بسم الله الرحمن الرحيم

Pharmacodynamics (2)

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2024

Receptor regulation

1- Down-regulation: It is the decrease in number &/or sensitivity of receptors due to prolonged stimulation by agonist.

In some receptors, continued stimulation of the receptors with the same dose of **agonist** results in decreased synthesis of new receptors or a state *desensitization* (also referred to as adaptation, refractoriness).

Clinically, Further administration of agonist will produce little effects (pharmacodynamic tolerance) in all cases of receptor down regulation.

Example of down regulation: **repeated** use of β-2 adrenergic receptor agonists as bronchodilators for treatment of asthma leads to diminished effect due to decrease number and signaling power of the beta 2 receptors.

2- Up-regulation: It is the increase in number &/or sensitivity of receptors due to prolonged inhibition by antagonist.

Prolonged contact of receptors with an antagonist leads to synthesis of more new receptors.

This can explain the worsening of angina pectoris in some patients following sudden withdrawal of a β-adrenergic receptor antagonist after long exposure.

On withdrawal of β-adrenergic receptor blocker; the up-regulated β-adrenergic receptors are excessively stimulated by normal concentration of circulating catecholamines (like adrenaline).

3- The number of certain receptors is regulated by regulatory factors and **hormones** that do not bind to these receptors at all (e.g. thyroid hormone excess in patients suffering from hyperthyroidism causes increase the number of cardiac beta- adrenoceptors).

4- The number and function of receptors can be affected by **diseases** like autoimmune antibodies which destroy the receptor itself or affect the coupling efficiency. Examples: diabetes due to destruction of insulin receptors; myasthenia gravis due to destruction of muscular nicotinic receptors

Drug Tolerance

Following the repeated administration of some drugs, **the intensity of response** may **decrease** during the course of therapy. Tolerance may be:

1- "**pharmacodynamic**" due to downregulation of receptors (examples include beta 2 agonists in treatment of asthma and most addicting drugs). A drug holiday (to stop drug administration for some time) and then to reuse it may solve the problem.

2- "**pharmacokinetic**" tolerance occurs due to increased rate of drug metabolism such as phenobarbital tolerance. In this condition, increasing the dose of the drug is required to get the same response.

When tolerance happens rapidly after the first few doses, is called "**Tachyphylaxis**".

Cross tolerance:

Development of tolerance to a chemically or pharmacologically related drugs; Examples:

- Opioids tolerance (Morphine/heroin).
- Benzodiazepines tolerance (Diazepam/lorazepam)
- Barbiturates tolerance (phenobarbitone/thiopental).
- CNS depressant tolerance (alcohol/ anesthetics/opioids/barbiturates)

Drug intolerance

- It is the great susceptibility to the drug action e.g., low dose of aspirin (1/2 tablet) may be fatal in some asthmatic patients due to intolerance.

Dose-response curve

It is an S-shape curve, and it shows a relation between doses (concentrations) and the corresponding responses using a logarithmic scale. The log scale allows a wider display of doses (concentrations) on the dose (concentration) axis.

Normally we plot data as **response** *versus* **log [Dose]**.

Types of dose response curves

1- Graded (quantitative): measured on a continuous scale: e.g. blood pressure value, blood glucose value, heart rate, etc.

2- Quantal (qualitative): All or non- response. Like occurrence of deaths, convulsions or arrythmias. In this case the response is measured by the percentage of occurrence of these events (e.g., dose 1 caused 10% convulsions, dose 2 caused 22 % convulsions).

