PHARMACODYNAMICS III

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B. QUANTAL DOSE–RESPONSE RELATIONSHIPS

the influence of the magnitude of the dose on the proportion of a population that responds.

- These responses are known as quantal responses, because, for any individual, the effect either occurs or it does not.

The desired response is either :

A. Specified in amount or magnitude :

e.g. increase in heart rate of 20 beats/min by a drug that stimulates heart.

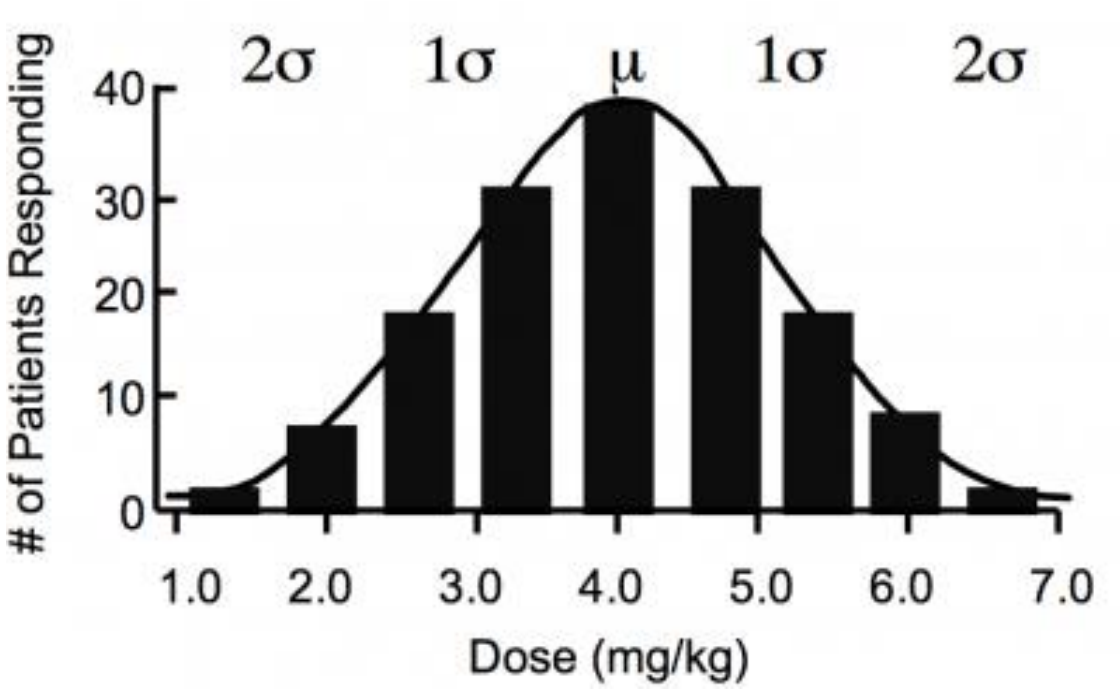
If the recorded response in any individual shows this amount or more, then this is regarded as positive response; otherwise, the response is negative

B. All-or-none response :

e.g. death; prevention of epileptic seizures; prevention of cardiac arrhythmias

- For most drugs, the doses required to produce a specified quantal effect in individuals are lognormally distributed; ie, a frequency distribution of such responses plotted against the log of the dose produces a gaussian normal curve of variation

