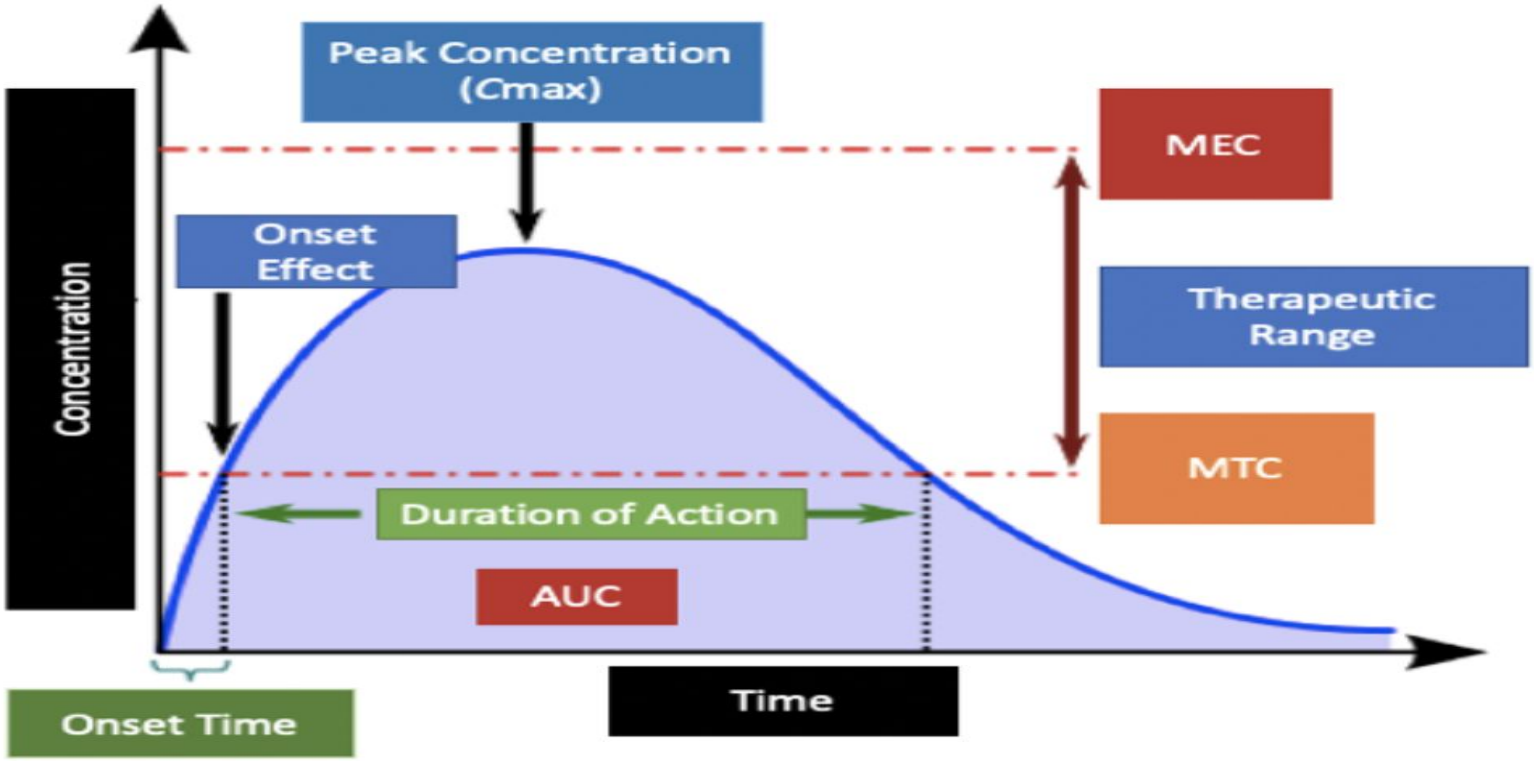
Pharmacodynamics L2

Figure 7
Principles of Pharmacokinetics



(Katzung, 2018; Radio89, 2013)

