# Basic concepts and processes in Pharmacology
Therapeutic Drug Monitoring

Plasma Drug Levels :There is a direct relation between plasma drug levels and drug response, therefore clinicians frequently monitor plasma drug levels in efforts to regulate drug responses. When measurements indicate that drug levels are inappropriate, these levels can be adjusted up or down by changing dosage size, dosage timing, or both.

Plasma Drug Levels are of special importance:

- Minimum effective concentration
- Therapeutic concentration
- Toxic concentration.
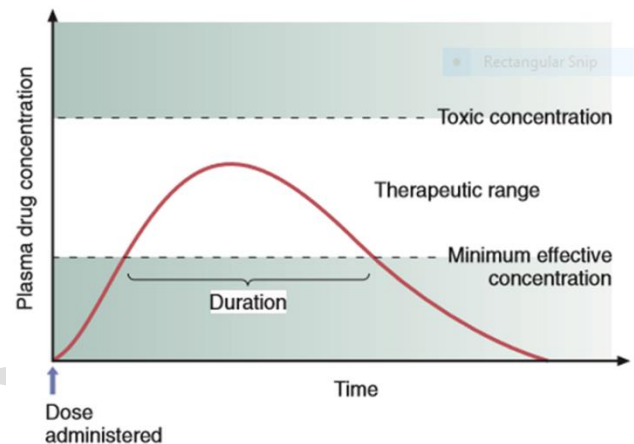
- **Minimum Effective Concentration** (MEC) defined as the plasma drug level below which therapeutic effects will not occur.
- A drug must be present in concentrations at or above the MEC to produce a therapeutic effect.
- **Toxic concentration:** the plasma drug level at which toxic effects begin. Toxicity occurs when plasma drug levels climb (raise) too high. Doses must be kept small enough so that the toxic concentration is not reached.
- Toxic concentrations may result from a single large dose, repeated small doses, or slow metabolism that allows the drug to accumulate in the body.
- **Therapeutic concentration:** The plasma drug concentration between the minimum effective concentration and the toxic concentration (also called the **therapeutic range** of the drug**)**.
- These values have great clinical significance.
- When plasma drug levels are within the therapeutic range, there is, enough drugs present to produce therapeutic responses but not so much that toxicity results. The goal of drug therapy is to maintain plasma drug levels within therapeutic range.

Therapeutic Index and Drug Safety

Therapeutic index (TI): is a value representing a drug's safety or drug's margin of safety = the relationship between therapeutic effects of a drug and its adverse effects and determined by the degree between: Therapeutic dose and toxic dose.

TI was frequently determined as lethal dose of a drug in 50% of the animals tested (LD_{50}) or Toxic dose – dose that will produce toxicity in 50% of a group of patients tested (TD_{50}) divided by the effective dose for 50% of a group tested (ED_{50}).

$$\text{Therapeutic index} = \frac{\text{median } TD_{50} \text{ or } LD_{50}}{\text{median } ED_{50}}$$

- Margin of safety → serum drug concentration within therapeutic range.

Drugs with a <u>narrow or low therapeutic index</u> have a narrow margin of safety – potentially danger – small safety range between an effective dose and a toxic one, therefore, drug dosage might need adjustment, and plasma (serum) drug levels need to be monitored.

On the other hand, a drug with <u>a high therapeutic index</u> has a wide margin of safety – safe drug – and poses less risk of toxic effects. Therefore plasma (serum) drug levels do not need to be monitored routinely.

The larger the TI, the safer a drug

E.g., Penicillin has a large TI, therefore therapeutic monitoring is not needed, whereas warfarin or digoxin that has a low or small TI and must have accurate therapeutic monitoring.
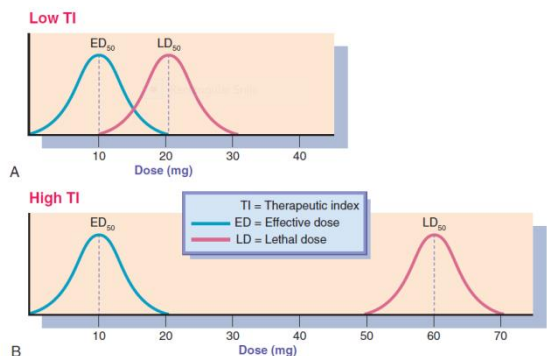
FIGURE 1–11 A, Low therapeutic index drug has a narrow margin of safety, and the drug effect should be closely monitored. **B,** High therapeutic index drug has a wide margin of safety and carries less risk of drug toxicity.