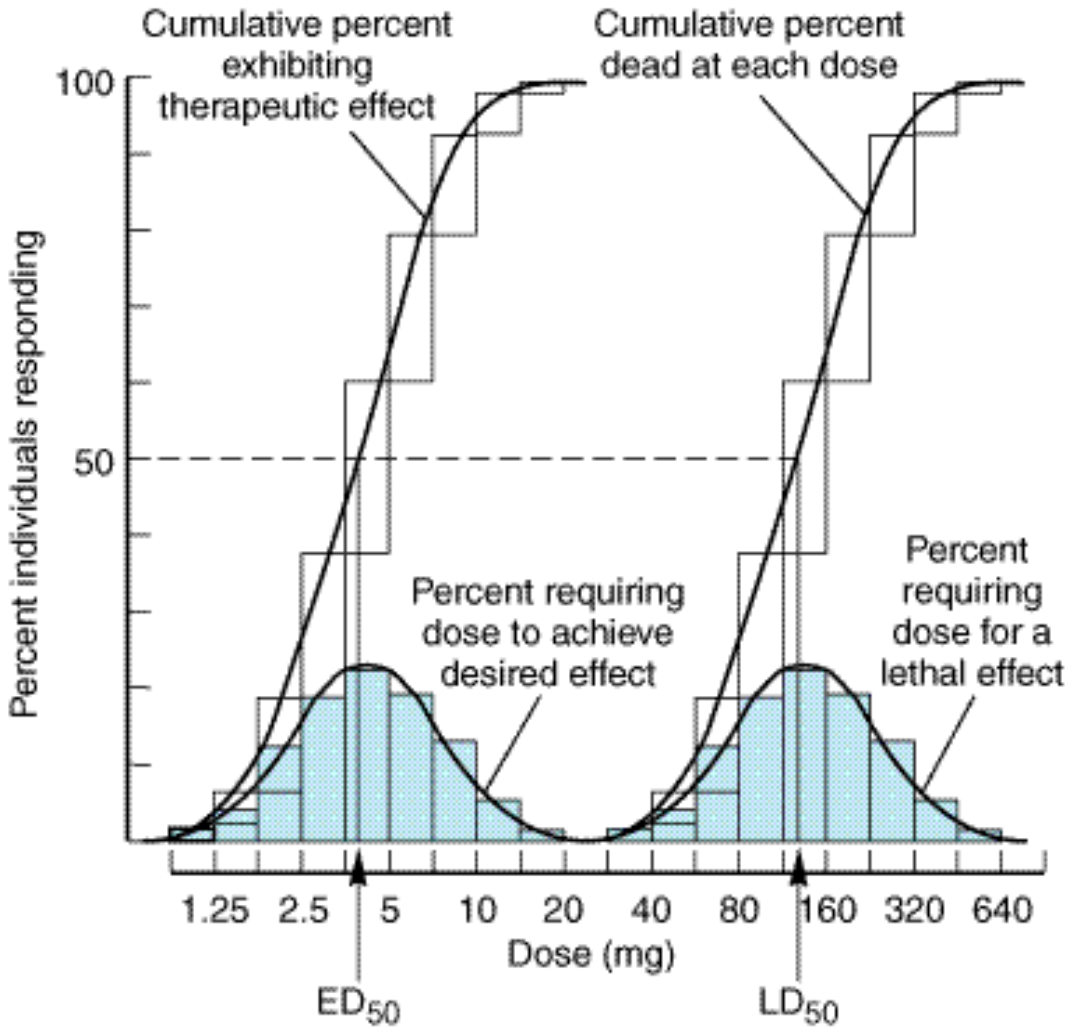
Determines minimum dose at which each patient responded with the desired outcome. The results have been plotted as a histogram, and fit with a gaussian curve. μ = mean response; σ = standard deviation.



- When these responses are summated, the resulting cumulative frequency distribution constitutes a quantal dose-effect curve of the proportion or percentage of individuals who exhibit the effect plotted as a function of log dose

Example:

- At 1.25mg/L, 2% respond, and 2.5mg/L 3% respond,
- Then at 1.25mg/L plot 2%, and at 2.5mg/L plot (2+3 = 5% etc.)



- The quantal dose-effect curve is often characterized by:

1. **median effective dose (ED50):** the dose at which 50% of individuals exhibit the specified quantal effect.

2. **median toxic dose (TD50):** the dose required to produce a particular toxic effect in 50% of Animals.