Professor Dr. Sinaa A. Kadhim
.M.B.Ch.B, GP.Rad., M.Sc., Ph.D

Factors affecting drug safety and effectiveness

Factors related to the drug -1

a- Side effect : undesired effect resulting from action of the drugs on **other sites**, and occurring at **therapeutic** .doses

Ex: N&V by morphine

b- Secondary effect: these are **indirect** effects resulting .from **primary** drug action

Ex: broad spectrum antibiotic and vitamin deficiency , destruction of intestinal flora by tetracycline

c- Toxic effect: these are either

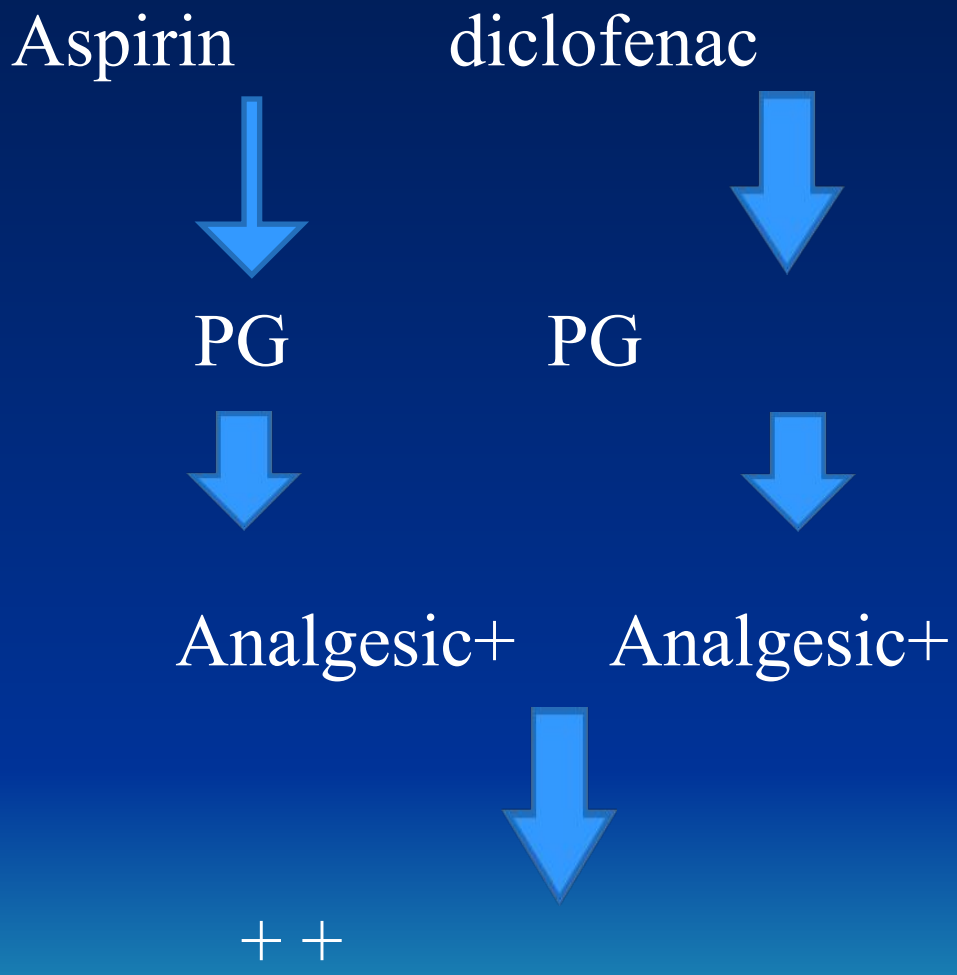
absolute by giving **high dose** of drug to normal individual **or**