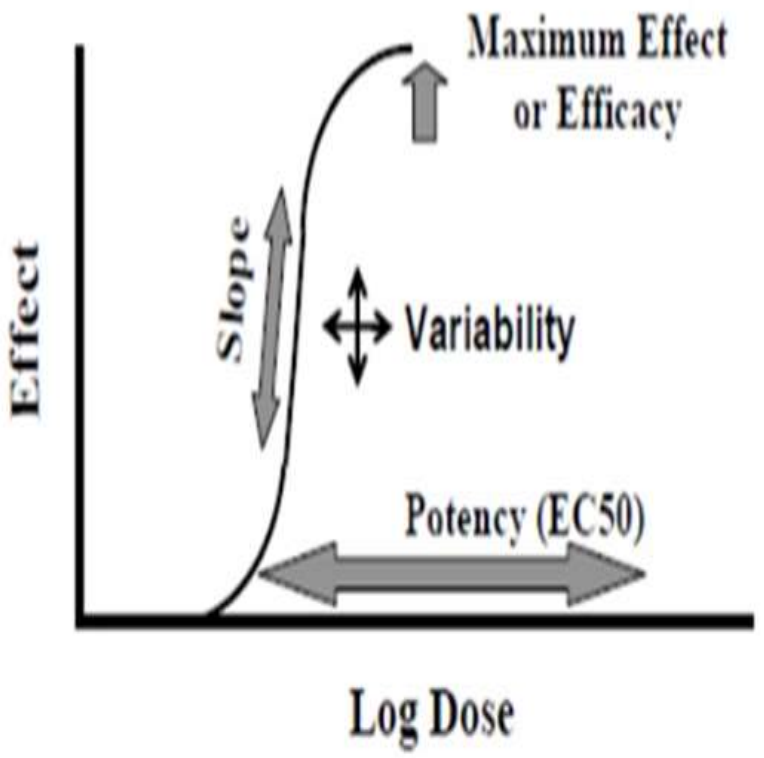
Characteristics of graded dose-response curve

From the graded dose response curve, four characteristic variables can be identified: potency, efficacy, slope and biological variation.

(1) Potency:

- It is represented by the **horizontal axis** of the curve (X- axis, dose axis).
- It depends on the **affinity of the drug to the receptors**.
- The drug is more potent when it gives response in a smaller dose.
- ED_{50} can be used for potency comparison.

Median Effective Dose "ED_{50}": in graded dose response curve, ED_{50} is the dose which produces 50 % of maximum response



Importance of potency:

a) When the potency of a drug is so low, very large dose (which may be not practical) is needed.

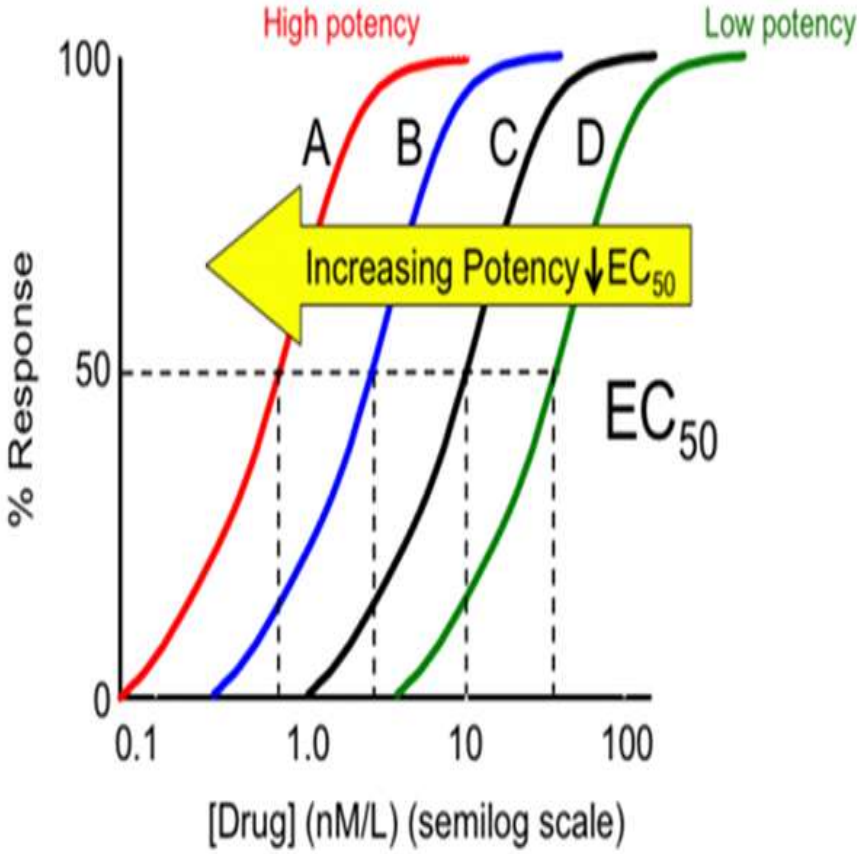
b) When the potency of a drug is so high, any **slight increase** in the dose, can lead to toxicity.

