Pharmacokinetics

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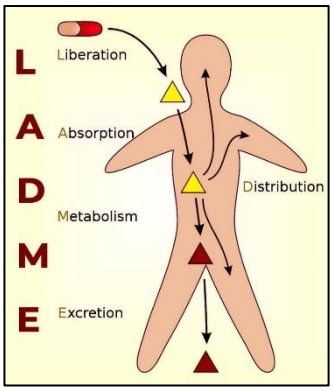
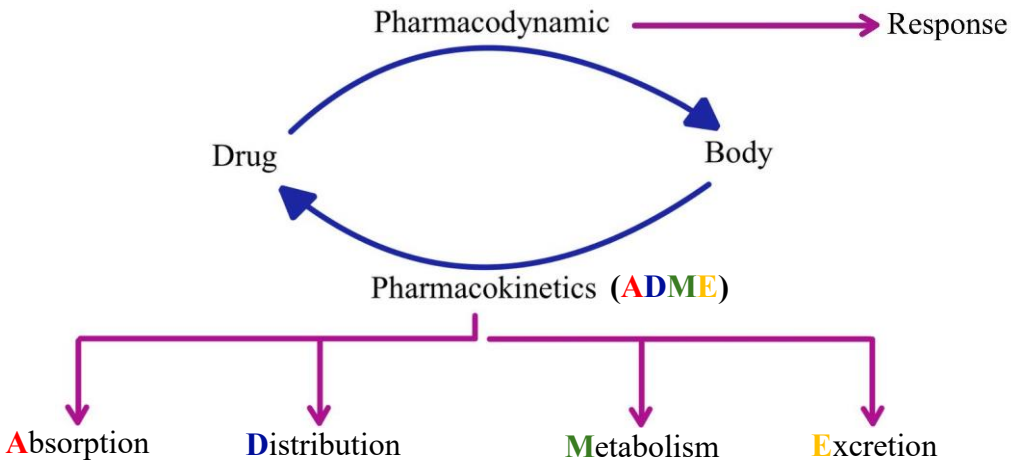
ARKAN ACADEMY

Pharmacokinetics

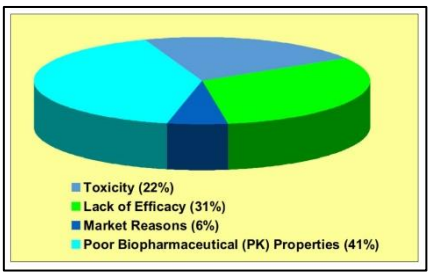
- Pharmacokinetics this naming derived from the Greek word *(pharmakonkinetikos):*
  - Pharmakon: *drug*
  - kinetikos: *movement*
- Pharmacokinetics: movement of drugs inside our bodies.





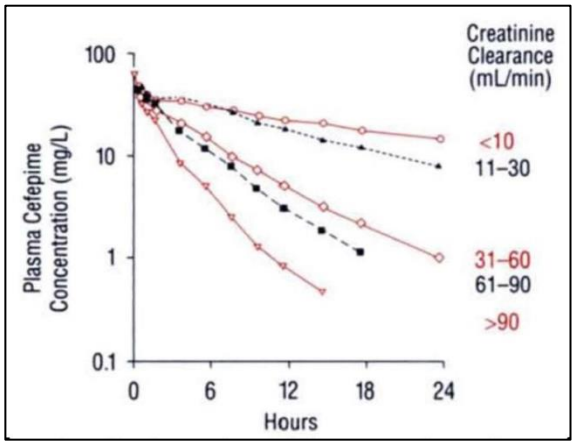
- Pharmacokinetics has many *applications* those include:
  - ***Bioavailability measurements*** and ***bioequivalence studies***
  - Determining the appropriate ***dosing regimen*** for a drug :
    - ✓ Dose
    - ✓ Dosing frequency
    - ✓ Duration of treatment
  - Determining the effect of ***physiological*** and ***pathological conditions***
    - ✓ ***Such as:*** renal or hepatic dysfunction
  - Estimating possible ***accumulation*** of drugs or metabolites and predicting drug toxicity
  - Evaluating ***drug interactions***
  - ***Clinical prediction***: Using pharmacokinetic parameters to ***individualize*** drug dosing regimen and thus provide the most effective drug therapy