Relative if we give normal dose to the patients with **.liver or renal diseases**

d- Drug interaction: occur when we give 2 or more :drugs, these are either

A – Agonism : the interaction here either

1-Additive: combined effect of two drugs acting by same mechanism (1+1=2)



synergism (Supra additive**):** occurs if two drugs with **-2** the **same** effect, when given together , produce an effect that is **greater** in magnitude than the sum of the effects when the :drugs are given individually

Eab > Ea + Eb , 1+1 > 2

Ex:-

1.Sulfamethaxazole+ Trimethoprim

2. Levodopa + Carbidopa.

Summation：occur if two drugs with the same effect, but **-3** with **different mechanism**, when given together produce an effect that is **equal** in magnitude to the **sum** of the effects when the drugs are given individually: Eab = Ea + Eb , 1+1=2

Ex: Aspirin Codiene

decrease PG Opiods receptor

Analgesic+ Analgesic+

++

potentiation: occurs if a drug lacking an effect **-4** of its own increases the effect of a second active :drug

Eab > Ea + Eb , 0+1 > 1

EX: Calvulenic acid + Amoxicillin

B-Antagonism : types mentioned before

e- Route of administration

f- Time of administration

g- Accumulation

h- Tolerance

i- Medication errors (like product formula, package and manufacturing).

Factors related to the patient -2

a-Biological variation: because of presence of some diseases, some patients show much greater response than normal response.

Ex:

asthmatic patients are sensitive to small dose of histamine

hyperthyroid patients are sensitive to small dose of adrenaline.

:b- Age, surface area and weight

: **Children** need small doses because of

Low weight*

Low albumine level*

Receptor changes*

ex: intolerant to some drugs like morphine

But

Elderly patients **need small doses** of drugs because : of

Decrease body weight*

Decrease GFR and*

.Decrease metabolic capacity of liver*

Thus ….Dose calculation is important, according to:

1. Body weight and surface area:

…dose for individual = **weight** in kg / 70 * adult dose

…dose for individual = **surface area** (m2)/ 1.7 * adult dose

2. Age :

child dose= age(years) / 20 * adult dose

c- Sex of patient

Male patients metabolize drugs **faster** than **female** so drug intoxication is higher in female

d- Psychological state

e- Pathological state

Lethal dose (LD50): the dose of the drug that kill 50% of experimental animals.

