Methotrexate pharmacokinetics

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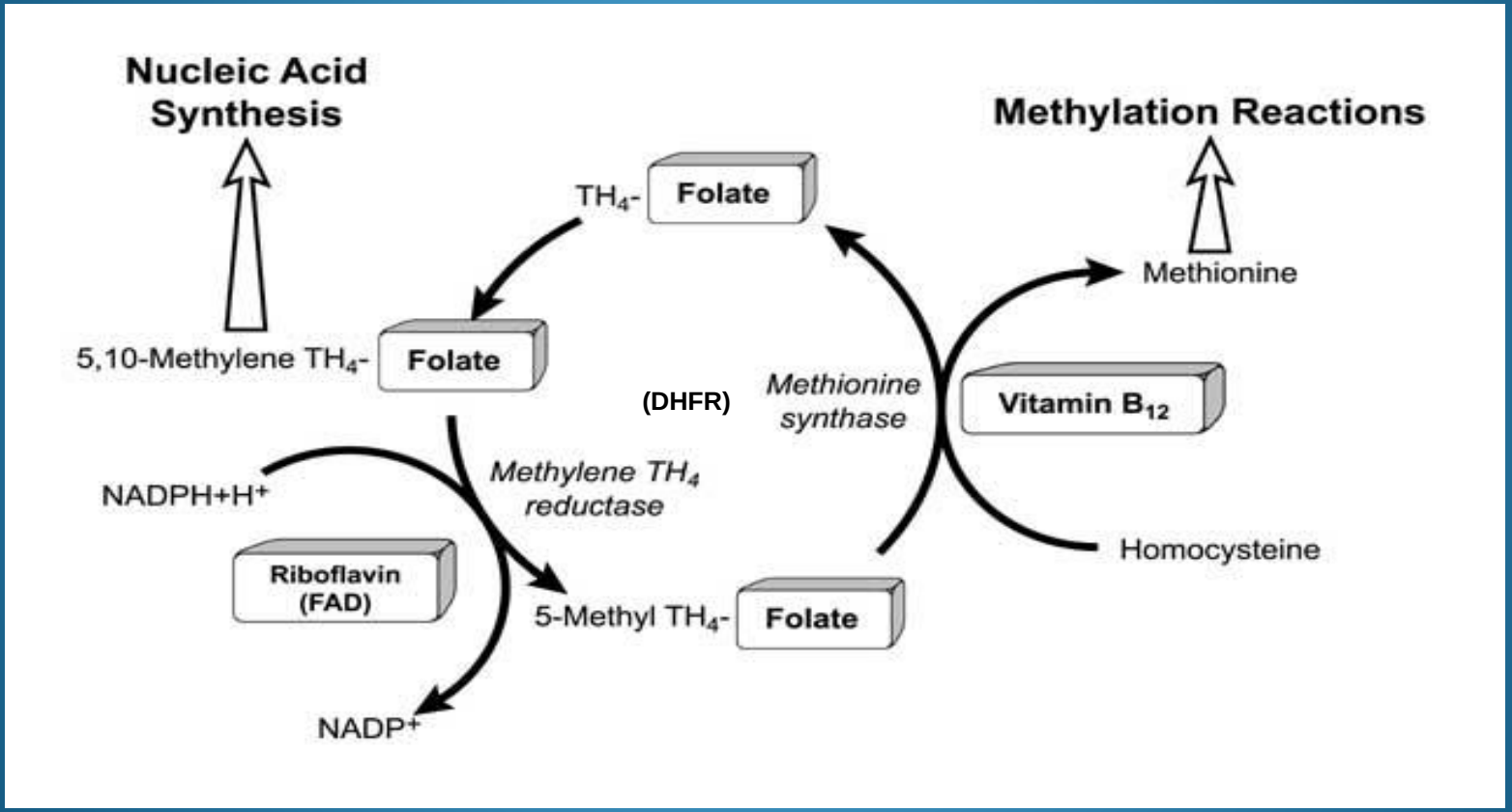
Antimetabolites

- Structural analogues of naturally occurring substances required for specific biochemical reactions.
- Substitute themselves for purines or pyrimidines or they can inhibit critical enzymes that are involved in nucleic acid synthesis.
  - They affect DNA, RNA, protein synthesis and cellular replication.
- 4 drug categories:
  1. Folate Antagonists
  2. Pyrimidine Antagonists
  3. Purine Antagonists
  4. Adenosine Deaminase Inhibitors

Folate Antagonists



Purpose of folate pathway is to produce reduced folate cofactors to act as donors of methyl groups necessary for synthesis of DNA base pairs and aminoacids

Folate Antagonists

1. Methotrexate (MTX)
2. Pemetrexed (Alimta®)
3. Leucovorin (Wellcovorin®)

Methotrexate – Mechanism of Action

- Reversibly binds to dihydrofolate reductase (DHFR)
  - Inhibits the formation folates
  - Results in:
    - Ineffective nucleic acid synthesis and DNA production
    - Strand breakage and ineffective repair mechanism
    - Ultimately cell death
  - Longer exposure to methotrexate allows for more cells to be replicating and be exposed to cytotoxic effects of methotrexate
  - Intracellularly addition of glutamyl residues forms methotrexate polyglutamate
  - Polyglutamates:
    - More likely to be formed with longer periods of drug exposure
    - Greater binding affinity for DHFR
    - Increases intracellular half-life of methotrexate
    - Occurs more readily in malignant cells leading to sustained levels and prolonged duration of action

