Pharmacology

Modified slides No. 6 (week 3 / Lec. 2)

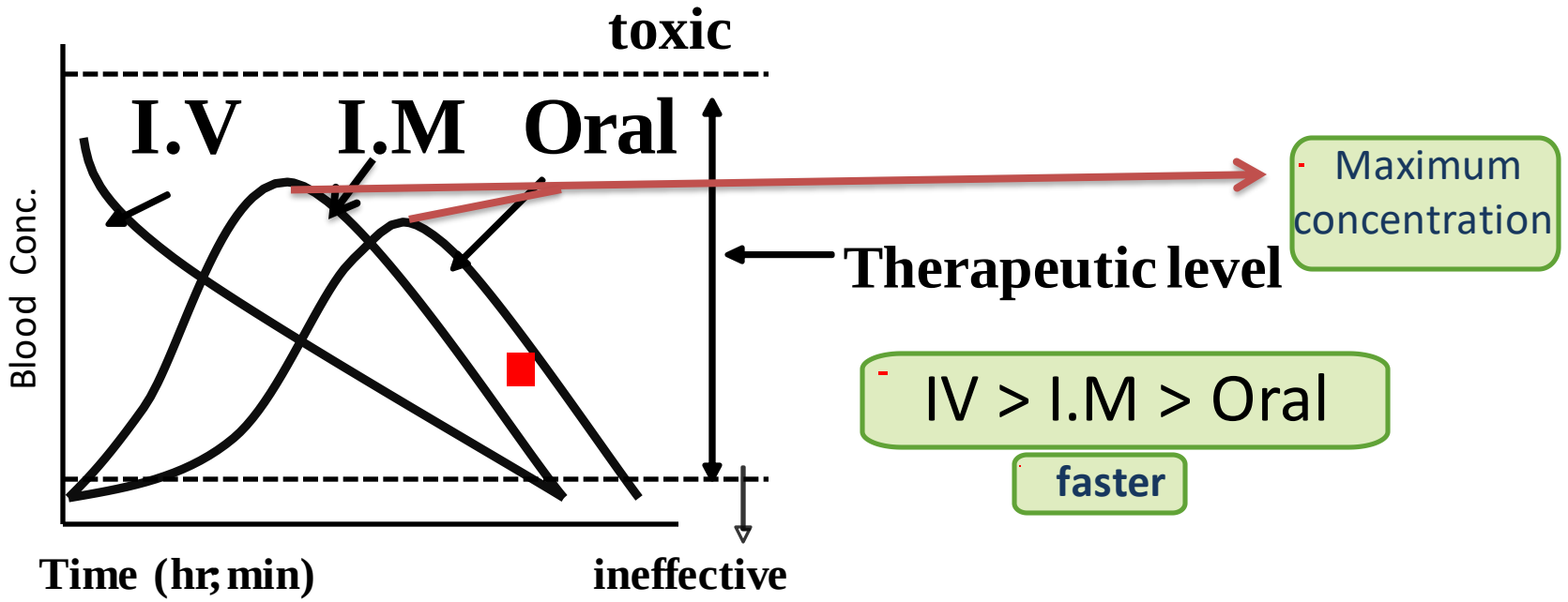
Writer :الفريق العلمي-طوفان الاقصى

Corrector:الفريق العلمي-طوفان الاقصى

Quick review

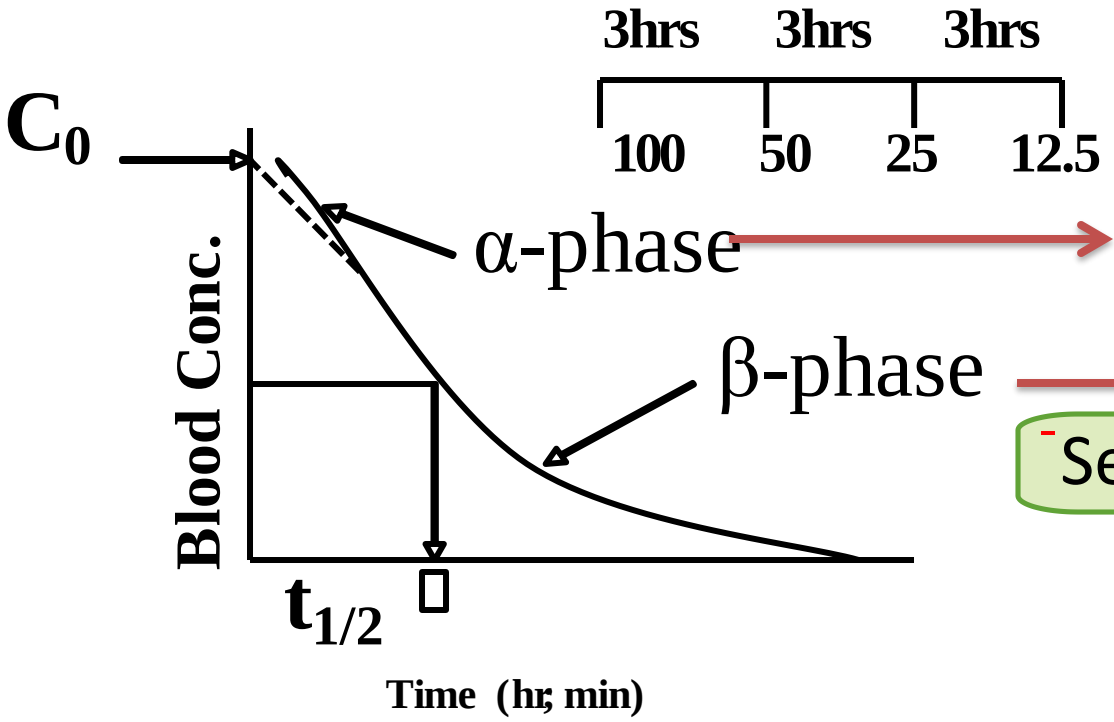
- In the previous lecture we talked about the last steps of pharmacokinetics (Metabolism & Elimination)
- When we discuses pharmacokinetics we answer many questions like how frequency should the drug be given and when?etc...
- In this lecture we are going to discuses some important concepts that is related to it

- This graph shows the relationship between concentration of the drug in the blood and time (depending on the type of ADMINISNTRATION)
- in oral administration: the drug's concentration will increase in the blood as a result of the absorption of the drug until all of its bioavailable dose is absorbed so it reaches its highest concentration (the peak)
- The cause of the initial decrease (fall) of concentration is mainly due to distribution (which means the movement of the drug from the blood to the intended tissue)