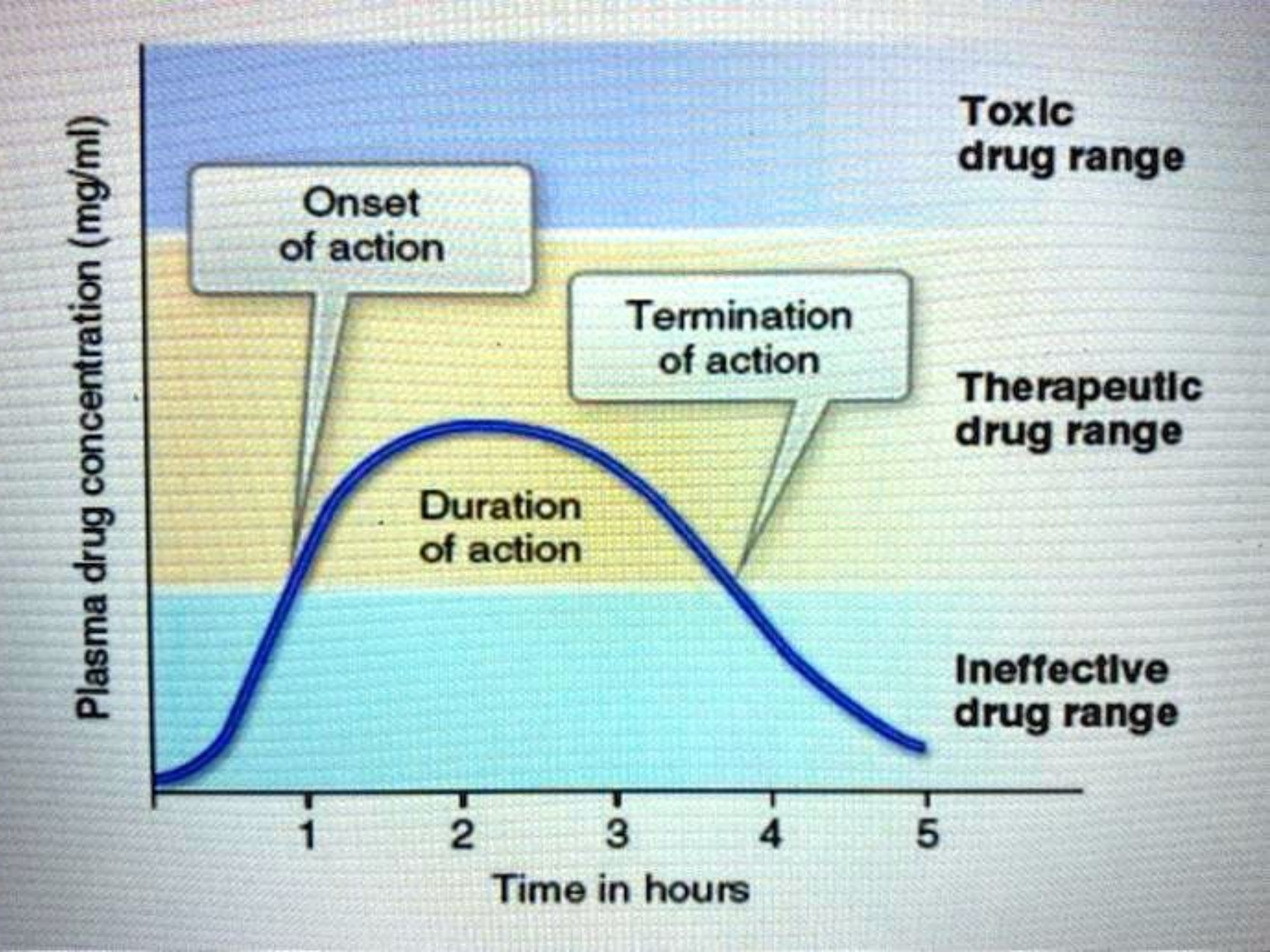
Toxic dose (TD50) : the drug dose that produces a toxic effect in 50% of patients.