Methotrexate – Mechanism of Resistance

- Resistance occurs via a variety of mechanisms
  1. Alteration of antifolate transport intracellularly
  2. Decreased intracellular polyglutamation
  3. Increased expression of intracellular catabolic enzyme gamma-glutamyl hydrolase
  4. Alterations in over-expression of Dihydrofolate Reductase (DHFR) or mutated DHFR

Methotrexate – Pharmacokinetics

- Absorption
  - Saturable oral absorption
    - Rapidly and well absorbed at low doses (<25 mg/m²)
      - 60% bioavailability (F)
    - Incomplete at large doses
      - 25 – 40 mg/m² ~ 40%
      - > 40 mg/m²< 20%
  - Time to peak concentration
    - Oral route 1 – 2 hours
    - IM route 10 – 30 minutes

Methotrexate – Pharmacokinetics

- Distribution
  - Very water soluble molecule
    - Primarily distributes to total body water
      - Low volume of distribution; 0.4 – 0.8 L/kg
      - 50% protein bound
  - Penetrates slowly into 3rd space fluids.
    - Subsequently exits slowly
    - Cause for potential prolonged MTX exposure
  - Poor distribution into CNS
    - High CSF levels can be obtained by IT administration
    - Enhanced levels after CNS irradiation
      - Blood-brain barrier returns to normal after ~ 4 weeks

Methotrexate – Pharmacokinetics

- Metabolism
  - Primarily form polyglutamates intracellularly
  - Extent of other routes of metabolism unknown
    - <10% degradation by intestinal flora by carboxypeptidase

- Elimination
  - Renal excretion accounts for 44 to 100%
    - 50-80% of IV dose eliminated unchanged in urine during first 12 hours
    - Not dialyzable
    - Terminal Half life = 8 – 12 hours
  - Biliary excretion accounts for about 10%
  - Intrathecal administration: Half life = 12 hrs

Methotrexate – Dosage & Administration

- Antineoplastic dosage range
  - Conventional = 10 - 100 mg/m^2
  - Intermediate = 1 – 2 gm/m^2
  - High = 10 – 12 gm/m^2

- Means of administration
  - Slow IV push
  - Short bolus infusion
  - Continuous infusion over 24 hrs
  - Intrathecal (IT)

Methotrexate – Regimens

- Trophoblastic neoplasms
  - 15 – 30mg/day PO/IM for 5 days, repeat in 7 days for 3 – 5 courses
- Mycosis fungoides (cutaneous T-cell lymphoma)
  - 2.5 – 10mg PO daily
  - 50mg IM once weekly or 25 mg IM twice weekly
- Bladder cancer
  - 30mg/m^2 IV on day 1, 15, and 22 every 4 weeks

Methotrexate – Regimens

- Breast Cancer
  - 40mg/m² IV on Day 1 and 8 every 3 – 4 weeks
- Gastric Cancer
  - 1500mg/m² IV every 4 weeks
- Primary CNS Lymphoma
  - MTX 1gm/m² IV plus intrathecal MTX followed by radiation and cytarabine 3gm/m² IV
- Osteosarcoma
  - 8 – 12gm/m² IV every 4 weeks

Methotrexate – Regimens

- Intrathecal use
  - 12 mg IT (age > 3 years old)

- Other Non-oncology uses
  - Rheumatoid arthritis
  - Psoriasis
  - Ectopic pregnancy

Methotrexate – Toxicities

1. Bone Marrow Suppression
   - Neutropenia – rarely Grade III or IV
     - Sever: ~ day 10
     - Duration: 14 – 21 days
     - More prevalent at higher doses
   - Anemia
   - Thrombocytopenia
2. Emetogenic Potential
   - Very low (< 10%) </=50mg/m²
   - Low (10% to 30%) 50-250mg/m²
   - Moderate (30 to 60%) 250-1000mg/m²
   - High (60 to 90%) >1000 mg/m²

Methotrexate – Toxicities

3. **Nephrotoxicity**
   - Potential to precipitate in kidneys when using intermediate or high dose MTX
   - Hydration and alkalinization may be used to prevent precipitation of MTX in the renal tubules
     - Hydration (3 L/m²/day)
       - Begin 12 hrs before infusion and continue until level undetectable
       - Urine output > 100 mL/hr (> 2 mL/kg/hr)
     - Urine alkalinization
       - Sodium bicarbonate in IV fluids (Add 50-150mEq per liter of hydration)
       - Maintain urine pH >7

Methotrexate – Toxicities

4. **Mucositis and diarrhea**
   - Onset 3 – 5 days after administration
   - Duration ~14 days
5. **Hepatotoxicity**
   - Acute elevations in transaminases and bilirubin
     - Usually returns to normal within 10 days
6. **Dermatologic Effects**
   - Rash, pruritis, photosensitivity, radiation recall