c) In pharmaceutical manufacturer, the production of potent drugs is considered as more economic as it consumes **less amount of the drug**.

Example:

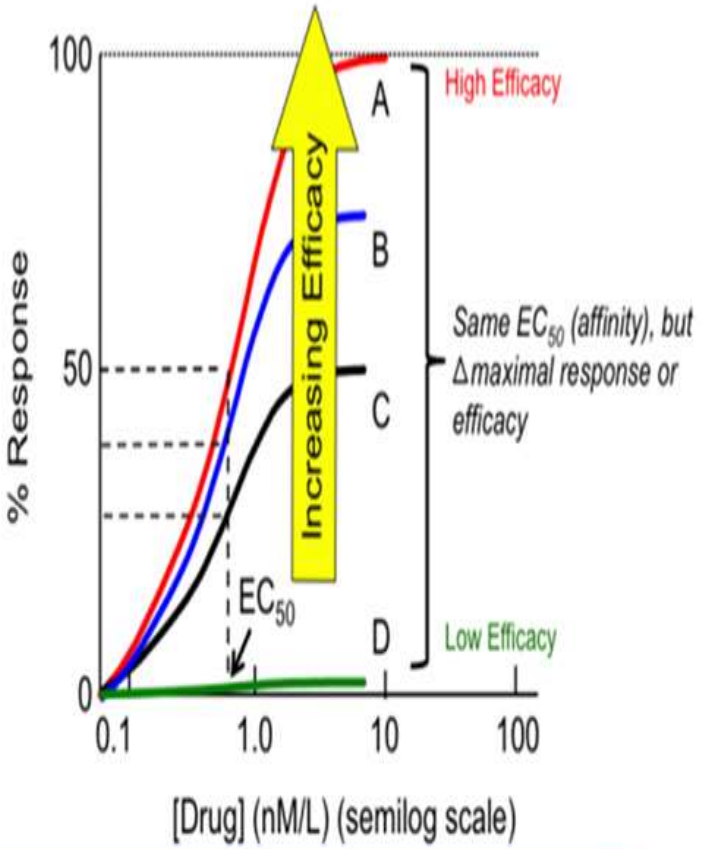
- the median effective dose (ED_{50}) or the median effective concentration (EC50) is used to compare between the potency of different drugs.
- the lower the ED_{50}, the more potent drug.

- Drug A >B>C>D in potency
- EC5 of drug D>C>B>A



2) Efficacy :

- It is the maximal ceiling effect of the drug, after which there is no increase in the response even if the dose is increased (due to full occupancy of the receptors), but toxicity appear.
- It is the most important character of the drug clinically.
- Efficacy depends on the intrinsic activity of the drug.



