Pharmacodynamics: General mechanism of drug action and the factors which modify drug action.

Pharmacodynamics is the study of drug effects on the body. It tells us about what drug do in body and how it does it in our body. Thus, it give us complete insight about the drug effects and the dose which is required to induce that effect.

PRINCIPLES OF DRUG ACTION

Drugs (except those gene based) do not impart new functions to any system, organ or cell; they only alter the pace of ongoing activity. However, this alone can have profound medicinal as well as toxicological impact. The basic types of drug action can be broadly classed as:

Stimulation It refers to selective enhancement of the level of activity of specialized cells, e.g. adrenaline stimulates heart.

Depression It means selective diminution of activity of specialized cells, e.g. barbiturates depress CNS.

Irritation This induces a nonselective, often noxious effect. Strong irritation results in inflammation, corrosion, necrosis and morphological damage.

Replacement This refers to the use of natural metabolites, hormones or their congeners in deficiency states, e.g. insulin in diabetes.

Cytotoxic action Selective cytotoxic action on invading parasites or cancer cells, inducing such effect without affecting the host cells. E.g. penicillin induce bactericidal effect.

Mechanism of the drug action:

Only few among all the drugs are capable of producing effect simply by their physical and chemical properties:

- Physical action: a physical property of the drug is responsible for its action. For example:
  - Mass of drug: bulk laxative (bran), protectives (dimethicone).
  - Absorptive properties: activated charcoal can absorb poisonous substances. Paraamino benzoic acid can absorb UV radiations.
  - Others: mannitol has osmotic activity hence used as a diuretic substance, various radioisotopes are used for their variable activities from one another.
- Chemical actions: the drug shows therapeutic activity by the virtue of its chemical property.
  - Antacids are known for neutralising the acidic pH.
  - Chelating agents (EDTA), sesquestring agents (cholestyramine), Anti-coagulants (calcium
    citrate) they all use their chemical properties to induce the therapeutic effect.

Majority of the drugs produce their effect by targeting various molecules (usually proteins) already present in the body. Such mechanism confers selectivity of action to the drug.

Functional proteins that are targets of drug action can be grouped into *four* major categories, *viz.* enzymes, ion channels, transporters and receptors.

i. Enzymes: almost all the biological reactions are carried out by the catalytic action of various enzymes present in human body. Thus these enzymes are very important target for drugs. These drugs will target these enzyme to catalyse the reaction, they can either increase or decrease the rate of enzymatically mediated reactions. For example: captopril will inhibit the Angiotensin converting enzyme which will inhibit the formation of angiotensin-1, adrenaline stimulate the glycogen phosphorylase.

ii. Ion channels: Proteins which act as ion selective channels participate in transmembrane signaling and regulate intracellular ionic composition. This makes them a common target of drug action. These channels are operated by signal specific molecules, which can either directly affect the ion channel (ligand gated ion channels) or indirectly affect the ion channel (g-protein regulated channels). Thus drugs can either increase the flow of ions through theses ion channels or can reduce it, to produce the specific action. For example: local anaesthetics, which obstruct voltage sensitive Na^+ channels.

iii. Transporters: Several substrates are translocated across membranes by binding to specific transporters (carriers) which either facilitate diffusion in the direction of the concentration gradient or pump the metabolite/ion against the concentration gradient using metabolic energy. Several drugs can interact with such transporters to induce therapeutic effect. For example: Desipramine and cocaine block neuronal reuptake of noradrenaline by interacting with norepinephrine transporter (NET).

iv. Receptors: The largest number of drugs do not bind directly to the above mentioned effectors (enzymes, channels, transporters), but act through specific regulatory macromolecules which control the above listed effectors. These regulatory macromolecules or the sites on them which bind and interact with the drug are called 'receptors'. Receptor is defined as "a macromolecule or binding site located on the surface or inside the effector cell that serves to recognize the signal molecule/drug and initiate the response to it, but itself has no other function is called a receptor". The drugs can alter the functioning of the receptor by interacting with them, these interaction will be of following types:

- Agonism: when an agent activate the receptor to produce the similar effect to that of physiological signal molecule, that interaction is called agonism and that agent is called agonist.

- Inverse agonism: when an agent activate the receptor to produce an effect opposite to that of physiological signal molecule, that interation is called inverse agonism and agent is called inverse agonist.

- Antagonism: when an agent bind to the receptor to avoid the effect of agonist, that interaction is called antagonism, and the agent inducing such effect is called antagonist.

    For example: cetirizine is an antihistaminic drug means it will bock the histamine receptor present in body.

Combined effects of the drugs:

1. **Synergism:** When the action of one drug is facilitated or increased by the other, they are said to be synergistic. They are further of two types:
   a. Additive: The effect of the two drugs is in the same direction and simply adds up:
      effect of drugs A + B = effect of drug A + effect of drug B
      For example: combination of paracetamol and aspirin will provide the effect of both *i.e.* antipyretic + analgesic.
   b. Supra-additive: The effect of combination is greater than the individual effects of   the   components:
      effect of drug A + B > effect of drug A +effect of drug B
      For example: combination of levodopa and carbidopa increase the effect of drug, because carbidopa inhibit the peripheral metabolism of levodopa.
2. **Antagonism**: When one drug decreases or abolishes the action of another, they are said   to   be   antagonistic.
   effect of drugs A + B < effect of drug A + effect of drug B
   for example: Glucagon and insulin on blood sugar level. Glucagon increase the blood sugar level where insulin reduce the blood sugar level. Hence, if they are given in combination they will act opposite to each other and the net effect will be nil.