Methotrexate – Toxicities

7. **CNS Toxicity**

- Three distinct neurotoxic syndromes associated with IT MTX
  - Chemical arachnoiditis
    - Arises immediately after administration
    - Severe headaches, vomiting, fever
  - Subacute form
    - Occurs after third or fourth course of IT therapy in ~10% of patients
      - consists of motor paralysis, cranial nerve palsy, and seizures or coma
      - Continued treatment with IT MTX may result in death
  - Chronic, demyelinating encephalopathy
    - Occurs primarily in children months to years after IT MTX therapy
    - Dementia, limb spasticity, and, in advanced cases, coma

Methotrexate – Toxicities

8. Pneumonitis
   - Self-limiting lung process
     - Characterized by fever, cough, and interstitial pulmonary infiltrates
     - No current recommended therapy
9. High dose MTX therapy
   - Occasionally associated with acute, transient cerebral dysfunction
     - Paresis, behavioral abnormalities, and seizures
       - Symptoms occur within 6 days of MTX treatment
       - Completely resolve within 48 to 72 hours
       - Incidence: 4 - 15% of patients

Methotrexate – Dosage adjustment

- Dosage in renal impairment
  - Conventional-Dose MTX
    - Clcr
      - 61 – 80 mL/min — Reduce dose by 25%
      - 51 – 60 mL/min — Reduce dose by 30%
      - 10 – 50 mL/min — Reduce dose by 50 – 70%
      - < 10 mL/min — Avoid use
  - High-dose MTX
    - Clcr
      - < 60 mL/min — Avoid use

- Dosage in hepatic impairment
  - T. bili
    - < 3 mg/dL — No adjustment necessary
    - 3.1 – 5 mg/dL or AST > 180 — Reduce dose by 25%
    - > 5 mg/dL — Avoid use

Methotrexate – Special Precautions

- Doses between 100 - 500mg/m² ***may*** require leucovorin rescue
- Dose > 500 mg/m² require leucovorin rescue
- Factors associated with toxicity and delayed clearance
  1. Renal dysfunction
  2. "Third space" fluid (pleural effusions, ascites, gastrointestinal obstruction)
  3. Hepatic dysfunction

Methotrexate – Drug Interactions

1. NSAIDs, salicylates
2. Bactrim and sulfa antibiotics
3. Penicillins, probenecid
4. Phenytoin
5. Thiazides
6. Cyclosporine

Methotrexate – Plasma Level Monitoring

- Used to guide use of leucovorin for rescue from methotrexate toxicity
- Plasma drug levels in excess of 50 µmol at 24 hours are often predictive of delayed methotrexate clearance.

Leucovorin – Mechanism of Action

- Antidote for folic acid antagonists
  - Supplies the cell with reduced folate whose production is blocked by methotrexate
  - Preferentially rescues normal tissue versus malignant cells
    - Prevents extensive toxicity to bone marrow and gastrointestinal epithelium

Leucovorin – Clinical Applications

- Methotrexate rescue
- In combination regimens with 5-fluorouracil for GI tumors
- Treatment of megaloblastic anemia

Leucovorin – Pharmacokinetics

- Absorption
  - Saturable depending on dosage
    - Doses < 25 mg 98% absorption
    - Doses > 25 mg less absorption
  - Onset of action 30 minutes
- Metabolism
  - Intestinal mucosa and hepatically converted to 5-methyl-tetrahydrofolate (5MTHF) active compound
- Elimination
  - 80 – 90% renal excretion of leucovorin and metabolites
    - Leucovorin half life = 15 minutes
  - 5 – 8% fecal

Leucovorin – Administration

- Methotrexate Rescue
  - Administered every 6 hours (either IV or PO)
  - Should be administered IV in patients with:
    1. GI toxicity
    2. Nausea, vomiting
    3. Individual doses >25 mg
  - IV infusion should not exceed 160 mg/minute