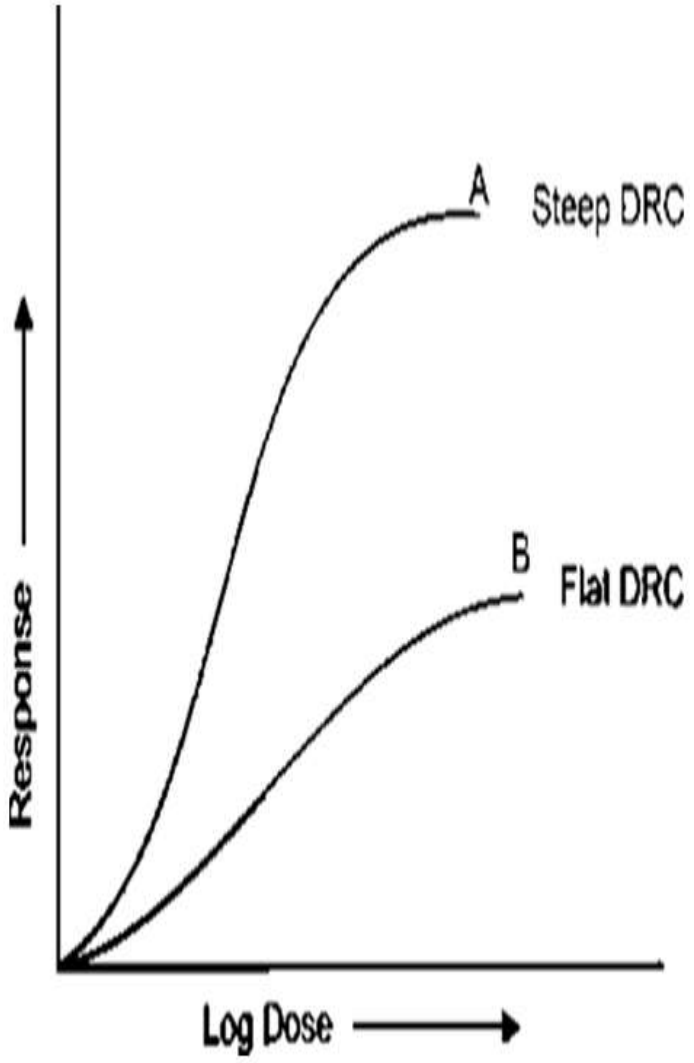
Examples:

i. Morphine can control any type of pain, but aspirin control only mild pain as the efficacy of morphine is higher than that of aspirin.

ii. Furosemide has efficacy higher than thiazide diuretics, so furosemide produces diuresis more than thiazide diuretics.

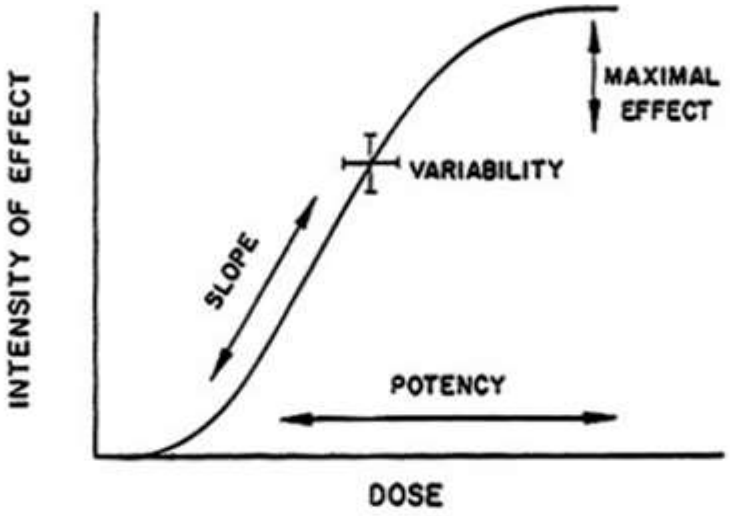
3) Slope:

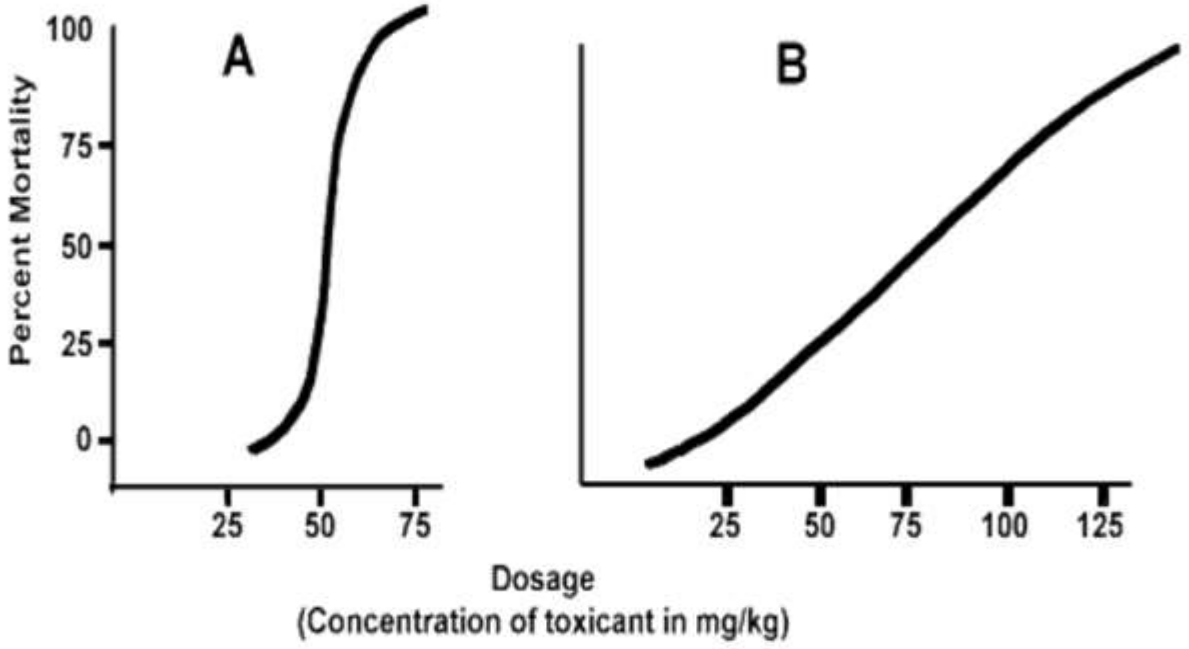
- It is the central linear part of the curve.
- If the drug has steep slope, this indicates that the ratio between the therapeutic dose and the toxic dose of this drug is low (drugs with narrow safety margin).
- If the drug has **flat slope**, this indicates that the ratio between the therapeutic dose and the toxic dose of this drug is high (**drugs with high safety margin**).



Examples:

Barbiturates has steep slope while ***benzodiazepine*** has flat slope, so benzodiazepines are considered safer than barbiturates.


INTENSITY OF EFFECT
MAXIMAL EFFECT
VARIABILITY
SLOPE
POTENCY
DOSE


Percent Mortality
100
75
50
25
0
A
B
25
50
75
25
50
75
100
125
Dosage
(Concentration of toxicant in mg/kg)

4) Variability of Effects:

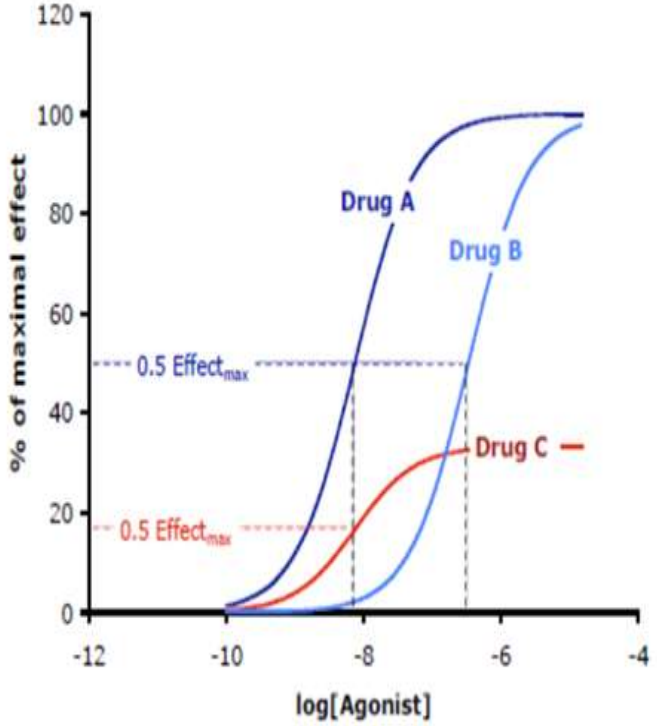
- Variability is another characteristic of the dose response curve, along with slope, efficacy and potency.
- A given drug at a given dose level will have different effects on different individuals and different effects on the same individual at different times.
- Causes of variability includes age, sex, race, co-medical conditions, past drug use, time of day, menstrual cycle, other drugs taken, etc.

Summary of graded dose response curve

1. ***Potency:*** *a comparative measure which refers to the different doses of two drugs needed to produce the same effect. For comparison of potency, ED50 is used.*
2. ***Efficacy:*** *is the maximum effect (Efficacy) of a drug. For comparison of efficacy, the maximum ceiling effects are compared.*

3. Slope: *The slope of the central linear part of the curve. When the slope is steep, it means that the ratio between the therapeutic dose and toxic dose of the drug is low i.e., the drug has a narrow margin of safety.*

4. Variability of effects *among different or the same individual at different tomes.*



Demonstration of different potencies of drugs (A,B,C) that produce the same effect. In this figure, Drugs A & B have the same efficacy. Drug A has greater potency than B or C because the dose of B or C must be larger to produce the same effect as A. Although Drug C has lower efficacy than B, it is more potent than B at lower drug concentrations.

