COMBINED EFFECTS OF DRUGS

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Protocol:

Summation
Additive effects
Synergism
Drug antagonism
EFFECT OF COMBINATION OF DRUGS

Combinations of two/more drugs, simultaneously or in quick succession

1. No interference with each other’s effects.

2. May oppose each other’s actions (antagonism)

3. May produce similar actions on the same organ (synergism)
Drug Synergism
Syn-together; ergon-work
Drug Synergism:

This is facilitation of the effects of one drug by another when given together.

Types:

a. Additive (summation)

b. Supra-additive (Potentiation)
Summation/Addition

Effect of drugs $A + B = \text{Effect of drug } A + \text{Effect of drug } B$

- Final effect is same as the algebraic sum of the magnitude of individuals drugs.
- Side effects do not add up

**Examples of Summation:** Different MOA
- Aspirin: (-) PGsynthesis $\rightarrow$ analgesia +
- Codeine: Opioid agonist $\rightarrow$ analgesia +

**Examples of Addition:** Same MOA
- Ibuprofen: (-) PGsynth $\rightarrow$ analgesia +
- Paracetamol: (-) PGsynth $\rightarrow$ analgesia +
Other **Additive** Drug Combinations

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Effect</th>
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<tr>
<td>Amlodipine + Atenolol</td>
<td>Antihypertensive</td>
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<tr>
<td>Glibenclamide + Metformin</td>
<td>Hypoglycemic</td>
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**Supraadditive (Potentiation)**

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

When two drugs are given together the final effect is much more than the simple algebraic sum of the magnitude of individuals drugs.

**Examples:**

Sulphamethoxazole & Trimethoprim---sequential blockade of two steps in synthesis of folic acid in micro-organisms.
Figure 46–2. Actions of sulfonamides and trimethoprim.
Synergism by altering Pharmacokinetics of the other:

- **Levodopa + Carbidopa**
Other supraadditive drug combinations

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<thead>
<tr>
<th>DRUG PAIR</th>
<th>BASIS OF POTENTIATION</th>
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<tr>
<td>Ach + Physostigmine</td>
<td>Inhibition of breakdown</td>
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<tr>
<td>Adrenaline + Cocaine</td>
<td>Inhibition of neuronal uptake</td>
</tr>
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<td>Tyramine + MAO inhibitors</td>
<td>Increasing releaseable CAT store</td>
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Drug Antagonism
Drug Antagonism

Definition:
Combined effect of two drugs is less than the sum of the effects of the individual drugs

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

One drug decreases / opposes / reverses / counters the effect of other drug by different mechanisms
Types:

a. Pharmacological Antagonism:
   i. Competitive (Reversible)
   ii. Non-competitive (Irreversible)

b. Chemical Antagonism

c. Physiological Antagonism

d. Physical antagonism
Pharmacological Antagonism:

**PHARMACODYNAMIC ANTAGONISM**

**Competitive**
- Reversibly competitive
- Irreversibly competitive
- Pseudo-reversibly competitive

Interfere “Down-stream events”

**Non Competitive**
- Act on “allosteric site”
Competitive Antagonism
D-R interactions

NO EFFECT
 agonist
= Antagonist
= Agonist

= Antagonist
= Agonist

= Antagonist
= Agonist

= Antagonist
= Agonist  = Antagonist
- Agonist

- Antagonist

= Agonist

= Antagonist
Reversible-Competitive

- Weak bond
- Same agonist site
- Short duration
Reversible-Competitive

LDRCshift to R

Conc dependant Dynamic Equilibrium
Competitive (Reversible) Antagonism / Competitive (Equilibrium) Antagonism

1. **Same receptor** by forming **Weak bonds**

2. Maximal response depends on **concentration** of both agonist and antagonist

3. The effect of antagonist can be overcome by increasing the concentration of agonist. The same **maximal response can be attained** by increasing dose of agonist---It is “surmountable antagonism”.