Leucovorin – Dosing

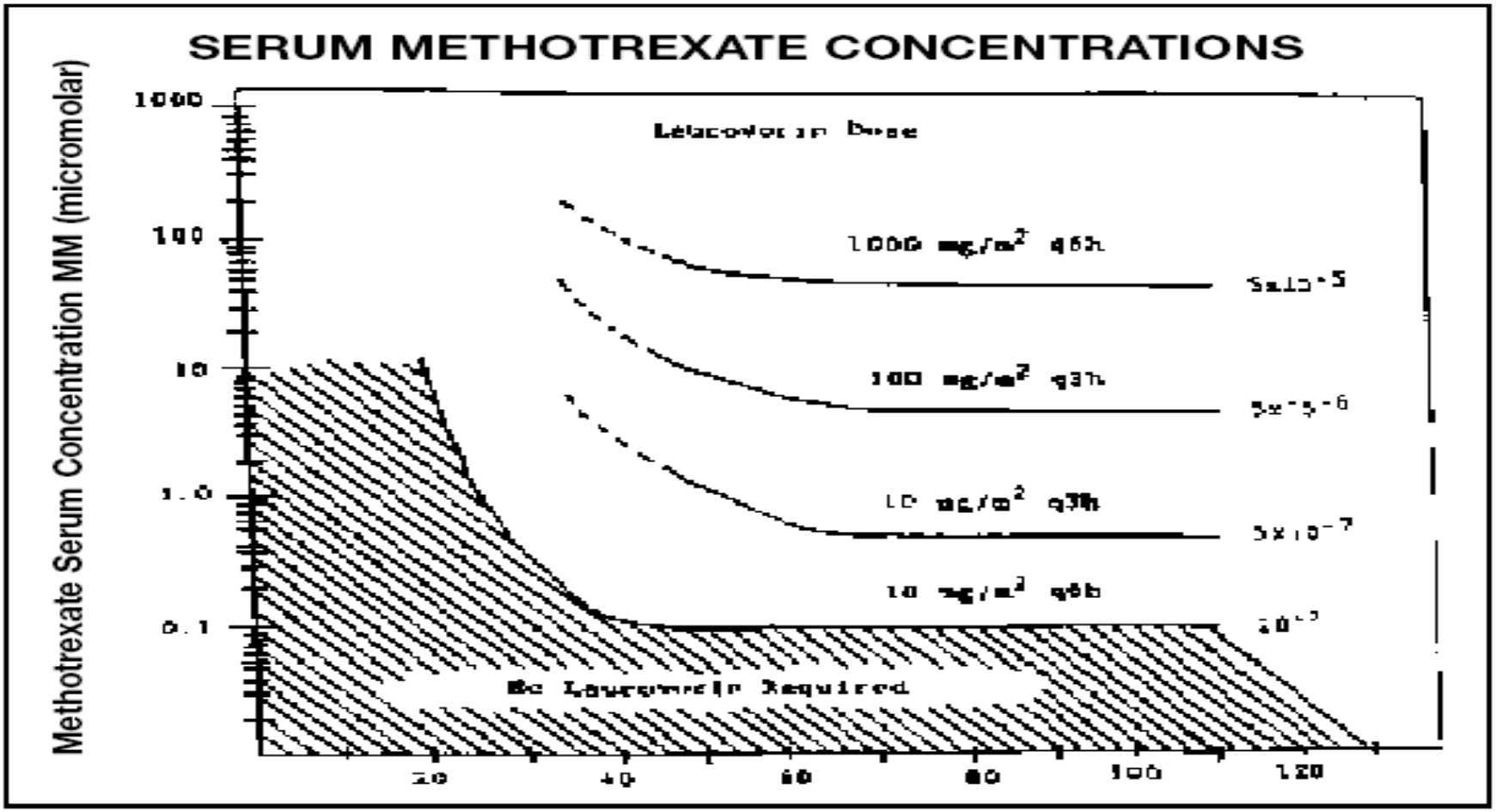
- Dosing for methotrexate rescue
  - Usually started 24 hours after methotrexate is administered
  - Toxicity to normal tissues is irreversible if leucovorin is not initiated by ~40 hours after the start of methotrexate
  - Initial Dosing
    - 10 - 25 mg/m^2 IV/PO every 6 hours until methotrexate level < 0.05 µmol/mL
    - Dose of leucovorin adjusted to methotrexate serum levels at 24-, 48-, and 72-hours after administration
  - MTX levels >10 µmol at 48 hrs post dose are ineffectively rescued by leucovorin
  - Use doses that are adequate but not excessive

Leucovorin – Methotrexate Rescue

Leucovorin Rescue of High Dose Methotrexate

MTX Levels in Micromoles (uM or 10^{-6})	Time after start of MTX in hours	Leucovorin Dose/Duration Note: Urine alkalinization (pH>6.5) required until MTX Level is less than 0.05uM.
Less than 5	24	10mg/m^2 q6 hrs x 72 hours or until MTX level is less than 0.05 uM.
0.05 to 1	48	
5-50	24	50mg/m^2 q 6 hrs until MTX level is less than 0.05uM. draw daily MTX levels.
1-5	48	
50-100	24	100mg/m^2 q 3 hrs until MTX level is less than 0.05uM. Draw daily MTX levels.
5-50	48	
>100	24	1000 mg/m^2 q 6 hrs until MTX level is less than 0.05uM. Draw daily MTX levels.
>50	48	

Leucovorin – Methotrexate Rescue



*WA Bleyer. New Vistas for Leucovoun in Cancer Chemotherapy. *Cancer* 1989; 63:995-1007.

Leucovorin – Toxicities

- Dermatologic
  - Rash, pruritis, erythema, urticaria
- Hematologic
  - Thrombocytosis
- Respiratory/Anaphylactoid reactions
  - Wheezing
- Gastrointestinal
  - Nausea, diarrhea
- Do not administer intrathecally/ intraventricularly

TQ

Introduction To The Pharmacokinetics ADME

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PHARMACOKINETICS

- **Pharmacokinetics** is the study of drug and/or metabolite **kinetics** in the body.

- The body is a very complex system and a drug undergoes many steps as it is being **absorbed**, **distributed** through the body, **metabolized** or **excreted** (**ADME**).

PK=ADME

Pharmacokinetics and Clinical pharmacokinetics

- ***Pharmacokinetics*** *is currently defined as the study of the time course of drug absorption, distribution, metabolism, and excretion.*

- ***Clinical pharmacokinetics*** *is the application of* pharmacokinetic principles to the safe and effective therapeutic management of drugs in an individual patient.