3. **Median lethal dose (LD50):** the dose required to produce a death in 50% of Animals.

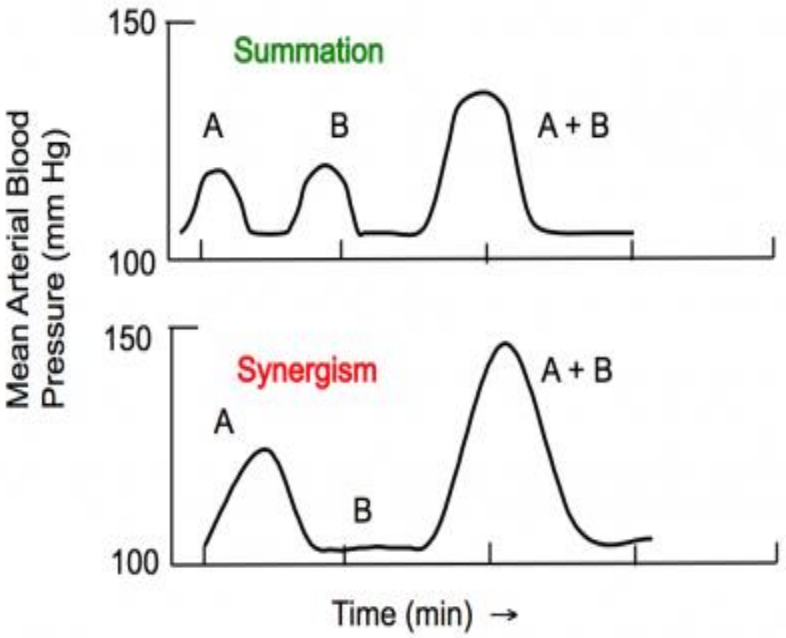
Summation and Potentiation

Two common types of "agonistic" drug interactions are :

1. **Summation:** When two drugs with similar mechanisms are given together, they typically produce **additive** effects.
2. **Potentiation** or **synergism :** if the effect of two drugs exceeds the sum of their individual effects.

➢Potentiation requires that the drugs act at different receptors or effector systems.

Example of potentiation would be the increase in beneficial effects noted in the treatment of AIDS by combination therapy with AZT (a nucleoside analog that inhibits HIV reverse transcriptase) and a protease inhibitor (protease activity is important for viral replication).



PREDICTION OF DRUG SAFETY IN MAN

- This may be obtained from knowledge of **Therapeutic Index (TI)** of drug.

the ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in a population of individuals

$$\mathbf{TI = TD_{50} / ED_{50}}$$

where :

TD_{50} = the drug dose that produces a toxic effect in half the population

ED_{50} = the drug dose that produces a therapeutic effect in half the population.

- A larger value indicates a wide margin between doses that are effective and doses that are toxic.

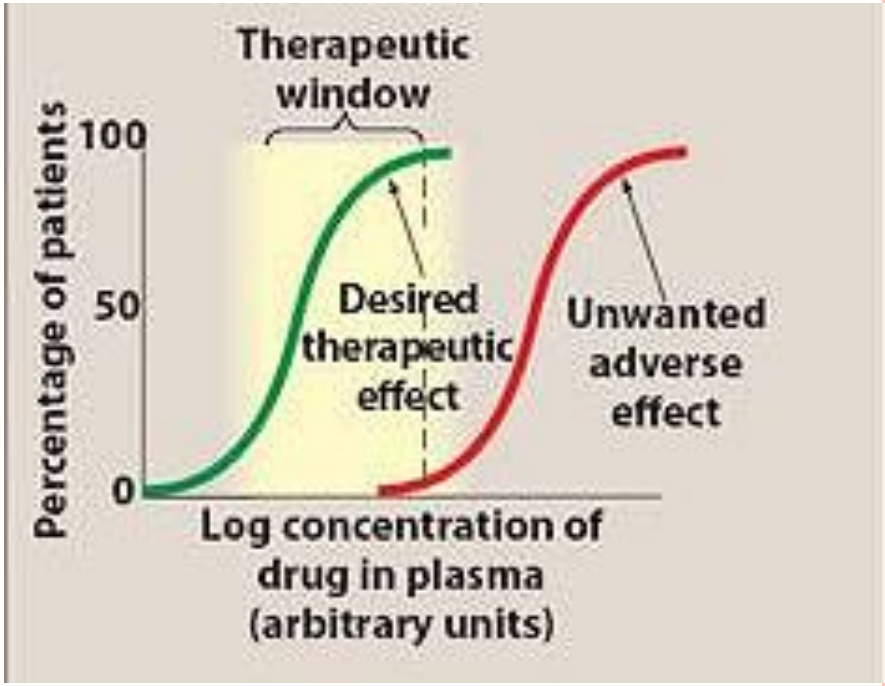
- TI is determined by measuring the frequency of desired response, and toxic response, at various doses of drug.