- ***Why Pharmacokinetics?***
  - Reasons for failure in Development
    - ✓ PK is important in drug development *because* huge % of failure due to ***poor PK properties of drug (41%)*** like:
      - Bioavailability: many molecules in animals have passed but when we go to humans have failed
      - When the drug achieves the liver⟶ complete metabolism by first pass metabolism or rapid excretion

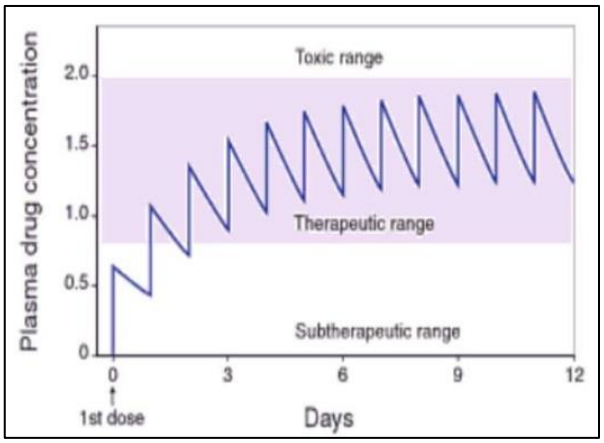


- ***Clinical applications of pharmacokinetics:***

✓ Effects of *physiological* and *pathological* conditions on drug disposition and absorption: plasma conc-time profile of cefepime after a 1000 mg IV infusion dose:

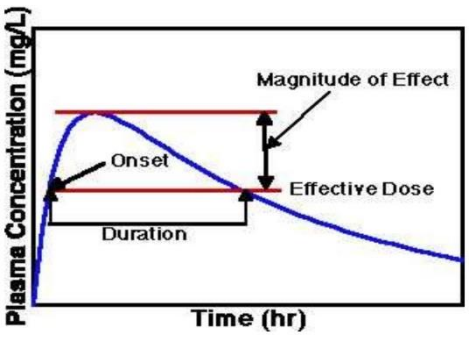


✓ Using pharmacokinetic parameters to design a dosing regimen and thus provide the most effective drug therapy:



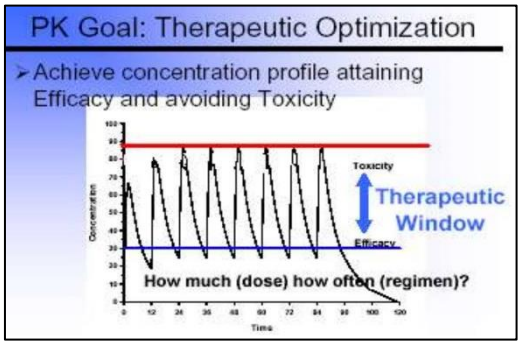
- ***Pharmacokinetics:*** is the mathematics of the time course of *Absorption, Distribution, Metabolism,* and *Excretion* **(ADME)** of drugs in the body.
  - The biological, physiological, and physicochemical factors which influence the transfer processes of drugs in the body also influence the rate and extent of ADME of those drugs in the body.
  - In many cases, pharmacological action, as well as toxicological action, is related to ***plasma concentration of drugs*** through the study of pharmacokinetics, the pharmacist will be able to individualize therapy for the patient.

- ***Therapeutic range:*** concentration between the *minimum effective conc* and *minimum toxic conc*
  - Probability of effect is high
  - Probability of toxicity is low
- ***Onset of action:*** time between the *administration of the drug* and *the appearance of the response* for the drug.
- ***Duration of action:*** time in which the *conc above the minimum effective conc*

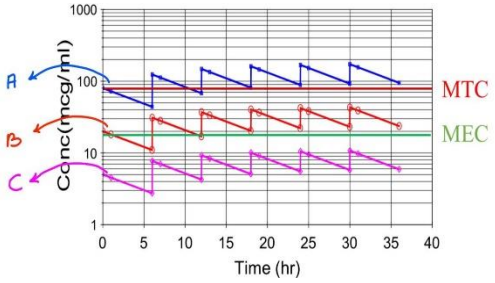


  - The onset of action and duration of action are *pharmacodynamic parameters*
- ***The accumulation*** one of the most important steps to reach the ***steady state***
  - To know whether the *conc* will be within the therapeutic range or not