Pharmacokinetics (PK) & pharmacodynamics (PD)

- PK - What the body does to the drug?
  - Absorption; distribution, metabolism, excretion (ADME)

- PD - What the drug does to the body?
  - Drug concentration at the site of action or in the plasma is related to a magnitude of effect

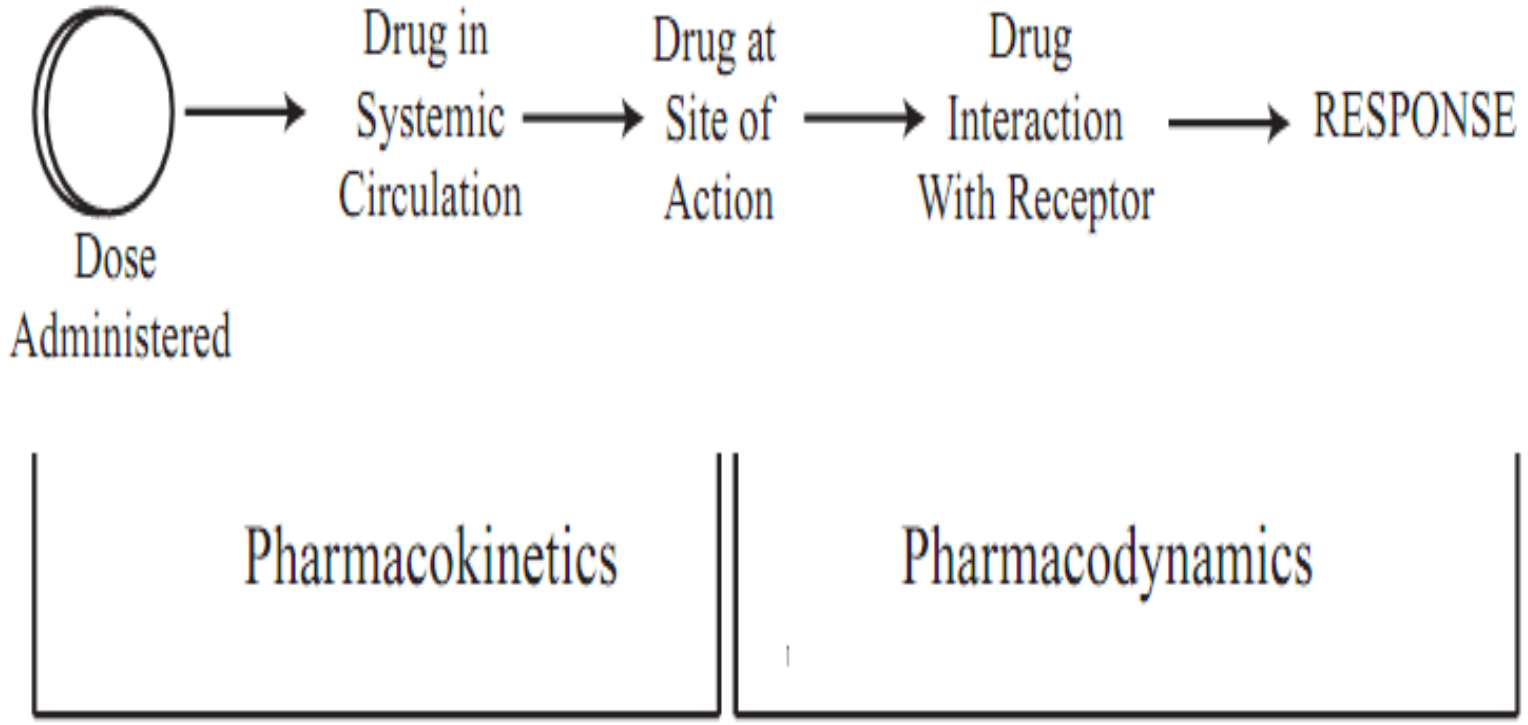


FIGURE 1.1 The two phases of drug action. The pharmacokinetic phase is concerned with the relationship between the value of the dose administered and the value of the drug concentrations achieved in the body; the pharmacodynamic phase is concerned with the relationship between drug concentrations at the site of action and the onset, intensity, and duration of drug response.

Pharmacodynamics

- **Pharmacodynamics** is the relationship between drug concentration and pharmacological response.
- It is extremely important for clinicians to realize that the change in drug effect is usually not proportional to the change in drug dose or concentration.

What is clinical pharmacokinetics ?

- Study of the time course of a drug's movement through the body.
- Understanding of what the body does to (or with) the drug.
- Application of Therapeutic Drug Monitoring (TDM) and individualization of drug therapy.

The LADME scheme

- LADME processes can be divided into two classes; drug input and drug output.
- **Input processes are**:
  - L = Liberation, the release of the drug from it's dosage form.
  - A = Absorption, the movement of drug from the site of administration to the blood circulation. (*rate and extent of drug input*)
- *The term commonly used is bioavailability????*
- *Drugs administered by intravenous routes exhibit essentially 100% bioavailability.*

The LADME scheme

- **Output processes**, or disposition of drug are:
- D = Distribution, the process by which drug diffuses or is transferred from intravascular space to extravascular space (body tissues).