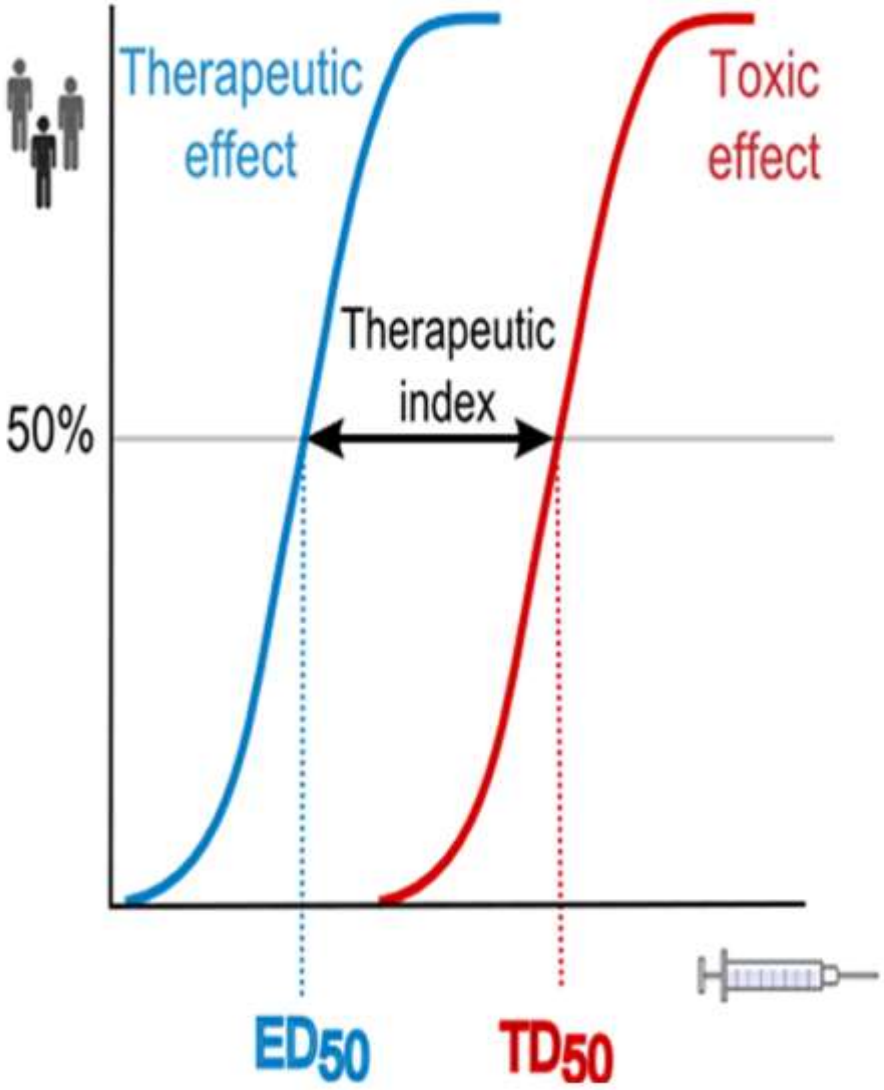
2- Quantal dose response curve

All or non- response are measured in percentage. Like occurrence of deaths, convulsions or arrythmias. It is used to determine the dosage causing toxicity and lethality to experimental animals.

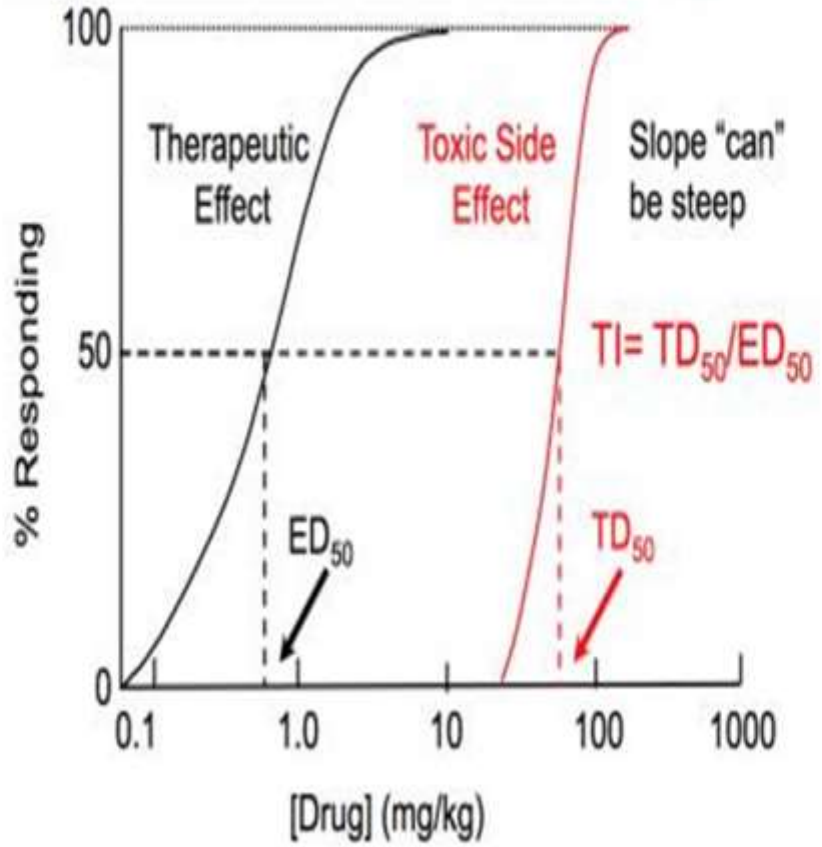
- Median effective dose (ED50) of quantal response = dose which produce a specific response in 50% of population.
- Median Toxic dose (TD50) = dose which produce a specific toxicity in 50% of experimental animals.
- Median lethal dose (LD50) = dose which produce death in 50% of experimental animals.