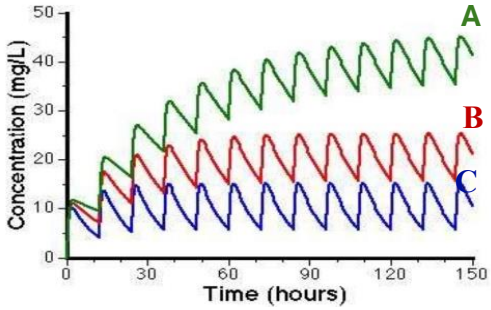
- ***There are many factors to reach state steady <u>depending on:</u>***
  - The drug itself
  - Half life
  - Volume
  - Clearance

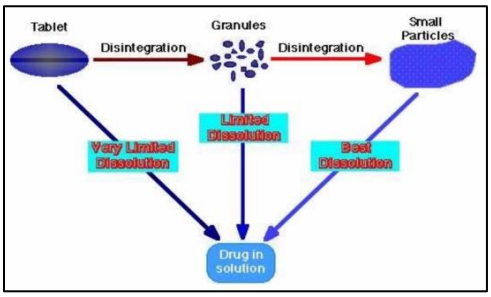


- ***Effect of changing dose (drug factor):***
  - The same patient has been given the drug with *three different doses* (different initial conc):
    - ✓ A: ***toxic*** effect (above MTC).
    - ✓ B: ***within therapeutic*** range.
    - ✓ C: ***subtherapeutic*** (below MEC).



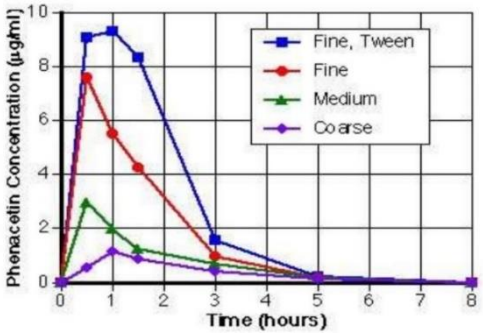
- ***Effect of different elimination rates (patient factor):***
  - The same dose has been given for *three different patients* (different elimination):
    - ✓ A: ***lowest*** elimination - ***slow*** metabolism – ***high*** *accumulation*.
    - ✓ B: ***intermediate*** elimination.
    - ✓ C: ***highest*** elimination - ***fast*** metabolism – ***low*** *accumulation*.



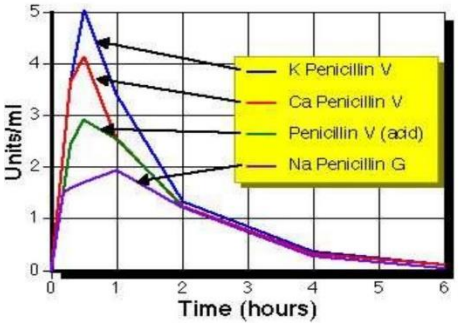


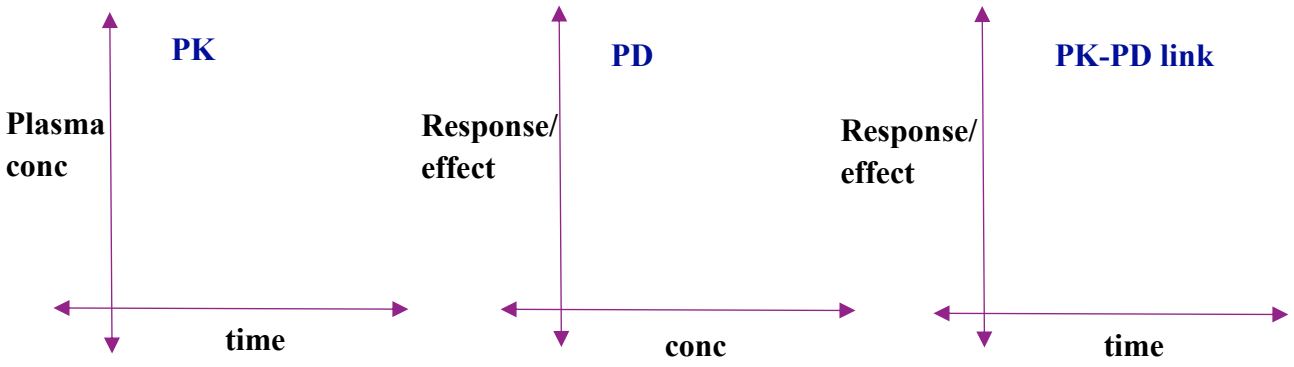
☑ ***Remember****:* the drug to be absorbed it should be in the solution form, so the dissolution and disintegration are *important steps*.