- M = Metabolism, the chemical transformation of drugs into compounds which are easier to eliminate.

- E = Excretion, the elimination of unchanged drug or metabolite from the body via renal, biliary, or pulmonary processes

ABSORPTION

- Is the movement of a drug from its site of administration to the systemic circulation and the extent to which this occurs.

Factors that Affect the Rate and Extent of Drug Absorption

1. Pharmaceutical factors
   - Additives, Dosage form / Drug formulation

Factors that Affect the Rate and Extent of Drug Absorption

2. Physicochemical Properties of the Drug (solubility, stability, dissolution rate)
   I. Molecular weight
   II. pH
   III. lipophilic vs hydrophilic

- Most drugs are weak acids or bases that are present in solution as both the non-ionized and ionized forms
- Non-ionized substances are usually more lipid-soluble and can diffuse readily across the cell membrane
- Ionized molecules have low lipid solubility and are unable to penetrate the lipid membrane

Factors that Affect the Rate and Extent of Drug Absorption

3. Physiologic variables
   - Gastric motility
   - PH at the absorptive site
   - Area of absorbing surface
   - Mesenteric blood flow
   - Pre-systemic elimination / first pass

pH at Absorptive site

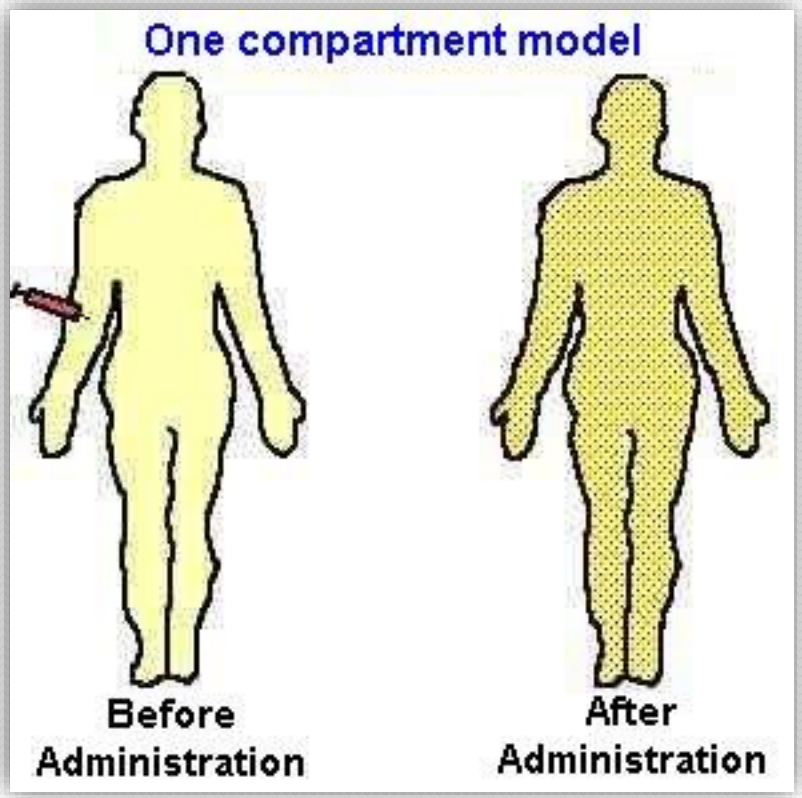
- Acidic PH
  - weak acid – more unionized – more lipid soluble
  - weak base – less unionized – less lipid soluble
- Alkaline pH
  - weak acid – less unionized – less lipid soluble
  - weak base – more unionized – more lipid soluble

The average pH values at different locations in GI tract

Location	Average pH in the fasted state	Average pH in the fed state
Stomach	1.3	4.9
Duodenum	6.5	5.5
Jejunum	6.6	5.2-6.0
Ileum	7.4	7.5

DISTRIBUTION

- Process by which a drug reversibly leaves the systemic circulation and enters the interstitial space and/or the cells of the tissues
- Once in the blood stream, the drug is distributed to the different tissues