- In humans, the therapeutic index of a drug is determined using drug trials and accumulated clinical experience. These usually reveal a range of effective doses and a different (sometimes overlapping) range of toxic doses.

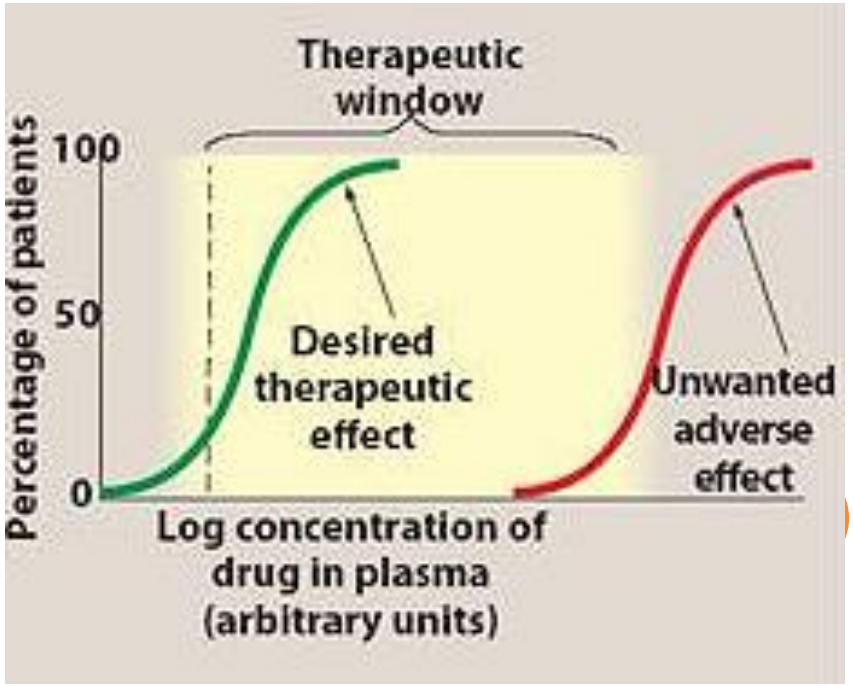
- The concentration range over which a drug produces its therapeutic effect is known as its **therapeutic window**

➢when the therapeutic index is low, it is possible to have a range of concentrations where the effective and toxic responses overlap

➢Agents with a low therapeutic index are those drugs for which bioavailability critically alters the therapeutic effects



➢When therapeutic index is large, it is safe and common to give doses in excess (often about ten-fold excess) of that which is minimally required to achieve a desired response. In this case, bioavailability does not critically alter the therapeutic effects.



Specificity vs. Selectivity

- **Specificity :** If a drug has one effect, and only one effect on all biological systems it possesses the property of specificity.

  a drug that has a particular effect and not another.

