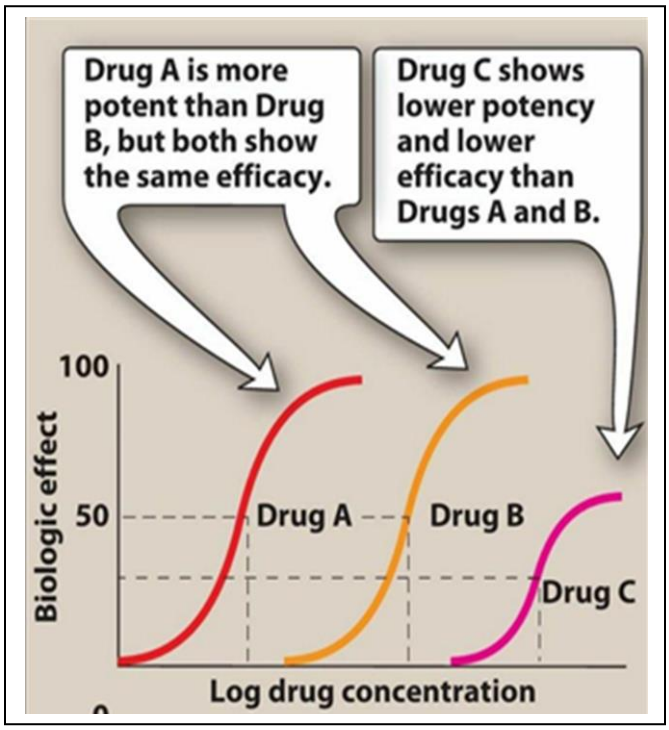
Relation between drug dose and clinical response:

1/ Graded Dose–Response Relationships

The pharmacological effect of a drug depends on its concentration at the site of action, which, in turn, is determined by the dose of the drug administered. Such a relationship is called ‘dose–response relationship ’.
As the concentration of a drug increases, its pharmacologic effect also gradually increases until all the receptors are occupied (the maximum effect). Plotting the magnitude of response against increasing doses of a drug produces a graded dose–response curve. Two important drug characteristics, potency and efficacy, can be determined by graded dose–response curves.

1. Potency: The amount of a drug required to produce a desired response is called the potency of the drug. The lower the dose required for a given response, the more potent is the drug. For example, the analgesic dose of morphine is 10 mg and that of pethidine is 100 mg. Therefore, morphine is ten times more potent than pethidine as an analgesic.

2. Efficacy: Efficacy is the magnitude of response a drug causes when it interacts with a receptor. Efficacy is dependent on the number of drug–receptor complexes formed and the intrinsic activity of the drug (its ability to activate the receptor and cause a cellular response). Efficacy is a more clinically useful characteristic than potency, since a drug with greater efficacy is more therapeutically beneficial than one that is more potent.



2/ Quantal Dose–Response Relationships: Another important dose–response relationship is that between the dose of the drug and the proportion of a population of patients that responds to it. These responses are known as quantal responses. Quantal dose–response curves are useful for determining doses to which most of the population responds. They have similar shapes as log dose–response curves, and the ED_{50} is the drug dose that causes a therapeutic response in half of the population.

Therapeutic index:

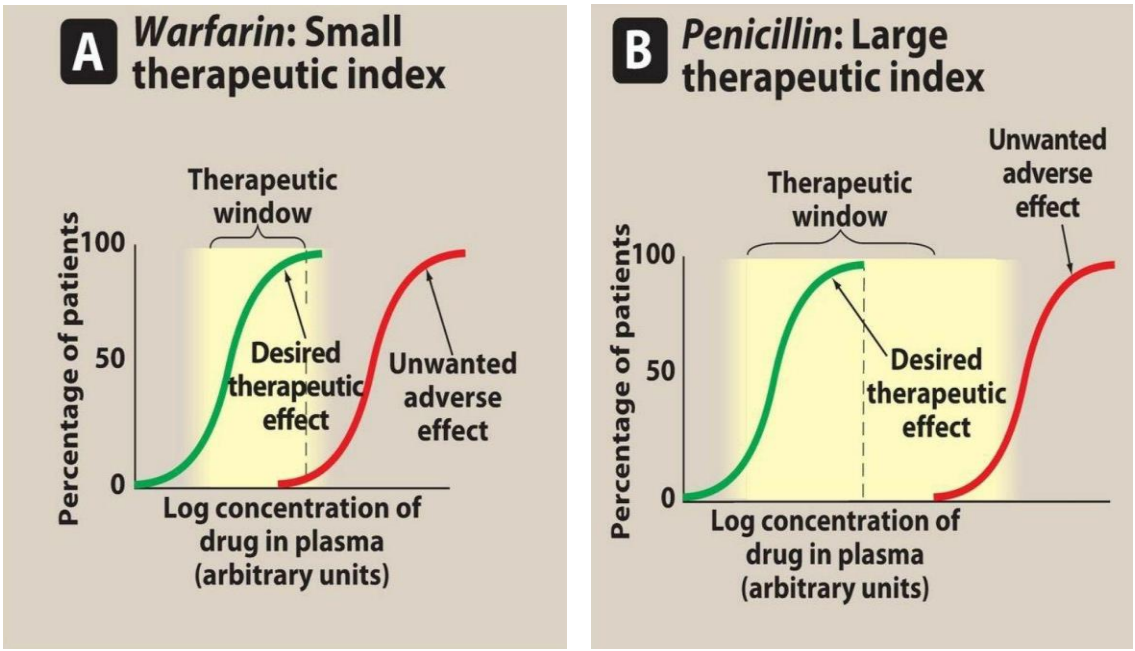
The therapeutic index (TI) of a drug is the ratio of the dose that produces toxicity in half the population (TD_{50}) to the dose that produces a clinically desired or effective response (ED_{50}) in half the population:

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

The TI is a measure of a drug's safety, because a larger value indicates a wide margin between doses that are effective and doses that are toxic.