:Duration of action

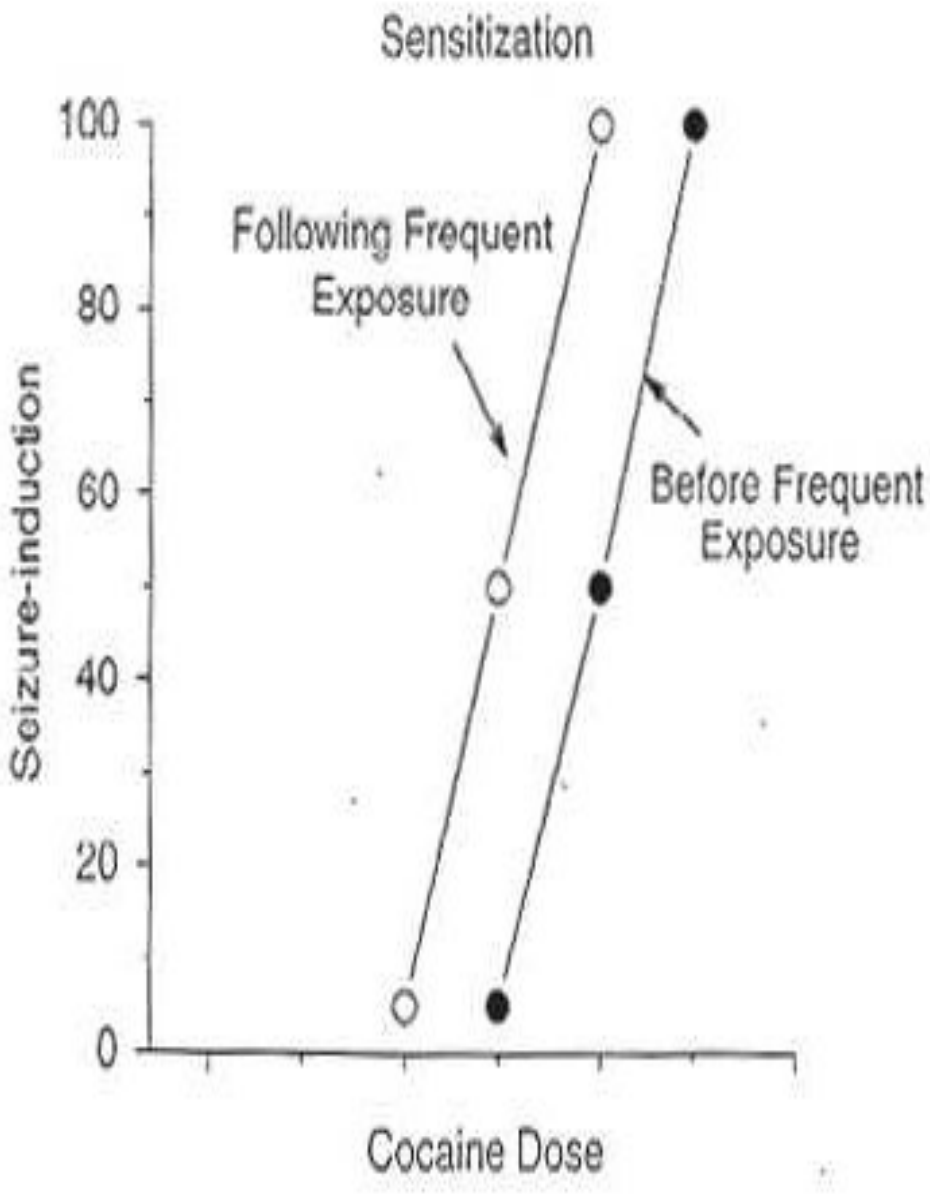
The length of time that a particular drug is effective

:onset of action

the time required after administration of a drug for a response to be observed.


Plasma drug concentration (mg/ml)
Toxic drug range
Onset of action
Termination of action
Therapeutic drug range
Duration of action
Ineffective drug range
1
2
3
4
5
Time in hours