- **Selectivity:** refers to a drug's ability to preferentially produce a particular effect and is related to the structural specificity of drug binding to receptors.

  a drug that acts on a particular target (receptor) and not another

- **For example**, a drug binds on a particular receptor-target (so its selective), but that target may be expressed in different tissues and thus may exert different biological effects (so no-specific).

ADVERSE EFFECTS OF DRUGS

These are **unwanted and/or harmful effects**

I. Predictable or dose-related or type A effects :

A. Side effects : These occur at therapeutic doses of a drug. They are usually minor, and decrease or disappear on reducing dose or sometimes with continued use of drug

B. Toxic effects : These are due to large toxic doses . They are usually serious, and need stopping drug use, and sometimes supportive treatment to save life is needed. They may be :

1. **Functional** e.g. respiratory depression OR
2. **Structural :** causing tissue damage e.g. damage to liver or kidney or heart or nerves

II. Unpredictable or Type B reactions :

A. Allergy : This is **due to activation of immune mechanisms by drug**. Drug acts as hapten to induce formation of antibodies by plasma cells or to sensitize T-lymphocytes .

Usually, allergic reactions have no dose-response relation ; they **are of 4 main types :**

Type 1 : Immediate type ; **it is the commonest type** ; **it is mediated by IgE** antibodies **that bind to** membrane of **mast cells in tissues or basophils in blood.**

After re-exposure and binding to their specific antigen, they **trigger release of histamine** and other mediators from granules of these cells.

This causes **urticaria** or , in severe cases , **anaphylactic shock** which is a life threatening emergency

Type 2 : Cyto-toxic reaction :

mediated by either IgM antibodies in plasma or IgG antibodies that causes tissue damage by fixing complement and activating complement cascade

e.g. **hemolysis ; liver or kidney damage** .

Type 3 : Immune complex mediated reaction :

Circulating immune complexes formed between antigen and IgG antibodies which become deposited in capillaries of skin , joints , and kidney. Clinical features occur after many days of exposure to drug e.g. **serum sickness**

Type 4 : Delayed cell-mediated reactions :

These are due to activation of sensitized T lymphocytes which release their cytokines and attract macrophages to site that also release tissue damaging cytokines

B. Idiosyncrasy :

abnormal drug reactions due usually to genetic factors affecting tissue enzymes or receptors.

Examples:

a. Hemolysis by sulfonamides or the antimalarial drug primaquin in patients with genetic deficiency of the enzyme glucose-6-phosphate dehydrogenase (G-6-PD) in their RBC

b. Resistance to vitamin D or to the oral anti-coagulant warfarin

III. Special toxicity including

1. Genotoxicity leading to Mutagenicity :

Alkylating agents

2. Teratogenicity :

Congenital disorder : drugs taken in pregnancy

3. Carcinogenicity : may take about 2 years .

- may be related to mutagenicity but less than is the case with teratogenicity

4. Reproductive toxicity recording pregnancy rate, number of live or stillbirths, & postnatal growth

IV . Others

1. **Delayed toxicity :** occurs sometime after stopping drug use e.g. idiosyncratic aplastic anemia due to chloramphenicol

2. **Chronic toxicity :** occurs with prolonged use of drug e.g. Cushing syndrome from long-term use of steroids

3. **Dependence :** occurs with prolonged use of CNS depressants e.g. alcohol ; opioids like morphine

Adverse effects may be caused by :

1. **Over-extension of same mechanism of action on same target tissue :** e.g. sedative-hypnotics; anticoagulants ; beta-adrenoceptor blockers
2. **Effect on same receptor type but in another tissue :**
   e.g. anti-muscarinic drugs ; beta-blockers
3. **Effect on different receptor or by different mechanism** on target or other tissues

The following groups are more susceptible to adverse drug reactions : foetus during pregnancy; elderly ; patients receiving many drugs (polypharmacy); patients with pre-existing disease ; patients with genetic enzyme defects in liver (poor oxidizers or slow acetylators) or tissues

THANKS