- Further decrease in blood concentration is due to excretion (+- metabolism if the drug needed metabolism in order to be excreted)
- Of course we need the drug to be in the therapeutic level (less —> ineffective) (Higher —> toxic level)
- Drug monitoring : MEASURING the drug concentration in the blood to decide the suitable dose **(MAKE SURE THAT THE DRUG IS STILL IN THE THERAPEUTIC LEVEL)**
- Of course there are other routes of administration but **THE ONLY** one that reach its highest concentration at time zero is (IV) **(it does not need to be absorbed- all drug enter the circulation directly)**

IV Administration



Distribution

Secretion & metabolism

- From the previous curve you can measure what is known of **t1/2 life** (the time it takes for the amount of a drug's active substance in your body to reduce by half (decrease by 50%))

  100 -> 50 -> 25 -> 12.5

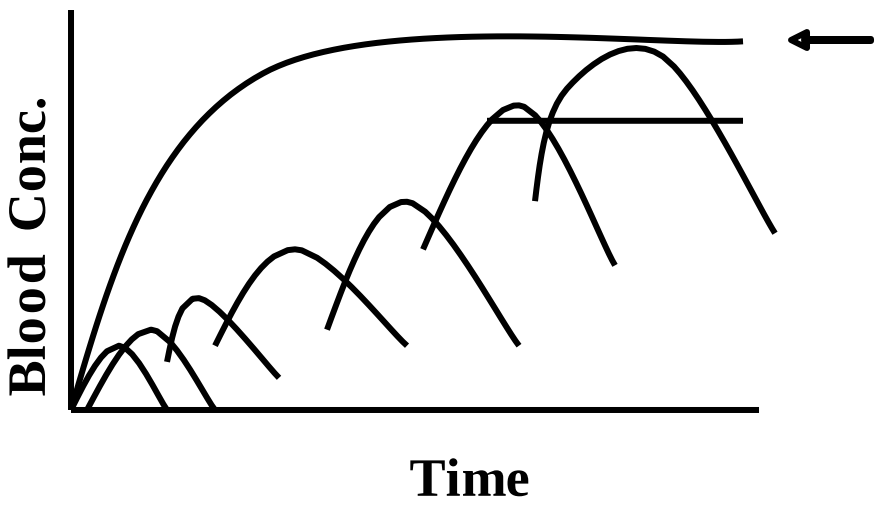
  t1/2 t1/2 t1/2

- **More lipid solubility —>more AVD —> high t1/2**
- **More protein binding —> t1/2 increases**