A. Warfarin (example of a drug with a small therapeutic index).

B. Penicillin (example of a drug with a large therapeutic index).

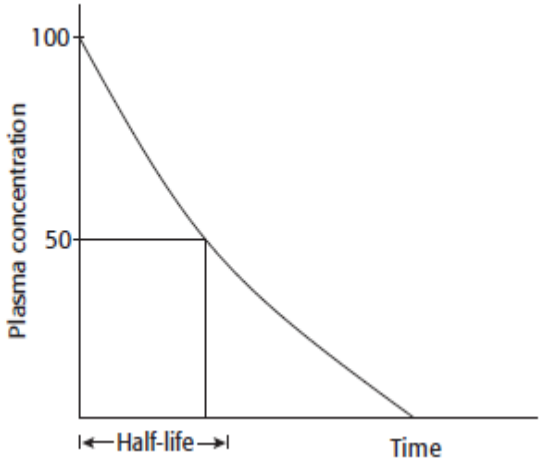


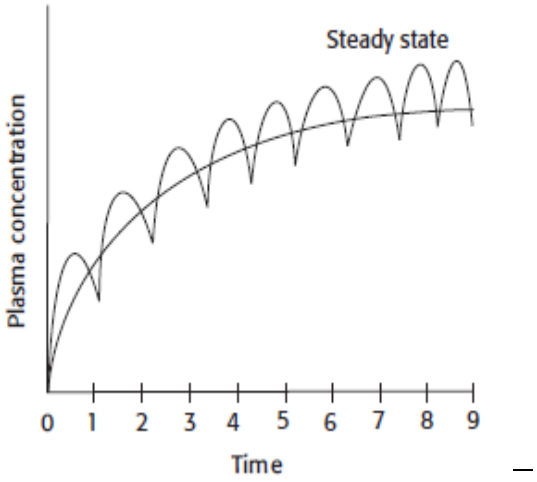
Half-life ($t_{1/2}$): It is the time required for the plasma concentration of the drug to decrease by 50% of its original value.

Clinical Importance of Plasma Half-life:

It helps to:

1. Determine the duration of drug action.
2. Determine the frequency of drug administration.
3. Estimate the time required to reach the steady state. At **steady state**, the amount of drug administrated is equal to the amount of drug eliminated in the dose interval. It takes approximately four-to-five half-lives to reach the steady state during repeated administration of the drug. A drug is almost completely eliminated in four-to-five half-lives after single administration.





Volume of distribution V_d: is defined as the theoretical volume of body fluid into which a drug is uniformly distributed at a concentration equal to that in plasma, assuming the body to be a single compartment.

$$V_d = \frac{\text{Total amount of drug in the body}}{\text{Concentration of the drug in plasma}}$$

V_d reflects the extent to which the drug is present in the extravascular tissue but not in plasma. Lipid solubility can affect V_d , as highly lipid soluble drugs have good cell penetration, resulting in high V_d. Plasma-protein binding, particularly to albumin reduces the V_d , while tissue binding increases it.

Drug clearance: Clearance (CL) estimates the volume of plasma from which the drug is cleared per unit of time. Total CL is a composite estimate reflecting all mechanisms of drug elimination and is calculated as follows:

$$CL = 0.693 \times V_d / t_{1/2}$$

The three major routes of elimination are hepatic metabolism, biliary elimination, and urinary excretion. [Note: Elimination is irreversible removal of drug from the body. It involves biotransformation (drug metabolism) and excretion. Excretion is removal of intact drug from the body.] Together, these elimination processes decrease the plasma concentration exponentially. That is, a constant fraction of the drug is eliminated in a given unit of time. Metabolism results in products with increased polarity, which allows the drug to be eliminated.

Factors affecting half-life $t_{1/2}$:

1. Volume of distribution (Vd) : half-life will increase as V_d increases.
2. Clearance (CL): half-life will increase as CL decreases.

Clinical situations resulting in changes in drug half-life:

When a patient has an abnormality that alters the half-life of a drug, adjustment in dosage is required.

- Patients who may have an **increase** in drug half-life include those with:

1) diminished renal or hepatic blood flow, for example, in cardiogenic shock, heart failure, or hemorrhage;

2) decreased ability to extract drug from plasma, for example, in renal disease;

3) decreased metabolism, for example, when a concomitant drug inhibits metabolism or in hepatic insufficiency, as with cirrhosis.

These patients may require a **decrease in dosage or less frequent dosing intervals**.

- In contrast, the half-life of a drug may be **decreased** by:

1)increased hepatic blood flow,

2) decreased protein binding,

3) increased metabolism.

This may necessitate **higher doses or more frequent dosing intervals.**