- ***Effect of PCP (drug factor):***
  - Different concentration time profiles for the Phenacetin, the same dose was given but there are *difference in the particle sizes of the drug*:
    - ✓ ***Smaller particle size***: faster dissolution then the faster absorption so we will reach *higher conc*, and the bioavailability may be improved.
    - ✓ ***Larger particle size***: slower dissolution then the slower absorption so we *won't reach high conc*, and the bioavailability may be lower than expected.



- ***Effect of PCP (drug factor):***
  - The same thing according to salt form will affect the solubility and that will be reflected to the *conc time profile.*

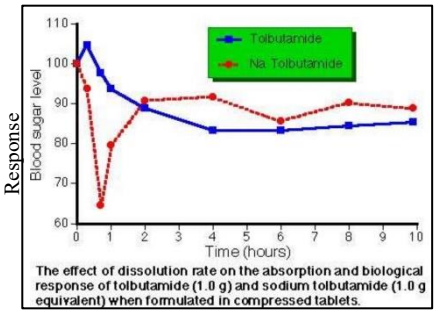




- Note:
  - ✓ ***X-axis:*** independent variable.
  - ✓ ***Y-axis:*** dependent variable.

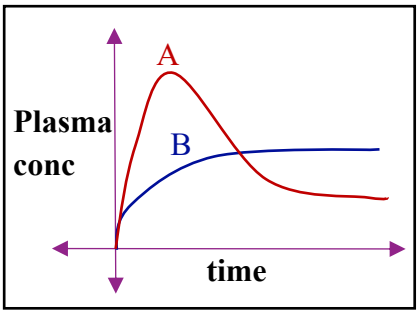
- ***Effect of PCP on Response (Linking PK and PD):***
  - ➢ ***Tolbutamide:*** is sulfonylurea drug for type 2 diabetes that stimulates insulin release to lower blood sugar levels.

PK-PD link

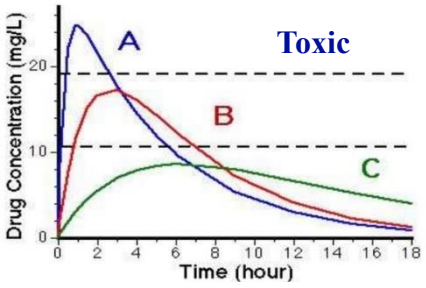


  - ➢ In the ***conc-time profile*** A is Na-Tolbutamide, because if we go back to the previous profile, *response-time profile*, we would see that the level of sugar using Na-Tolbutamide is lower, which means that Na-Tolbutamide ***higher response*** and hence it has the ***higher conc*** in plasma.

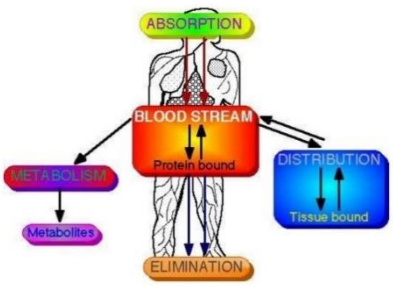
PK



- ***Bioequivalence (evaluated through PK):***
  - ➢ **B**: reference
  - ➢ **A** and **C** ***aren't bioequivalence*** to **B**, in bioequivalence the rule is as good as or as bad as.
  - ➢ May anybody says that **A** is more effective because it has higher conc but no it's ***toxic***!