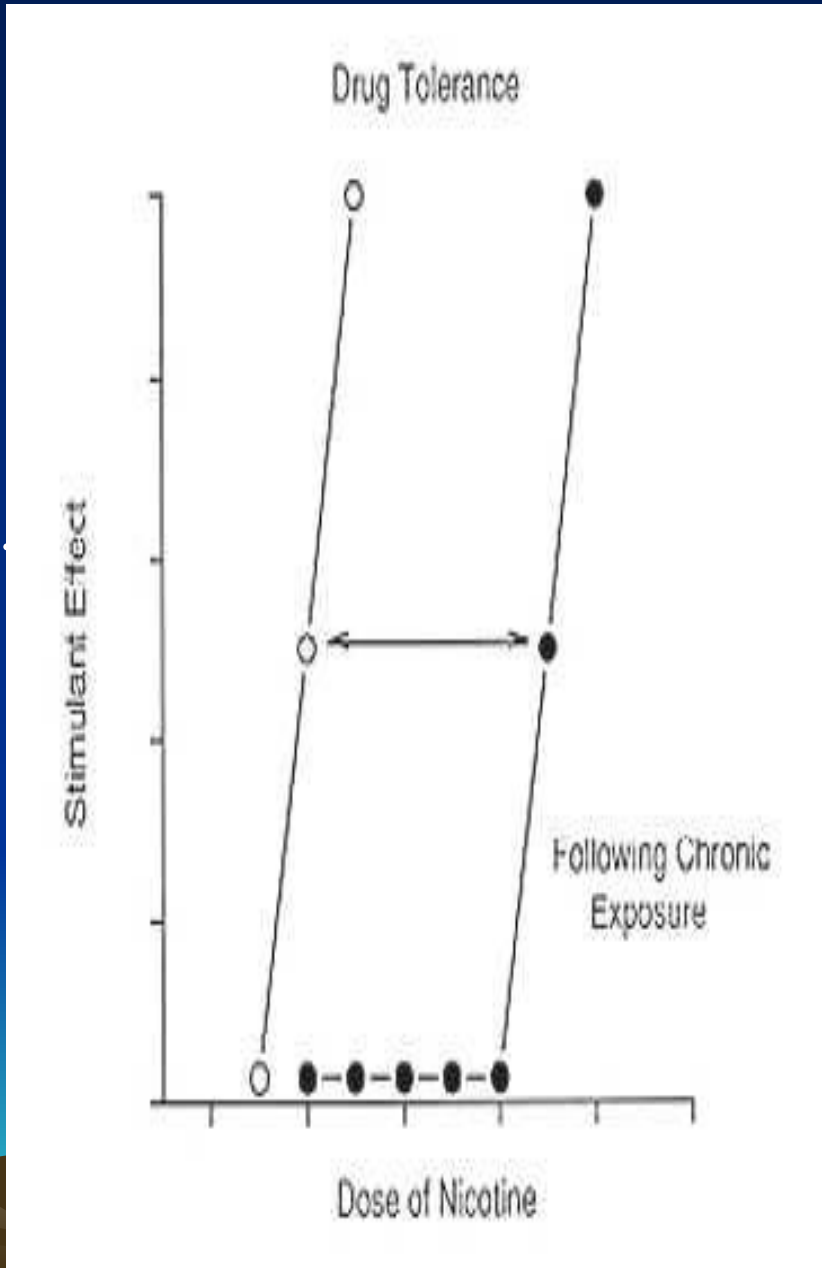
Sensitization



- Increased response to same dose with repeated exposure
- *or* less drug needed to achieve same effect
- Left-ward shift in D-R curve
- Sometimes occurs in an acute dose (e.g. amphetamine)
- Can develop across drugs (cross-sensitization)

Tolerance (desensitization)

- Decreased response to same dose with repeated (constant) exposure
- *or* more drug needed to achieve same effect
- Right-ward shift of D-R curve
- Sometimes occurs in an acute dose (e.g. alcohol)
- Can develop across drugs (cross-tolerance)



:Thus Tolerance mean

The ability of the body to tolerate a given dose of a certain drug .with gradual loss of effect

:Types of Tolerance

.**Natural**: bs of biological variations -1

Acquired occur after **prolong use** of some drugs which may -2 :be due to

a- Receptor changes (down regulation)

.b- Enzyme induction

Cross tolerance : tolerance to one drug cause tolerance to**-3** some drugs with similar action of similar or dissimilar structure . ex: tolerance to alcohols or morphine cause tolerance to pethidine, chloropromazine **or general .anesthesia**

Mechanisms of Tolerance and Sensitization

- **Pharmacokinetic**
  - changes in drug availability at site of action (decreased bioavailability)
    - Decreased absorption
    - Increased binding to depot sites
- **Pharmacodynamic**
  - changes in drug-receptor interaction
    - G-protein uncoupling
    - Down regulation of receptors

- **Psychological**
  - As the user becomes familiar with the drug's effects, s/he learns tricks to hide or counteract the effects.

