Pharmacokinetic/Pharmacodynamic correlation in Drug therapy

- Most phaimacological responses are due to non covalent interaction between drug and receptor. nature of interaction is assumed to be reversible and conforms to law of mass action.

$$[\text{Drug}] + [\text{receptor}] \rightleftharpoons [\text{Drug-receptor complex}] \rightarrow \text{Response}$$

This scheme explains occupation theory and following assumptions are made.

1. Binding is fully reversible
2. Assumes a single type of receptor binding site which one binding site per receptor molecule.
3. Drug combines with receptor as a bimolecular association and resulting drug receptor complex disassociates as unimolecular entity.

- Basically, 3 types of responses may occur at the receptor:

1. Agonist: elicits maximal pharmacologic response

2. Partial agonist: elicit partial response
3. Antagonist: elicit no response from the receptor but inhibit the receptor interaction of a second agent.

Rate theory:

.States that the pharmacologic response is not depended on drug receptor complex concentration but rather depends on the rate of association of drug and receptor each time a drug molecule hits a receptor, a response is produced.

Rate theory predicts that an agonist will associate rapidly to form a receptor complex, which dissociates rapidly to produce a response. Antagonist associates rapidly to form a receptor drug complex and dissociates slowly to maintain the antagonist response.

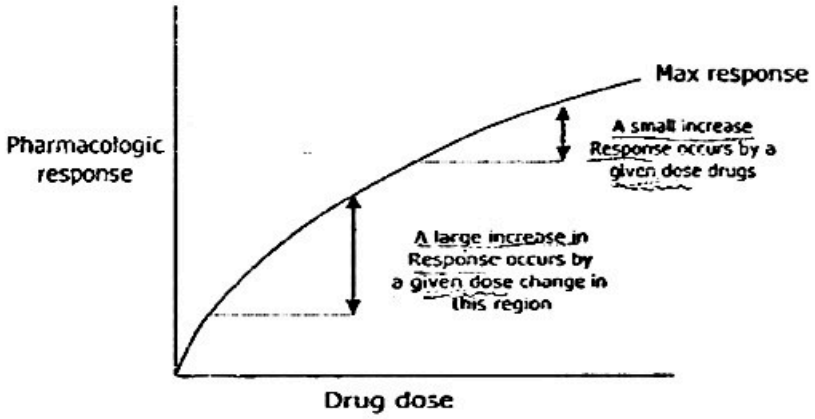
i- Relation of dose to pharmacologic effect:

.Onset intensity and duration of effect depend on

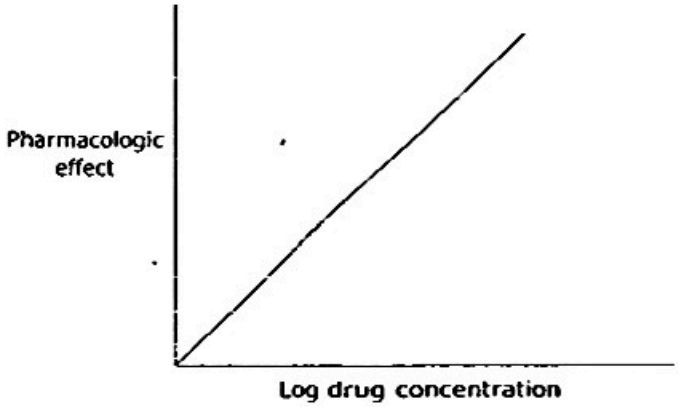
the dose and pharmacokinetics of drug.

-As dose increases, drug concentration at receptor site increases and response increase upto a maximum effect.

- A plot of pharmacologic effect to dose on a linear scale generally results in a hyperbolic curve with maximum effect at plateau.
- **When plotted as log linear scale, results in a sigmoidal curve.**



- **Plot of pharmacologic response versus dose on a linear scale**



- Mathematically, the relationship may be expressed by the following equation.

  E = mLogC+e

  E : Drug effect

  C : Drug concentration

  M : Slope and e-extrapolated intercept

  for Log C yields

$$LogC = \frac{E-e}{m}$$

- **After Iv. dose, the concentration of drug in the body in a one compartment open model is described as follows:**

$$\boxed{Log\,C = Log\,C_0 - \frac{Kt}{2.3}}$$

$$\boxed{\frac{E-e}{m} = \frac{E_0 - e}{m} - \frac{Kt}{2.3}}$$

$$\boxed{E = E_0 - \frac{Kmt}{2.3}}$$

E_0 = Effect at concentration C_0

II – Relation between dose and duration of activity, single Iv injection

- After an Iv dose, assuming one compartment model, the time needed for any drug to decline to a concentration C is given by following equation, assuming the drug takes effect immediate

$$\boxed{t = 2.3\frac{(Log\,C_0 - Log\,C)}{K}}$$

Using C_{eff} to represent the minimum effective concentration, duration of action can be obtained as follows

$$\boxed{T_{eff} = \frac{2.3[Log(D_0/V_0) - Log\,C_{eff}]}{K}}$$

For example, a doubling of the dose will not result in doubling of the effective duration of pharmacologic action. On the other hand doubling of $t_{1/2}$ or corresponding decrease in K will result in a proportion increase in duration of action.

- **Effect of both dose and elimination half life on duration of activity:**

A single equation can be desired to describe the relationship of dose D_0 and the elimination half life ($t_{1/2}$) on the effective time for therapeutic activity (t_{eff}). This expression is derived below

$\ln c_{eff} = \ln c_0 - Kt_{eff}$

$\ln C_{eff} = \ln \left[\frac{D_0}{C_{eff}}\right] - Kt_{eff}$

Substitute $C_0 = D_0/V_D$

$$t_{eff} = \frac{1}{K} \ln \left[\frac{D_0/V_0}{C_{eff}}\right]$$

- Effect of elimination half life on duration of activity:

- Because elimination of drugs is due to the process of excretion and metabolism, an alteration of any of these elimination pruess will effect the thalf of the drug.