In clinical practice, measuring serum drug levels is useful in several circumstances:
1) When drugs with a low or narrow therapeutic index are given. These are drugs with a narrow margin of safety because their therapeutic doses are close to their toxic doses (e.g., digoxin, aminoglycoside antibiotics, lithium, and theophylline).
2) To monitor unexpected responses to a drug dose. This could be either a lack of therapeutic effect or increased adverse effects.
3) When a drug overdose is suspected

Drug half-life (t_{1/2}) is defined as the time required for the amount of drug in the body to decrease by 50% (a percentage – not a specific amount – of drug is lost during one half-life).

A few drugs have half-lives that are extremely short—on the order of minutes. In contrast, the half-lives of some drugs exceed 1 week.

Drugs with short half-lives leave the body quickly. Drugs with long half-lives leave slowly.

Knowledge of the drug half-life is important in planning the frequency of dosing (dosing interval – how much time separates each dose).

A drug with a short half-life requires more frequent administration. Conversely, if a drug has a long half-life a long time can separates doses without loss of effects.

Plasma drug levels change over time

Onset of drug action: when the therapeutic effect or drug action is actually starts and its determined by the rate of absorption and route of drug administration.

After administration of a single dose of an oral medication, the plasma drug levels rise as the medicine undergoes absorption. The drug level continues to climb as more of the drug is absorbed, until it reaches **peak drug level –** the highest plasma concentration of drug at a specific time (maximum therapeutic response has been achieved).

Then drug levels decline as metabolism and excretion eliminate the drug from the body. Unless another drug dose is given **trough drug level is reaches** the lowest plasma concentration of a drug (drug action stops).
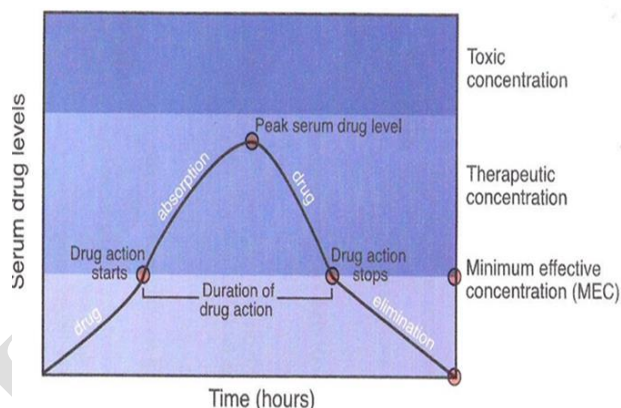

The duration of action is the length of time that the drug produces its therapeutic effect – how long drug effects will persist and is determined largely by the combination of metabolism and excretion.

When a patient takes repeated doses, the drug will continue to accumulate until a **steady state or plateau** has been achieved – in which the amount of drug eliminated between doses equals the amount administered. Theoretically, it takes approximately four half-lives to reach this equilibrium.

The plateau may be reached faster by administration of loading doses followed by regular maintenance doses (repeated doses) .

A **loading dose:** Initial high dose (often maximum dose) used to "prime" the bloodstream with a sufficient level of drug (often followed by a series of lower maintenance doses).

Maintenance doses: Doses required to keep the drug blood level at a steady state in order to maintain the desired effect.

Drug action in relation to serum drug levels with repeated doses.
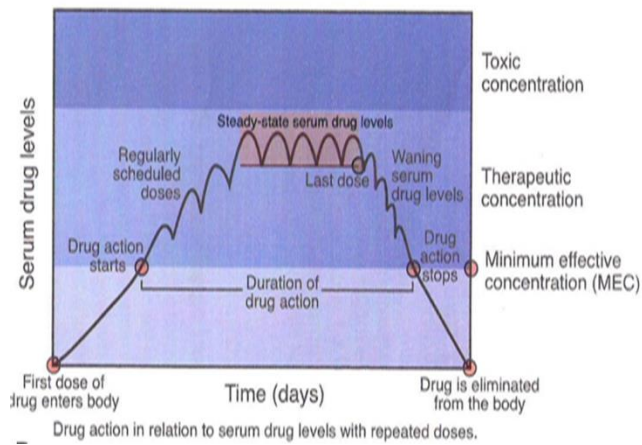
- Loading doses allow a therapeutic drug level to be reached rapidly.
- Repeated dosing allows a plateau drug plasma level to be reached.
- When drug administration is discontinued, most (94%) of the drug in the body will be eliminated over four half-lives.