4. Parallel rightward shift of DRC
= Agonist  = Antagonist
Examples: Atropine and Acetylcholine at Muscarinic-R
Naloxone and Morphine at opioid-R
Propranolol and NE at $\beta_2$-R
Irreversibly Competitive or Non-Equilibrium Competitive Antagonism:

1. Have affinity for the same receptor sites and bind in an irreversible manner by covalent bond

2. Effects cannot be overcome even by increasing the concentration of the agonist (unsurmountable)

3. LDR curves of agonist (in presence of antagonist) would show reduced efficacy but unaltered potency
Irreversibly- Competitive

- Same agonist site
- Strong bond
- LDRC flattening efficacy (flatten)
- Long duration
Antagonists: Nonsurmountable (Irreversible)

Effect

log (Dose)

Agonist Alone

+ Antagonist

+ More Antagonist
Effect of antagonists

Competitive antagonist + Agonist

Irreversible antagonist + Agonist
• DOA of irreversible antagonist is longer
• Equilibrium between Antagonist - Agonist cannot be established even after increasing the dose of agonist hence the term “Non-equilibrium competitive antagonism”
• E.g. Dibenamine and NE at $\alpha_1$ adrenoceptors
Pseudo-reversible Antagonism:

• Lesser degree of receptor occupancy by the antagonist & availability of spare receptors
• Increasing conc. of agonist- shift LDR to right
• Increasing conc. of antagonist- reduction in maximal response.
• Hence the term “Pseudo-reversible Antagonism”
Pseudo-Reversible Competitive

- Strong bond
- Spare receptors
- Agonist overcomes antagonist
- Same agonist site
- LDRC
Antagonists: Pseudo-competitive Reversible Competitive

Inc. dose of agonist  log (Dose)
E.g.

Phenoxybenzamine - at $\alpha_1$ adrenoceptor

Methysergide - at 5HT receptor

(5HT receptor blocker)
Non Competitive Antagonism
Non Competitive Antagonism

• Via Allosteric Modulation
• Receptor-Effector pathway modulation
  (Down-stream regulation)

NO Competition for Agonist site
Antagonism through Allosteric receptor site binding:

- Different Receptor site
- DR interaction ineffective
- No Reversal
- LDRC flatten
Antagonism through Allosteric receptor site binding:

i. Binds to site other than the agonist site

ii. Prevent the receptor activation by the agonist

E.g.

- Flumazenil by binding to BZD site antagonises the effects of BZD by preventing the binding of GABA to GABA_{A} receptor

- Bicuculline and BZD
Antagonism through Allosteric receptor site binding:

- GABA binding site
- Channel blocker (Picrotoxin)
- Modulatory Site
- Channel modulators (barbiturates)
- Inverse agonists (β-carbolines)
- Flumazenil (antagonists)
- Benzodiazepines

- Cl⁻
Receptor-Effector pathway modulation (Down-Stream Regulation)
Receptor-Effector pathway modulation (Down-stream regulation)

- NE
  - α₁-R
  - AT₁-R
  - Prazosin Comp. Ant
  - LT₃, DAG
  - Losartan Comp. Ant

- Ca²⁺ Channel blocker (e.g., Nifedipine, non-competitive antagonist)
- Ca²⁺ channel Activation
- Free Ca²⁺ entry
- Vasoconstriction
Effects on log DRC

- There is downward shift. The slope is reduced and maximum response is diminished.
- The parallelism is not maintained.
- No shift of curve on dose axis.
• **Competitive Antagonism (equilibrium or reversible)**
  - Action of agonist is blocked if conc. of antagonist is ≥
  - Antagonism can be overcome by ≥ conc. of agonist
  - Agonist can produce max. response in higher conc.
  - Competitive antagonist shifts $L_{DRC}$ of agonist to right
  - $ED_{50}$ of agonist ≥ in presence of antagonist, e.g., Ach & atropine; Adr & Prop.; Morphine & Naloxone

• **Non-competitive (non-surmountable Antagonist)**
  - Antagonist binds to another site of receptor
  - $L_{DRC}$ is flattened + max. response is ≥
  - e.g. Diazepam and bicuculline
Chemical Antagonism

A type of antagonism where a drug counters the effect of another by simple chemical reaction / neutralization (not binding to the receptor)

1. Protamine sulphate & Heparin
2. Calcium sodium edetate form insoluble complexes with arsenic / lead
3. Neutralization of gastric acid by antacids like Aluminium hydroxide, Magnesium hydroxide, Sodium bicarbonate
Definition:
A type of antagonism in which one drug opposes / reverses the effect of another drug by binding to a different receptor and producing opposite physiological effects.

Examples:
1. Histamine and adrenaline on bronchial muscles and BP
2. Glucagon and insulin on blood sugar level
Physical antagonism

Based on the physical property of drugs e.g. Charcoal adsorbs alkaloids and can prevent their absorption - used in alkaloidal poisonings