****It is **possible** to develop tolerance to some **side effects** AND **sensitization** to other side effects of the same drug

Tachyphlaxis: rapidly developing tolerance. Caused by receptor changes or depletion of neurotransmitters in .nerve ending .ex: amphetamine

: Drug allergy

It is **altered immunological** response to drug due to previous exposure, it is either antibody or cell mediated type. This reaction is qualitatively different from primary .drug action

EX: asthma or anaphylaxis (intermediate reaction) or contact dermatitis are delay type

:Therapeutic index (window) TI

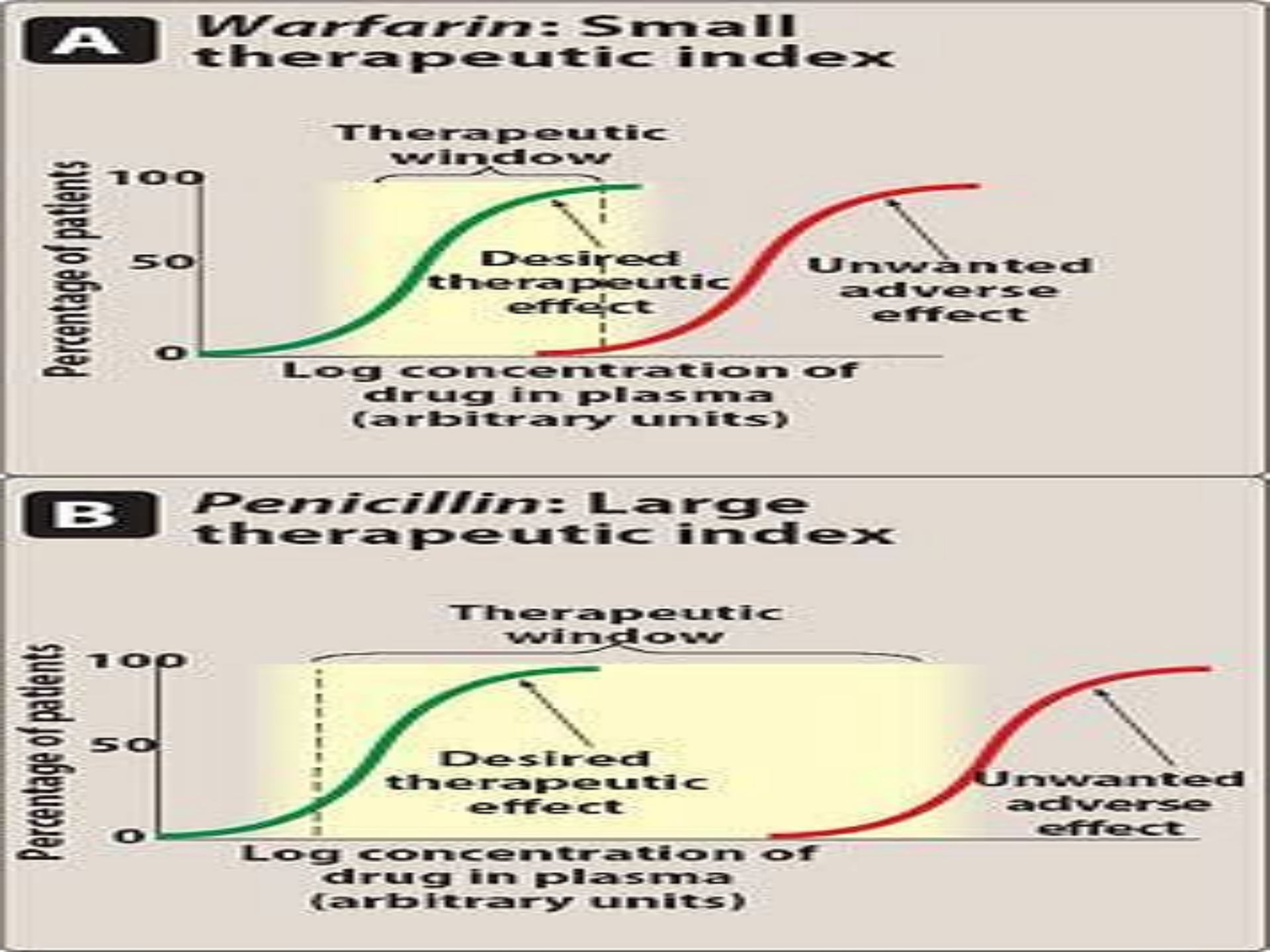
Useful range of concentration over which a drug is therapeutically beneficial. Therapeutic window may vary from patient to patient