   Factors affecting drug action:

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

   Body size: It influences the concentration of the drug attained at the site of action. The average adult dose refers to individuals of medium built. For exceptionally obese or lean individuals and for children dose may be calculated on body weight (BW) basis:

$$\text{Individual dose} = \text{BW (kg)}/70 \times \text{average adult dose}$$

   It has been argued that body surface area (BSA) provides a more accurate basis for dose calculation, because total body water, extracellular fluid volume and metabolic activity are   better   paralleled   by   BSA.

$$\text{Individual dose} = \text{BSA (m2)}/1.7 \times \text{average adult dose}$$

   The BSA of an individual can be calculated from Dubois formula:

$$\text{BSA (m2)} = \text{BW (kg)}^{0.425} \times \text{Height (cm)}^{0.725} \times 0.007184$$

Age The dose of a drug for children is often calculated from the adult dose

Child dose= age/ (age+12)   (young's formula)

Child dose= Age/ 20 X Adult dose   (dilling's formula)

It can also be calculated (more accurately) on BW or BSA basis (see above), and for many drugs, manufacturers give dosage recommendations on mg/kg basis. Average figures for children are given below.

Age	Ideal BW (Kg)	BSA (m^2)	% of adult dose
Newborn	3.2	0.23	12.5
1 month	4.0	0.26	15
3 months	5.5	0.32	18
6 months	7.5	0.4	22
1 year	10	0.47	25
3 years	14	0.62	33
5 years	18	0.73	40
7 years	23	0.88	50
12 years	37	1.25	75

However, infants and children are not small adults. They have important physiological differences from adults. The newborn has low g.f.r. and tubular transport is immature. Similarly, hepatic drug metabolizing system is inadequate in newborns —chloramphenicol can produce gray baby syndrome. chloramphenicol can produce gray baby syndrome. Blood-brain barrier is more permeable—drugs attain higher concentration in the CNS (accumulation of unconjugated bilirubin causes kernicterus). Drug absorption may also be altered in infants because of lower gastric acidity and slower intestinal transit.

After the first year of life, drug metabolism is often faster than in adults. theophylline, phenytoin, carbamazepine t½ is shorter in children. Also, higher per kg dose is needed for drugs which are primarily excreted unchanged by kidney, e.g. daily dose of digoxin is about 8–12 µg/kg compared to adult dose of 3–5 µg/kg.

In the elderly, renal function progressively declines compared to young adults. Drug doses have to be reduced, There is also a reduction in the hepatic microsomal drug metabolizing activity and liver blood flow: oral bioavailability of drugs with high hepatic extraction is generally increased, but the overall effects on drug metabolism are not uniform.

Sex: Females have smaller body size and require doses that are on the lower side of the range. Subjective effects of drugs may differ in females because of their mental makeup. Maintenance treatment of heart failure with digoxin is reported to be associated with higher mortality among women than among men. A number of anti-hypertensives have potential to interfere with sexual function in males but not in females.

In women consideration must also be given to menstruation, pregnancy and lactation. Drugs given during pregnancy can affect the foetus. There are marked and progressive physiological changes during pregnancy, especially in the third trimester, which can alter drug disposition.

Species and race: Among human beings some racial differences have been observed, e.g. blacks require higher and mongols require lower concentrations of atropine and ephedrine to dilate their pupil. B-blockers are less effective as antihypertensive in Afro-Caribbeans. Indians tolerate thiacetazone better than whites. Considering the widespread use of chloramphenicol in India and Hong Kong, relatively few cases of aplastic anaemia have been reported compared to its incidence in the west. Similarly, quiniodochlor related cases of subacute myelooptic neuropathy (SMON) occurred in epidemic proportion in Japan, but there is no confirmed report of its occurrence in India despite extensive use.

Route of administration Route of administration governs the speed and intensity of drug response. Parenteral administration is often resorted to for more rapid, more pronounced and more predictable drug action. A drug may have entirely different uses through different routes, e.g. magnesium sulfate given orally causes purgation, applied on sprained joints—decreases swelling, while intravenously it produces CNS depression and hypotension.

Environmental factors and Several environmental factors affect drug responses. Exposure to insecticides, carcinogens, tobacco smoke and consumption of charcoal broiled meat are well known to induce drug metabolism. Type of diet and temporal relation between drug ingestion and meals can alter drug absorption.

Time of administration Subjective effects of a drug may be markedly influenced by the setup in which it is taken. Hypnotics taken at night and in quiet, familiar surroundings may work more easily. It has been shown that corticosteroids taken as a single morning dose cause less pituitary-adrenal suppression.

Psychological factor Efficacy of a drug can be affected by patient's beliefs, attitudes and expectations. This is particularly applicable to centrally acting drugs, e.g. a nervous and anxious patient requires more general anaesthetic; alcohol generally impairs performance but if punishment (which induces anxiety) is introduced, it may actually improve performance by relieving anxiety.

Disease: Not only drugs modify disease processes, several diseases can influence drug disposition and drug action. Certain g.i. diseases can alter absorption of orally administered drugs. Similarly liver disease can alter the metabolism of the drug and Kidney disease can alter the excretion of the drug.

Other drugs Drugs can modify the response to each other by pharmacokinetic or pharmacodynamic interaction between them.