Substituting $K = \frac{0.693}{t_{1/2}}$

$$t_{eff} = 1.44\, t_{1/2} \ln \left[\frac{D_0}{V_0 C_{eff}}\right]$$

- Pathophysiologic changes in hepatic and renal function decrease elimination thus prolonging $t_{1/2}$. This in turn will lead to retention of drug in body, thereby increasing duration of activity of drug as well as increasing possibility of drug toxicity.

- To improve the antibiotic therapy with the penicillin

Pharmacodynamics: the study of the biochemical and physiological effects of drugs and the mechanisms of their actions, including the correlation of their actions and effects with their chemical structure. / Study of what the drug does to the body.

and cephalopod clinicians have intentionally prolonged the elimination of these drugs by giving a second drug probenecid which competitively inhibits the renal excretion of the antibiotic.

- Rate of drug absorption and pharmacodynamic response.

Rate of drug absorption influences rate in which drug gets to the receptor and subsequent pharmacologic effect. For drugs that exert an acute pharmacologic effect, usually a directly acting drug agonist, extremely rapid drug absorption may have an intense and possibly delerimental effect.
Eg: Niacin is a vitamin given in large doses to decrease elevated plasma cholesterol and triglycerides. Rapid systemic absorption of Niacin when given as immediate release tablet will cause vasodilation, leading to flushing postural hypotension. Extended release products are preferred because more slowly absorbed niacin allows the baroreceptors to adjust to the vasodilation and hypotensive

effects of drug.

Drug tolerance:

Drug tolerance is a quantitative change in sensitivity of drug and is demonstrated by decrease in pharmacodynamic effect after repeated exposure to same drug. It depends on dose and frequency of drug.

Ex: opaids

Physical dependency:

Appearance of withdrawal symptoms after cessation of the drug.

Ex: Workers exposed to volatile organic nitrates in workplace may initially develop headaches and dizziness followed by tolerance with continuous exposure. After leaving workplace for a few days workers may demonstrate nitrate withdrawal symptoms.

• Drug-receptor theory relating pharmacologic response

-Wanger derived a kinetic expression that relates drug concentration to pharmacologic effect. This theoretical development transformed the semiempirical dose effect relationship into the theoretical equation that relates pharmacologic effect to pharmacokinetic.

• Because equation was developed for a drug receptor with single or multiple drug binding, many drugs, with a sigmoid concentration effect profile may be described by this model. Slope provides some insight into drug receptor interaction.

$$\underset{(Sc)}{\text{Drug}} + \underset{(a-b)}{\text{receptor}} \underset{K_2}{\overset{K_1}{\rightleftharpoons}} \underset{(b)}{\text{drug receptor}} \longrightarrow \text{complex response}$$

a: total number of drug receptors

c: concentration of drug

S: number of moles of drug that combine with one receptor

b: number of drug receptors

$$Db/dt = k_1 C_s (a-b) - bk_2$$

where $k_1 C_s (a-b)$ = rate of receptor complex formation

bk_2 = rate of dissociation of receptor complex

Db/dt = rate of change in number of drug receptor complex

at steady state, $Db/dt = 0$ and equation reduces to:

$$b/a = k_1 C_s / (k_1 C_s + k_2)$$

$$= 1/1 + (k_2 / k_1 C_s)$$

- Forming drugs, the pharmacological response (R) is proportional to the number of receptors occupied.

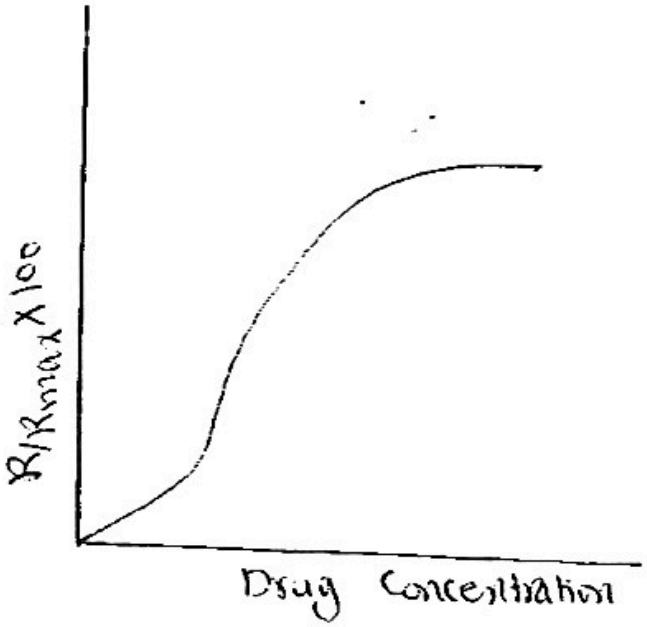
$R \times b/a$

R is related to R_{max}, concentration of drug and rate of change in no. of drug receptor complexes.

$$R = \frac{R_{max}}{1 + \left[\frac{k_2}{k_1 C_s}\right]}$$

- Graph of $R/R_{max} \times 100$, versus concentration of

Drug gives response concentration curve. This is not completely linear over the entire dosage range.



- The total pharmacologic response elicited by a drug is difficult to quantitative in terms of intenity and duration of drug response.
- The integrated pharmacologic response is a measure of the total pharmacologic response and is mathematically expresses as the product of these two factors summed up over a period of time.