- **Remember : K e=×0.693/t1/2(min)**

Steady state level (chronic administration)

With chronic or repeated administration the amount of drug in the blood accumulates until it reaches the plateau (steady state level — > The amount of drug given = the amount that is eliminated) STILL WITHIN THERAPEUTIC LEVEL



Plateau

input=output

Reached after 5 $t_{1/2}$ lives

Loading dose (initial large dose) followed by maintenance dose e.g. digitalization...etc

For your information / not required

Steady state level could be calculated from this equation:

$$Cp = \frac{f \cdot D}{AVD \cdot K_e \cdot T} = 1.44 \times \frac{f \cdot D}{AVD} \times \frac{T_{1/2}}{T}$$

Cp = Average steady state plasma conc. of drug

f = fraction of dose absorbed; bioavailable fraction

D = dose of given drug

K_e = first order reaction rate constant

AVD = apparent volume of distribution

T = time interval between doses

$T_{1/2}$ = biological half-life

1.44 = 1/0.693

Trough and peak drug levels:

Used to establish the effectiveness of a drug

Trough: is the lowest drug level that is needed to reach therapeutic range (1 hr. to half hr. before the next dose)

Peak: is drawing the serum blood levels (30 min parenteral; 1-2 hr oral) after the drug is administered range (1 hr. to half hr. after the last dose)

Trough is drawing the serum blood levels right (30 min-1 hr) before the next dose

(If trough or peak levels are > than normal, the patient is at risk for adverse effects)

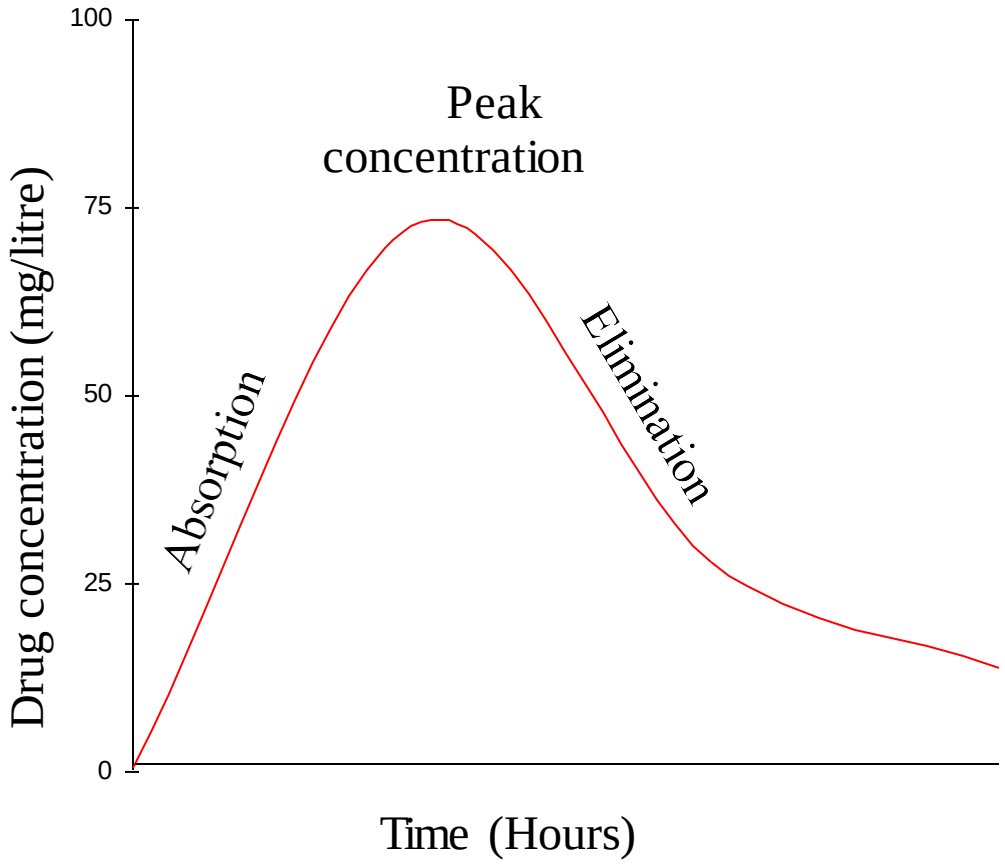
Before giving the next dose to reach the steady state level we should measure the trough dose and make sure it is in the therapeutic level