Therapeutic index (TI)

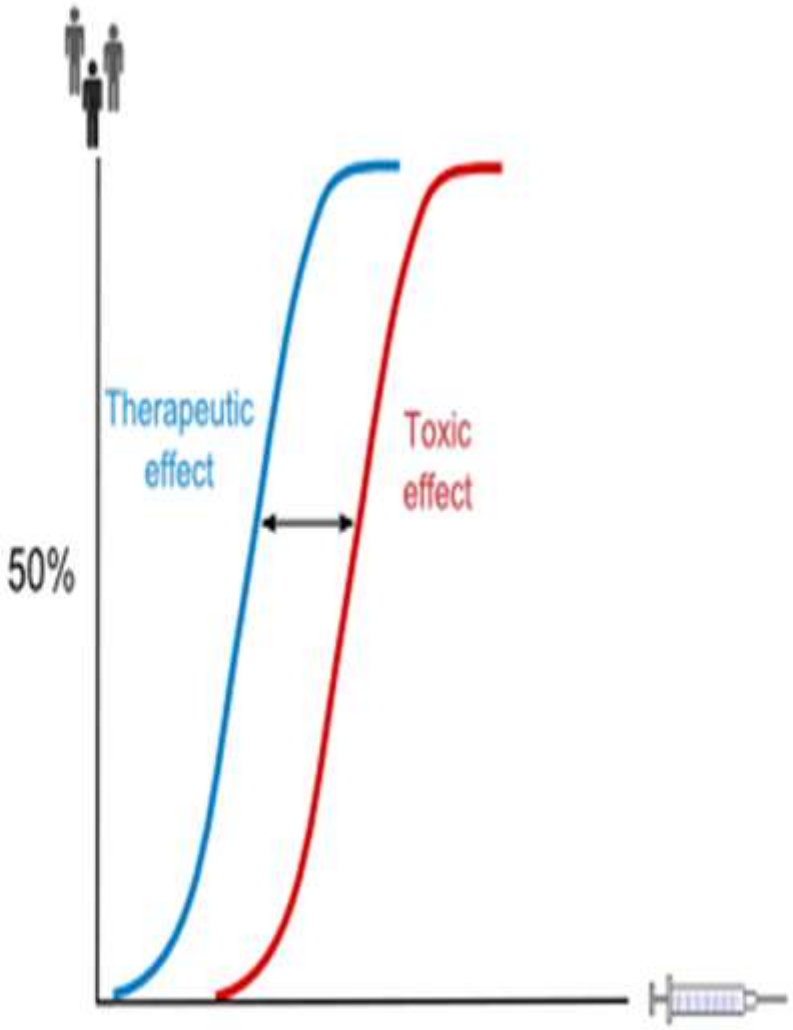
- Therapeutic index (TI) is a quantitative measurement of the relative safety of drugs.
- It is the ratio of TD50 or LD50 to ED50.
- TI = *TD*50 / *ED*50
- ***Therapeutic index should be greater than 1.***
- ***If TI =1; the drug is a poison***


Therapeutic effect
Toxic effect
Therapeutic index
50%
ED50
TD50

Drug Safety - Therapeutic Index



Narrow TI



Generally, a drug or other therapeutic agent with a narrow therapeutic range (i.e., having little difference between toxic and therapeutic doses) may have its dosage adjusted according to measurements of the actual blood levels achieved in the person taking it. This may be achieved through therapeutic drug monitoring (TDM) protocols.

Medication with a small therapeutic window must be administered with care and control, frequently measuring blood concentration of the drug, to avoid harm. Medications with narrow therapeutic windows include **digoxin**, **lithium**, **aminoglycosides**, **immunosuppressive** drugs, **antiepileptic** drugs, some **anticancer** drugs and **warfarin.**


Thank
you