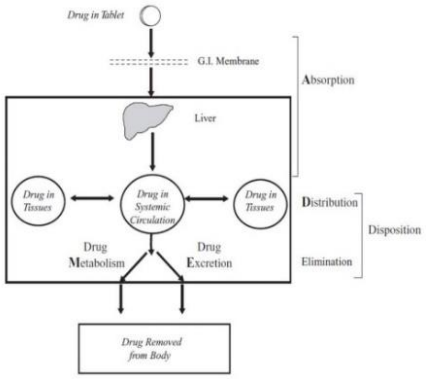


  - ➢ Note:
    - ✓ ***Absorption:*** irreversible
    - ✓ ***Distribution:*** reversible
    - ✓ ***Elimination (metabolism + excretion):*** irreversible



ADME Processes

- ***Absorption***: is defined as the net transfer of drug:
  - ✓ From: the site of absorption.
  - ✓ Into: the circulating fluids of the body.



  - ➢ For oral absorption, two steps are required:
    - ✓ ***Crossing*** the epithelium of the gastrointestinal membrane either by transcellular or paracellular pathways and ***entering*** the blood stream via capillaries.
    - ✓ ***Passing*** through the hepatoportal system intact into systemic circulation.
  - ➢ If the drug is ***metabolized*** prior to reaching systemic circulation, it is said to have undergone presystemic or first-pass metabolism.

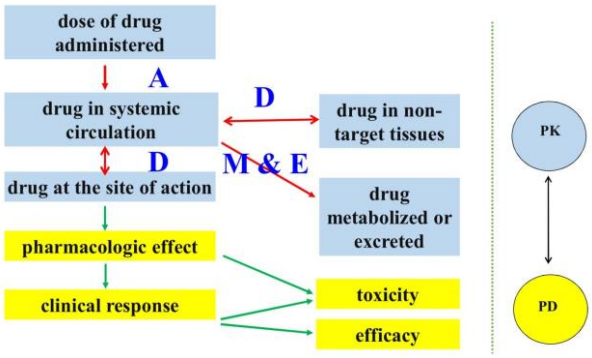
- ***Distribution***: drug distribution means the *reversible transfer* of drug:
  - ✓ From: one location.
  - ✓ To: another within the body.
  - ➢ Once a drug has ***entered*** the vascular system it becomes ***distributed*** throughout the various tissues and body fluids in a pattern:
    - ✓ Reflects the physico-chemical nature of the drug
    - ✓ The ease with which it penetrates different membranes.
  - ➢ We will discuss ***compartmental concepts*** related to drug distribution:
    - ✓ ***The one-compartment model:*** the body is considered:
      - Single.
      - Uniform/Homogeneous compartment.
      - Suitable for drugs that are: lipophilic, unionized, and small.
    - ✓ ***The two-compartment model:*** divides the body into central and peripheral compartments to account for drugs that distribute variably across different tissues.

- ***Metabolism:*** is the bioconversion of drug to:
  - ✓ *Another chemical* form.
  - ✓ *Metabolite*.
  - ➢ Mostly by endogenous enzyme systems involving:
    - ✓ ***Phase I reactions***, such as:
      - Oxidation (often by the cytochrome P-450 system).
      - Reduction.
      - Hydrolysis.
      - Dealkylation.
    - ✓ ***Phase 2 reactions***, such as:
      - Acetylation.
      - Sulfation.
      - Glucuronidation.

- ***Excretion:*** is the *removal of unchanged drug* from the body primarily via urine and occasionally via feces, bile, sweat, or exhaled air.

- ***Pharmacodynamics:*** is the study of:
  - The ***biochemical effect*** of drugs on the body.
  - The ***physiological effect*** of drugs on the body.
  - This includes:
    - *The mechanisms of drug action.*
    - *The relationship between effect and drug concentration.*

- ***Pharmacokinetics & Pharmacodynamics:***



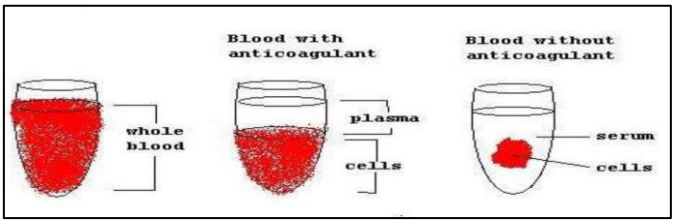
- ***Pharmacokinetic approaches***: the study of pharmacokinetics involves both:
  - ***Experimental*** approaches, **involves:**
    - The development of ***biologic sampling procedures***.
    - The development of ***analytical methods*** for the measurement of drugs and metabolites.
    - The development of ***procedures*** that facilitate data collection and manipulation.
  - ***Theoretical*** approaches, **involves:**
    - The development of ***pharmacokinetic models*** that predict drug disposition after drug administration.

