

Pharmacodynamics: (Combined Effect of Drugs & Factors affecting action of Drugs)

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Combined Effect of Drugs

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- ✓ When two or more drugs are given simultaneously or in quick succession, they may be either indifferent to each other or exhibit **synergism** or **antagonism**.
- ✓ The interaction may take place at **pharmacokinetic level** or at **pharmacodynamic level**.

I. SYNERGISM: (Greek words "Syn" = together, "ergon" = work)

- ✓ When the action of one drug is facilitated or increased by the other, they are said to be synergistic.
- ✓ In a synergistic pair, both the drugs can have action in the same direction or given alone one may be inactive but still enhance the action of the other when given together.
- ✓ Synergism can be **Additive** or **Supra-additive**.

Synergism

contd...

(i) **Additive:** The effect of two drugs are in the same direction and simply add up i.e.

Effect of drug A + B = Effect of drug A + Effect of drug B

Examples :

Aspirin + Paracetamol = As analgesic antipyretic

Nitrous oxide + Ether = As general anaesthetic.

(ii) **Supra-additive (Potentiation):** The effect of the combination is greater than the individual effects of the components, i.e.

Effect of drug A + B > Effect of drug A + Effect of drug B

Examples :

ACh + Physostigmine = Inhibition of ACh breakdown

II. ANTAGONISM:

- ✓ When one drug decreases or inhibits the action of another, they are said to be antagonistic, i.e.

Effect of drugs A + B < Effect of drug A + Effect of drug B

1. **Physical antagonism:** Antagonism is based on physical property of drugs. i.e. charcoal adsorbs alkaloids and can prevent their absorption. This phenomenon is employed in **alkaloidal poisonings**.

2. Chemical antagonism: The two drugs react chemically and form an inactive product.

Examples-

KMnO_4 oxidizes alkaloids.

Chelating agents (like BAL, CaNa_2EDTA) complex with metals (like As, Pb etc.).

Drugs may react when mixed in the same syringe or infusion bottle. e.g. Thiopentone Na + Succinylcholine chloride.

3. Physiological/ Functional antagonism: Two drugs act on different receptors, or by different mechanisms, have opposite overt effects on the same physiological function i.e. have pharmacological effects in opposite direction.

Examples -

Histamine & adrenaline on bronchial muscles & B.P.

Glucagon and Insulin on blood sugar level.

4. Antagonism by Receptor Block:

- The antagonist interferes with binding of the agonist with its receptor or inhibits the generation of response consequent to such binding.
- It may be competitive or non-competitive.

(a) Competitive antagonism:

(i) Reversible, competitive antagonism:

- Agonist and antagonist compete with each other, because the receptor can bind only one drug molecule at a time.
- At a given agonist concentration, the agonist occupancy will be reduced in the presence of the antagonist.
- However, because the two are in competition, raising the agonist concentration can restore the agonist occupancy (and hence the tissue response).
- Reversible competitive antagonism is the commonest and most important type of antagonism.
- Examples - ACh + Atropine, Morphine + Naloxone.

(ii) Irreversible, non-equilibrium, competitive antagonism:

- It occurs when the antagonist dissociates very slowly, or not at all, from the receptors, with the result that no change in the antagonist occupancy takes place when the agonist is applied.
- This kind of antagonism occurs with drugs which possess reactive groups that form covalent bonds with the receptor.
- **Examples** : Irreversible enzyme inhibitors that act similarly like aspirin, omeprazole, monoamine oxidase inhibitors etc.

(b) Non-competitive antagonism:

- This kind of antagonism describes the situation where the antagonist blocks at some point the chain of events that leads to the production of a response by the agonist.
- Example - Drugs such as verapamil and nifedipine prevent the influx of Ca^{2+} through the cell membrane and thus block non-specifically the contraction of smooth muscle produced by other drugs.

Factors modifying Drug Action

(1) Species variation:

The response of a drug is not uniform among different species.

Examples -

Morphine produces CNS depression in man and dog but excitation in cat.

Rabbits can thrive on Belladonna leaves which are too toxic to other species.

(2) Individual variation:

- A drug at equal doses in similar animals will not produce identical magnitude of the response.
- This is due to normal biological variation between the individuals in a population, as determined by genetic factors.
- This is known as **Idiosyncrasy**. There may be some specific genetic defects which lead to discontinuous variation in drug responses.

(3) Age of the animal:

- Very young (new born) and very old animals are more sensitive to the drug effects than the normal adults.
- In the former, the organs of biotransformation (liver) and excretion (kidneys) are not functionally developed to full capacity.
- These mechanisms are defective in very old animals.
- The renal clearance of drugs in these animals is also poor (low GFR i.e. glomerular filtration rate).
- Young and old animals need relatively low doses of a drug as compared to the adults.

(4) Sex of the animal:

- ✓ Generally female animals are more sensitive to the effects of drugs than the males. This is also true for effects of toxic substances. The relative resistance of males is due to presence of high concentrations of testosterone.
- ✓ Gynaecomastia is a side effect (of ketoconazole, metoclopramide, chlorpromazine, digitalis etc.) that can occur only in men.
- ✓ Ketoconazole causes loss of libido in men, not in women.