Problems that will affect the peak:

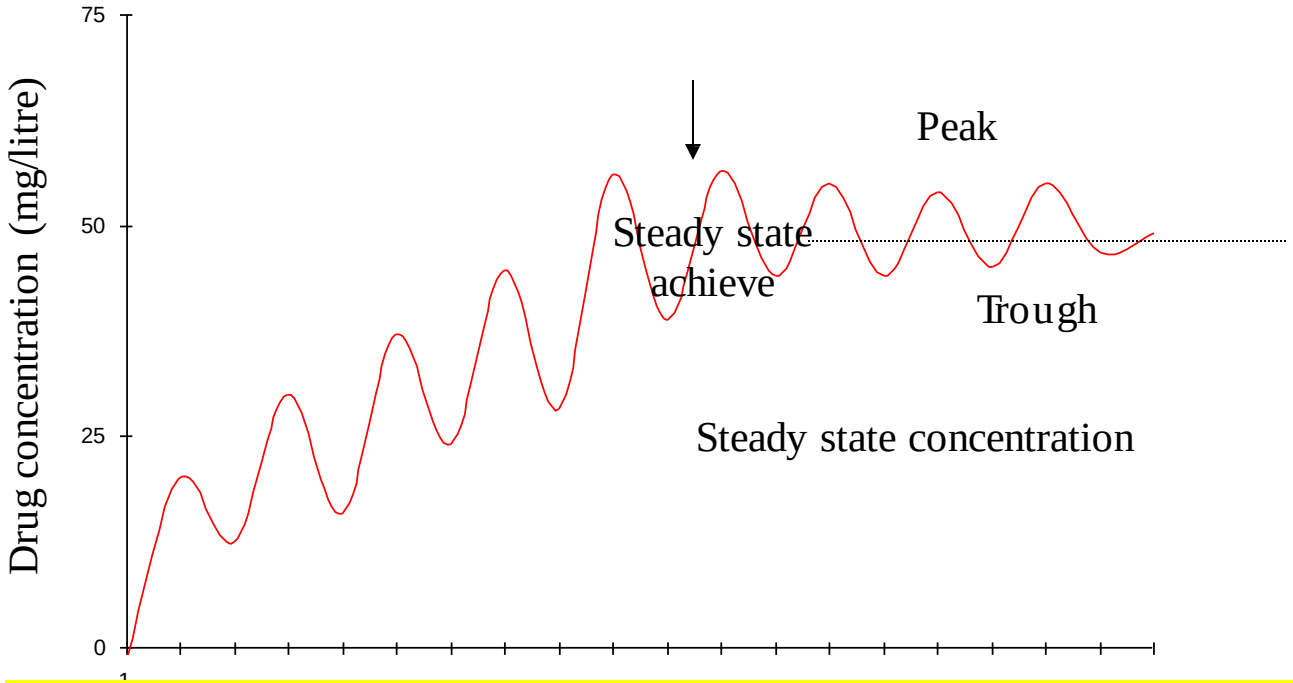
ex. 1) You don't take the drug in the right time 2) change the dose

Drugs with long half lives

In order to reach a quicker steady state level we give what is known as loading dose (large initial dose given to a patient in order to control acute manifestations)



Plasma concentration-time curve following a single oral dose



Plasma concentration of a drug given at half-time intervals steady state is achieved after five doses **after five half lives**

studies that are important before marketing (a comparison between the drug manufactured by a company and the original drug (generic drug))

note: they belong to phase one in drug studies (healthy individuals not patients)