- ***Measurement of drug/metabolite concentrations:***
  - Drug concentrations are an important element in determining pharmacokinetic parameters of drug.
  - Drug concentration provides information such as:
    - The amount of drug *retained in.*
    - The amount of drug *transported* into region of the tissue or fluid.
    - The likely *pharmacologic* or *toxicological* outcome.
  - Drug concentrations are measured in specific biologic samples, such as:
    - Milk.
    - Saliva.
    - Plasma.
    - Urine.
  - Sensitive, accurate, and precise ***analytical methods*** are used, especially chromatographic methods *to determine* the concentration of various drugs/metabolites.

- ***Sampling biologic specimens can be conducted through:***
  - ***Invasive methods:*** such as sampling:
    - Blood.
    - Spinal fluid.
    - Synovial fluid.
    - Tissue biopsy.
    - Any biologic material that requires parenteral or surgical intervention in the patient.

- ***Non-invasive methods:*** including:
  - ✓ Urine.
  - ✓ Feces
  - ✓ Saliva.
  - ✓ Expired air.
  - ✓ Any biologic material that can be obtained **without** parenteral or surgical intervention.

- ***Measurement of drug concentration (levels) in the blood, serum, or plasma***:
  - The most direct approach to assessing the pharmacokinetics of the drug in the body.



  - Drug concentrations are more often measured in *plasma*.
  - ***Pharmacologic*** or ***toxic effect*** of a drug is directly related to the *concentration of the drug at the target site (receptors) in the tissue cells*.
  - It is difficult to measure the drug concentration at its ***site of action***.
  - Since plasma perfuses all the tissues of the body, including the *cellular elements* in the blood.
  - Assuming that a ***drug in the plasma*** is in dynamic equilibrium with the tissues, then changes in the drug concentration in plasma will reflect changes in tissue drug concentrations thus plasma drug level is responsive to the pharmacologic action and used to ***monitor drug's therapeutic behavior.***

- ***Plasma level of the drug:***
  - Monitoring of plasma drug concentrations allows for the adjustment of the drug dosage in order to:
    - ✓ ***Individualize*** therapeutic drug regimens.
    - ✓ ***Optimize*** therapeutic drug regimens. (why is optimization needed?).
  - Pharmacokinetic models allow more accurate interpretation of the relationship between:
    - ✓ ***Plasma drug levels.***
    - ✓ ***Pharmacologic response.***
  - In addition to pharmacokinetic parameters, *pharmacodynamic response* is used to monitor therapeutic effects (example ? Warfarin).

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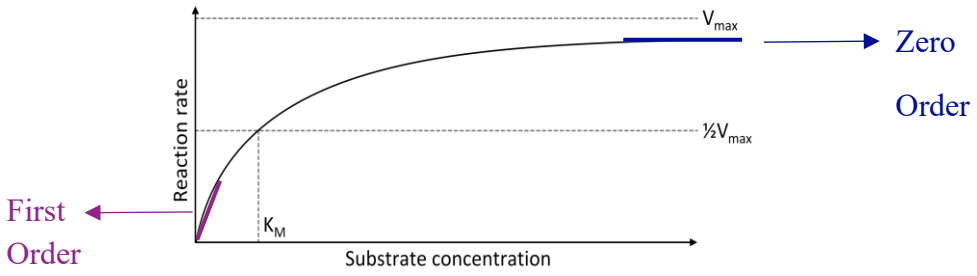
Rates of Reactions

- The order of a reaction refers to the way in which the *concentration of drugs or reactants* influence ***the rate of a chemical reaction or process***.
- ***Remember:***



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