(5) Body weight of the animal:

- It indicates the extent of tissues that are exposed to the action of drugs.
- Therefore, the dose of a drug is based on the body weight of the animal.
- While computing dose rates of drugs in ruminants, the weight of rumen contents should be taken in consideration.
- The other conditions such as pregnancy (weight of foetus), oedema (fluid) and fat deposits (obese pigs) also need to be considered.

(6) Route of administration:

- Route of administration governs the speed and intensity of drug response.
- The onset of action following administration of drugs by different routes is in the order :
I.V. > I.M. > I.P. > S.C. > I.D. > oral.
- A drug may have entirely different uses through different routes.
- For instance, MgSO_4 given orally causes purgation, applied on inflamed areas decreases swelling, while intravenously it may produce CNS depression and hypotension.

(7) Time of administration:

- Subjective effect of a drug may be markedly affected 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.

(8) Psychological factor:

- Efficacy of a drug can be affected by patients belief's, attitudes and expectations.
- "Placebo" - A Latin word meaning "I shall please".
- Placebo is an inert substance which is given in the garb of a medicine.
- It works by psychological rather than by pharmacological means and often produces responses equivalent to the active drug.
- A patient responds to the whole therapeutic setting; placebo effect largely depends on the physician - patient relationship.

(9) Drug Interactions:

(A) Pharmacokinetic interactions:

■ Absorption:

- Tetracyclines are not absorbed when given orally with metallic antacids (due to formation of insoluble chelates).
- Adrenaline along with local anaesthetics prolongs the duration of local anaesthesia by causing capillary constriction (delays absorption).

■ Distribution:

- Phenylbutazone, frusemide, digoxin, propranolol, diazepam and quinidine are extensively bound to plasma proteins. If their displacement from protein binding occurs they show intense effects.

■ Metabolism:

- Barbiturates stimulate the metabolism of oral anticoagulant coumarin; and that of DDT and griseofulvin.

■ Excretion:

- Probenecid inhibits renal excretion of penicillin G.

(B) Pharmacodynamic interactions:

- These interactions occur due to the **action of drugs at a common receptor site** or at different sites, resulting in increase or decrease in response of a drug.
- For example, α -adrenergic receptor antagonism by phenoxybenzamine.

(10) General state of health of animal:

- Generally weak and debilitated animals are more sensitive to drug effects than the normal healthy animals.
- The reason being low hepatic glycogen stores in the former, contributing to reduced metabolic capacity of the organ.
- Drugs having high fat affinity may cause toxic effects in lean animals.
- Similarly, fatty and obese animals (pigs) require more doses of a fat soluble drug than that is required for a lean animal in producing identical therapeutic effect. Hepatic and renal diseases increase the intensity and prolong the effects of drugs.

(11) Drug Tolerance:

- It means requirement of higher dose of a drug to produce a given response.
- Tolerance is widely occurring adaptive biological phenomenon.
- Drug tolerance may be natural or acquired.

(A) Natural drug tolerance:

- The individual/ species is inherently less sensitive to the drug.
- Examples:
 - Rabbits are tolerant to atropine (due to the presence of atropinase enzyme).
 - Chicks are tolerant to strychnine (due to underdevelopment of spinal cord in chicken).

(B) Acquired drug tolerance:

- It occurs by repeated use of a drug in an individual who was initially responsive.
- Body is capable of developing tolerance to most drugs, but the phenomenon is very recognized in the case of CNS depressants (e.g. morphine, barbiturate, tranquilizers etc.).
- Tolerance need not develop equally to all actions of a drug.
- Examples are -
 - Tolerance develops to sedative action of chlorpromazine but not to its antipsychotic action.
 - Tolerance occurs to the sedative action of phenobarbitone but not to its antiepileptic action.

Cross tolerance:

- It is the development of tolerance to pharmacologically related drugs.
- Closer the two drugs are, the more complete is the cross tolerance between them.
- For example, there is partial cross tolerance between morphine and barbiturates but complete cross tolerance between morphine and pethidine.

Tachyphylaxis (tachy = fast, phylaxis = protection) :

- When certain drugs are administered at the same dose at frequent short intervals, the response will decrease progressively. This is called as tachyphylaxis.
- However, the response returns to normal magnitude if sufficient gap is given in between two consecutive doses.
- This kind of tolerance is usually seen with indirectly acting drugs, e.g. ephedrine, tyramine, nicotine etc which act by liberating catecholamines in the body, synthesis of which is unable to match release because stores get depleted.

Drug Resistance:

- It refers to tolerance of micro-organisms to inhibitory action of antimicrobials. e.g. Staphylococci to penicillin etc.
- Mechanism of drug tolerance:
 - Pharmacokinetic/ Drug disposition tolerance: Effective concentration of the drug at the active site is decreased, mostly by enhancement of drug elimination on chronic use. For example, barbiturates etc.
 - Pharmacodynamic/ Cellular tolerance: Drug action is lessened, cells of the target organ become less responsive, e.g. morphine, barbiturates, nitrates etc. This may be due to down regulation of receptors (destruction of receptors), weakening of response effectuation or other compensatory homeostatic mechanisms (e.g. antihypertensives).

Thank You