It represent the **ratio** of **toxic dose** to the **effective dose** , it is the indication of **drug safety**

$$\mathbf{TI = LD_{50}/ED_{50}}$$

Large value means a **big safety** margin between toxic dose .to the effective dose. Ex: penicillin & paracetamol

Small therapeutic index means a **low safety** margin and .any small **increase** in drug doses will cause **toxicity**


A
Warfarin: Small therapeutic index
Therapeutic window
Percentage of patients
100
50
0
Desired therapeutic effect
Unwanted adverse effect
Log concentration of drug in plasma (arbitrary units)
B
Penicillin: Large therapeutic index
Therapeutic window
Percentage of patients
100
50
0
Desired therapeutic effect
Unwanted adverse effect
Log concentration of drug in plasma (arbitrary units)

:Standard margin of safety

The therapeutic index may be misleading if the dose-response curve for effectiveness and toxicity have **different slopes** (i.e. are not parallel). Therefore, the standard margin of safety is used, which
: **calculated** by

100 *[1 – (TD1 / ED99)]

TD1: dose that produce toxicity in 1 % of population*

ED99 : dose that produce theraprutic effect in 99 % of population*

EX: if 100 mg of a drug causes toxicity in 1% of the population and 10 mg is effective in 99%, then the .drug's standard margin of safety is 900

:Pharmacogenetics

.Is the since that concerned with **hereditary** drug response

:The genetic factors affecting are

.Rate of drug metabolism in the liver -1

.Tissue metabolism -2

.Receptor affecting -3

some thing causing anatomical changes. Ex: patient with **shallow** -4 anterior chamber of eye after application of **medriatics** this causes .sudden increase in **IOP**

:Idiosyncrasy

it is altering in response due to **genetic** abnormality affecting the **enzyme** and rarely the **receptor** . Their action is qualitatively .different from primary drug action

Ex 1 of genetic effect of drug metabolism , we have fast and slow acetylator of INH (isoniazid) : **slow** aceytelator are more prone to peripheral **neuropathy** while **fast** aceytelator are more prone to INH .induce **hepatitis**

Ex 2 : slow aceytelator of **hydrolyzin** are more prone to SLE (systemic .lupus erythromatosis) like syndrome

Ex 3: patient with **G6PD deficiency** are more prone to hemolysis after .exposure to oxidative stress like antimalarial agents and aspirin

Ex 4: chlorimphenicol associated aplastic anemia which is of 2 types : .dose dependent and idiosyncrasy

Others

Note: Search for other examples •

:NOTE

$$\frac{[DR]}{[R_t]} = \frac{[D]}{K_d + [D]} \quad (1)$$

where **[D]** = the concentration of **free** drug; **[DR]** = the concentration of **bound** drug; **[R_t]** = the **total** concentration of receptors, and is equal to the sum of the concentrations of unbound (free) receptors and bound receptors and; **K_d** = [D][R]/[DR], and is the **dissociation** constant for the drug from the receptor. The value of **K_d** can be used to **determine** the **affinity** of a drug for its receptor. The **higher the K_d** value, the **weaker** the **interaction** and the **lower the affinity**. The converse occurs when a drug has a low K_d.

$$[E_{max}] / [E] = [D] + [K_d] / [D]$$

where

the **effect** of the drug at **concentration [D]** and **= [E]**

.the **maximal effect** of the drug = **$[E_{max}]$**

Types of drug dosing

Fixed dose fixed interval like antibiotics -1

.Variable effective dose like antihypertensive -2

Minimal effective dose like steroid -3

Maximal effective dose like anticancer -4


Thank
you!