Bioavailability-bioequivalence studies: To prove that 2 drugs have the same

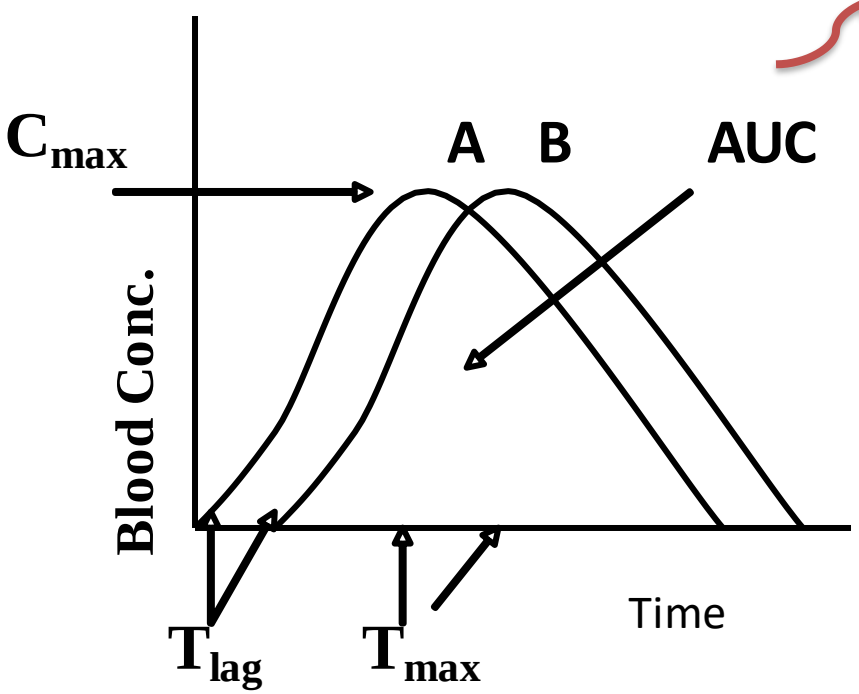
- **Chemical structure (chemical structure of both drugs should be similar— active ingredients as well as inactive ingredients)**
- **Bioavailability (Both should have the same bioavailability)**
- **Biochemical activity**
- **Therapeutic effects**

After that we can say the drug is equivalent to the generic one

T lag is the time needed for initial rise of concentration
T max is the time to reach maximum concentration

Again such studies are conducted on normal, healthy individuals

- Area under the carve = bioavailability



K_T; K_m; K_e; $T_{1/2}$; clearance...etc

Terms and definitions

- **Dose :** It represents the amount of a drug to produce an effect

- **Therapeutic dose**: A dose which is required to produce a therapeutic effect

- **Toxic dose**: The dose which produces a toxic effect

- **Half-life ($t_{1/2}$)**: It is the time by which plasma concentration of a drug falls or declines by 50% of its maximum concentration

- **Steady state concentration :** It is the concentration of a drug at which the rate of administration is equal to that of elimination of that drug. It usually takes 5 to 6 half-lives of a drug

- **Loading dose**: A large initial single or multiple doses are given for some drugs to achieve a rapid steady state concentration

- **Maintenance dose** : The dose which is used to maintain the steady state concentration or to maintain the therapeutic effect of a drug. It is given at a fixed interval time

- **Tolerance :** When repeated administration of an equal doses of a drug for a prolonged period of time (chronic administration) results in decreased responses.

Original responses can be obtained by increasing the dose (e.g. drugs of addiction)

- In general It is not a good phenomena , however it helps in decreasing the side effects with time
- We give it in severe cases like terminal cancer
- These drugs can't be cut off suddenly (it could be fatal) SLOW WITHDRAWAL (decreasing the dose day by day until you reach dose zero)

- **Tachyphylaxis** :Rapidly developing tolerance. When repeated administration of a drug produces decreased responses within a short period of time (even with 2 or 3 doses). This phenomenon is usually observed in the laboratory

Capacity limited processes

1. First-order (exponential) kinetics

All pharmacokinetic processes (abs., distr., met. excr.) occur at a rate directly proportional to conc. of drug e.g. **increasing dose increases these processes**

2. Zero-order (saturation) kinetics

Apply mainly to met. and elimination where their rates reach saturation (maximum) and **a further increase in rates is impossible despite an increase in dose** (these processes are independent of the conc. (absorption from SR tab. or continuous infusion are good examples)

First order kinetics may become zero order when high conc.'s of drug are present

First-order kinetics:

It represents that the rate of elimination of the drug from the body is proportional to the concentration of the drug in the plasma or blood

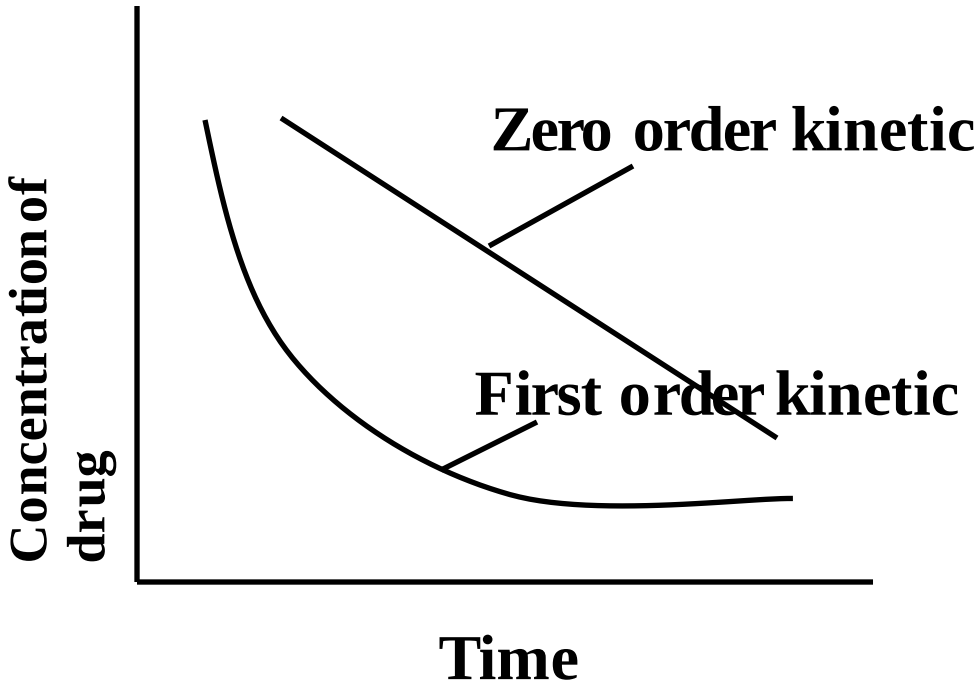
A percentage of the drug is eliminated per unit time. Half-life of the drug is constant irrespective of the doses used. Most of the drugs are eliminated by this process. The curve is exponential

Zero-order kinetics:

The rate of elimination is not proportional to the concentration in the blood or plasma. A certain fixed amount of the drug is eliminated per unit time

This process is saturable and half-life may be increased if the dose of the drug is increased. A few drugs follow this process. The curve is a straight line i.e. not exponential

ORDER OF KINETICS



- **Indications:** Clinical uses of drugs
- **Contraindications:** Situations when not to use drugs

E.g: pregnancy (the drug give +ve mutagenicity test) , allergy

- **Idiosyncrasy:** Abnormal responses to a drug due to **genetic** (heriditory) abnormality **related to the side effects**. Rapid acetylators show therapeutic failure while slow acetylators show toxicity to a drug

Drug interactions:

The effect of one drug on another. Takes many forms:

↑ or ↓ absorption; ↑ or ↓ protein binding; ↑ or ↓ metabolism; ↑ or ↓ excretion; ↑ or ↓ toxicity; ↑ or ↓ binding to receptors… etc

** **Rule:** **one drug is better than two; two drugs are better than three…etc**

- Side effects and drug toxicity

Unwanted, untoward, undesirable, adverse reactions to a given drug (Different Termonology)

Drugs are intended to produce a specific effect. But no drug is specific in its action. Thus, the additional, unwanted effects that are observed in addition to the desired effect of a drug, is called adverse drug effects

- Types of side effects

Type A: It is the extension of known pharmacological effect of a drug e.g. dry mouth after atropine administration

Type B: It is unrelated to the known pharmacological actions of a drug e.g. hypersensitivity reactions to penicillins (hypersensitivity reactions or drug allergy are abnormal responses to a drug due to immunological mechanism. Previous exposure to the offending drug is required)

- The most severe side effect : death
- Allergic reactions are considered a universal side effect that is shared between all drugs

THE END

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