decrease of blood flow in gut due to vasoconstriction as in haemorrhagic shock decreases absorption of drugs.

f. **First pass effect:** Some drugs, e.g. glyceryl trinitrate, isosorbide dinitrate, isoprenaline, propanolol, chlorpromazine, etc. undergo first pass metabolism in gut wall and liver during passage through portal circulation which decreases their therapeutic effects. These drugs are better administered sublingually to reach the systemic circulation directly by passing gut wall and hepatic metabolism.

ii. ***Pharmaceutical factors (extrinsic factors):*** These are drug related factors:

a. **Physical state of drug:** Drugs given in liquid dosage forms are better and rapidly absorbed from gut than when given in solid dosage forms. Colloids are slowly absorbed than crystalloids.

b. **Water or lipid solubility of drug:** Drugs given in aqueous solution mix more readily with the aqueous phase of the absorbing surface than when given in oily solution and so rapidly absorbed from gut. At the cell surface, a lipid-soluble drug penetrates the cell membrane more easily than a water-soluble drug and so better absorbed from gut.

c. **Particle size of drug:** Solid dosage forms of drugs that contain smaller particles (microfine crystals) are better absorbed from gut, e.g. aspirin, griseofulvin, chloramphenicol, warfarin, tolbutamide, corticosteroids, etc. They should be given in smaller dose to avoid systemic toxicity. Solid dosage forms that contain larger particles, e.g. bephenium, streptomycin, neomycin, etc. are very little absorbed from gut and so used for local effects. Larger tablet breaks down more quickly than the highly compressed small tablet and so more rapidly absorbed from gut.

d. **Disintegration time of drug:** It is the time taken for a solid dosage form (e.g. tablet) of a drug to disintegrate (break down) into finer particles in the gut completely. It depends on the type of drug and the excipient (binding agent) used in it. If the disintegration time is longer, the absorption of the drug is delayed.

e. **Dissolution time of drug:** It is the time taken for a solid dosage form (e.g. tablet) of a drug to go into the solution in the gut after it has been disintegrated. Solution as a rule is absorbed faster than the solid form.

f. **Enteric coating of drug:** Some tablets or dragees are made enteric coated by means of cellulose, acetate or phthalate, which resist disintegration and dissolution of the drug in the gut by acid gastric juice but permit disintegration and dissolution of the drug by the alkaline intestinal juice. This produces an uniform and sustained blood level of the drug without requiring too frequent dosing. Some sustained release (S.R.) and time release (T.R.) capsules are now avai-

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