Factors that Affect Distribution

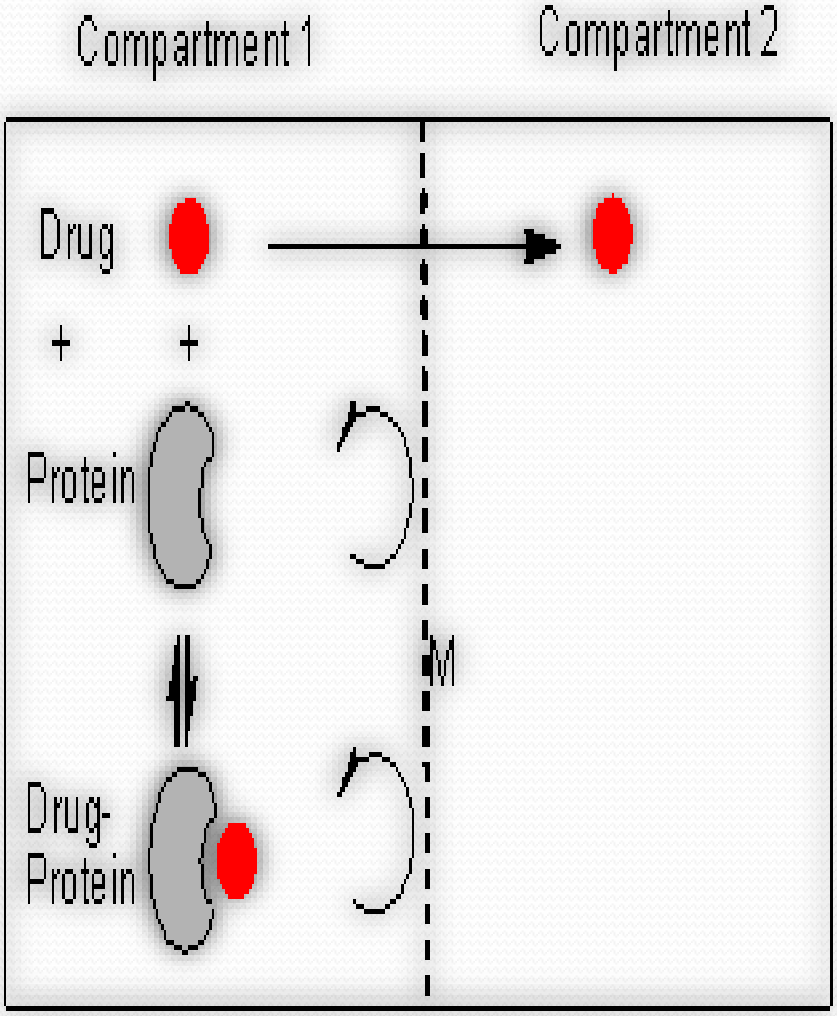
1. Plasma Protein Binding
2. Cardiac Output an Regional Blood Flow
3. Permeability and Perfusion of Membranes
4. Diseases

Factors that Affect Distribution

1. Plasma protein binding
   - Weakly acidic drugs – albumins
   - Weakly basic drugs – α -1-acid glycoproteins
   - Free, unbound drug is the active form of the drug

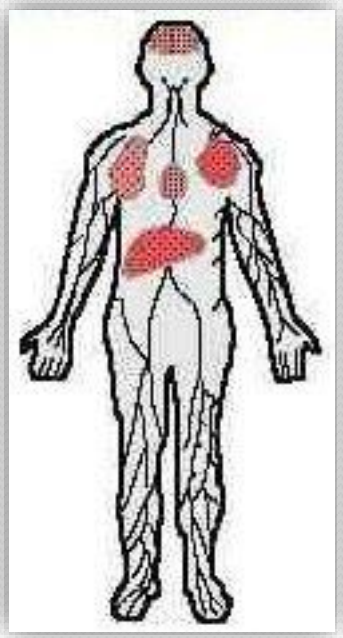
Factors that Affect Distribution:

- Plasma protein binding
  - Drugs bound to proteins are not readily distributed and are inactive
  - High protein binding prolongs onset and duration of action



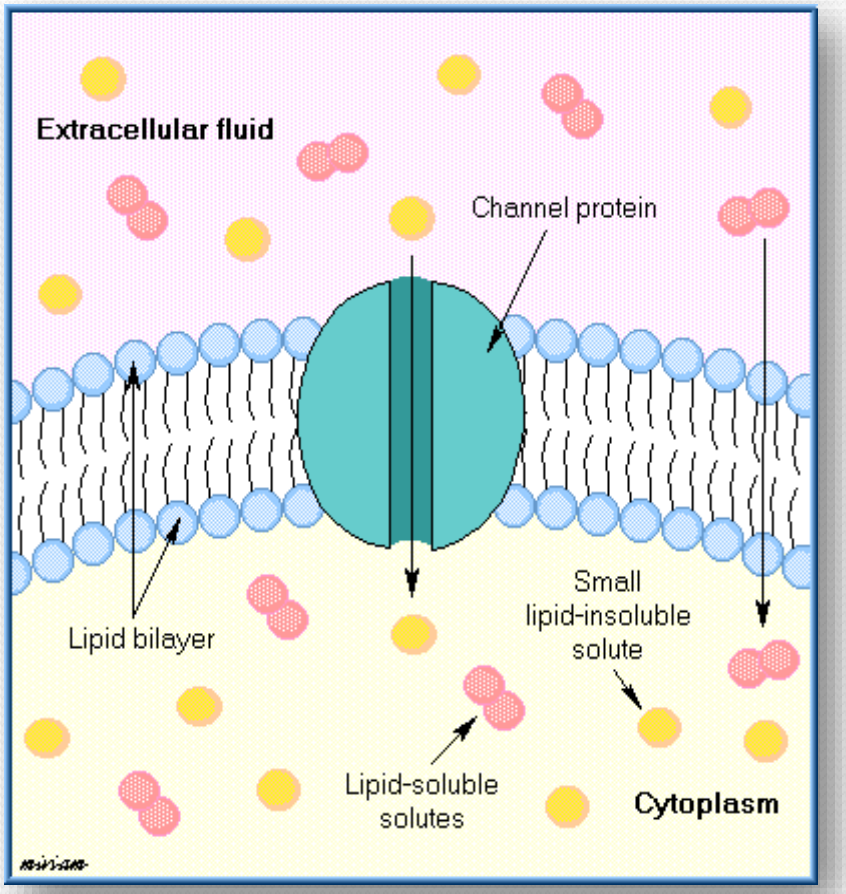
Factors that Affect Distribution:

2. Cardiac output and blood flow to the tissues
   - Highly vascular organs receive more of the drugs



Factors that Affect Distribution:

3. Permeability and Perfusion of Membranes



Factors that Affect Distribution:

- Natural barriers
  - Blood brain barrier
  - Placental barrier
  - Blood-ocular barrier

  - Prevent distribution of drug to areas where their effects may be dangerous

Factors that Affect Distribution

4. Diseases
   - renal, cardiac failure
   - plasma albumin Conc: ↓ in malnutrition, hepatic and renal diseases
   - alpha-1-acid glycoprotein Conc: ↓ in pregnancy and post MI

Metabolism / Biotransformation

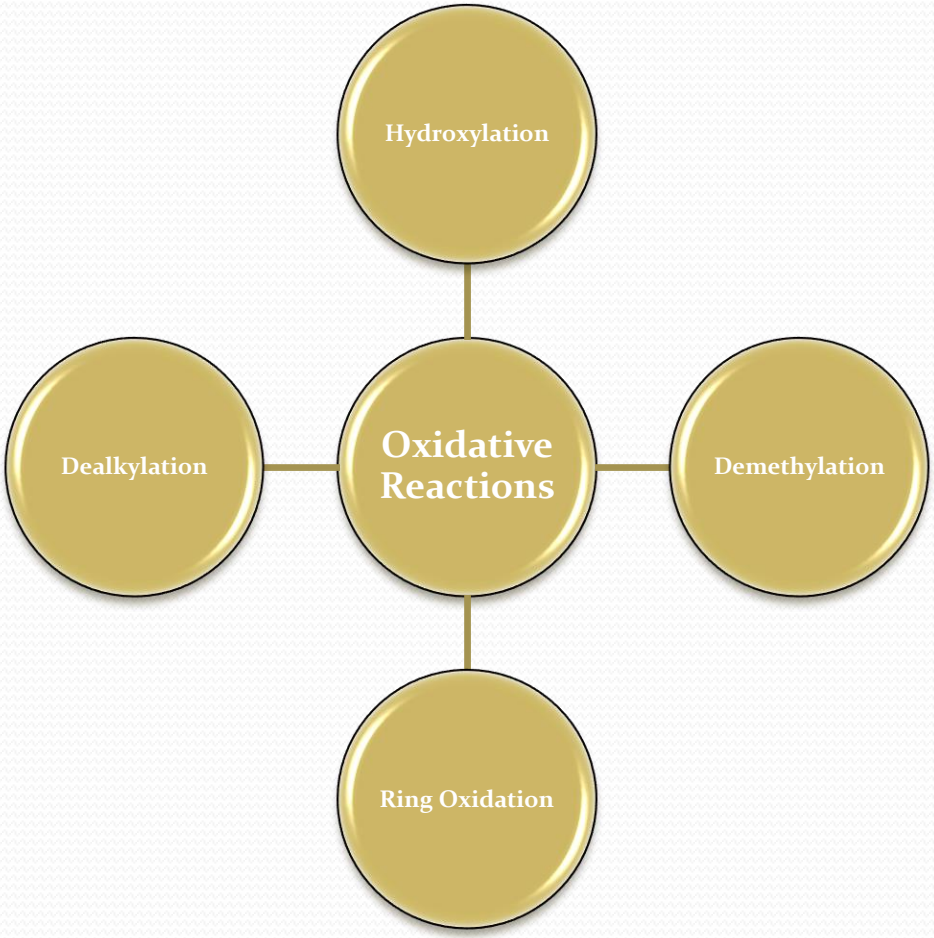
- Process by which a drug is altered chemically into another compound called “metabolites” which may be more active or less active than the parent drug

- Primarily occurs in the liver
  - can also occur in the stomach, small intestines, plasma, kidney, lung, skin, other tissues

Metabolism / Biotransformation

- Two Phases:
  1. Phase I reaction
     - oxidation, hydrolysis, reduction
     - mediated by cytochrome P450 (drug metabolizing enzymes)
  2. Phase II reaction
     - glucuronidation, sulfation, glutathione conjugation, n-acetylation, methylation

CYP-450 REACTIONS



Metabolism

- Significance:
  - Defensive mechanism
  - Increases polarity of drug molecules
    - Restricts penetration thru cellular membrane
    - Reduces distribution
    - Promotes elimination

Factors Affecting Drug Metabolism

1. Non – Genetic
   - Age
   - Sex
   - Liver size / function
   - Diet / Nutrition
   - Environmental
2. Genetic
   - Acetylating – slow and fast
   - Oxidation – poor and extensive

Frequency of Poor Metabolizers in Different Populations

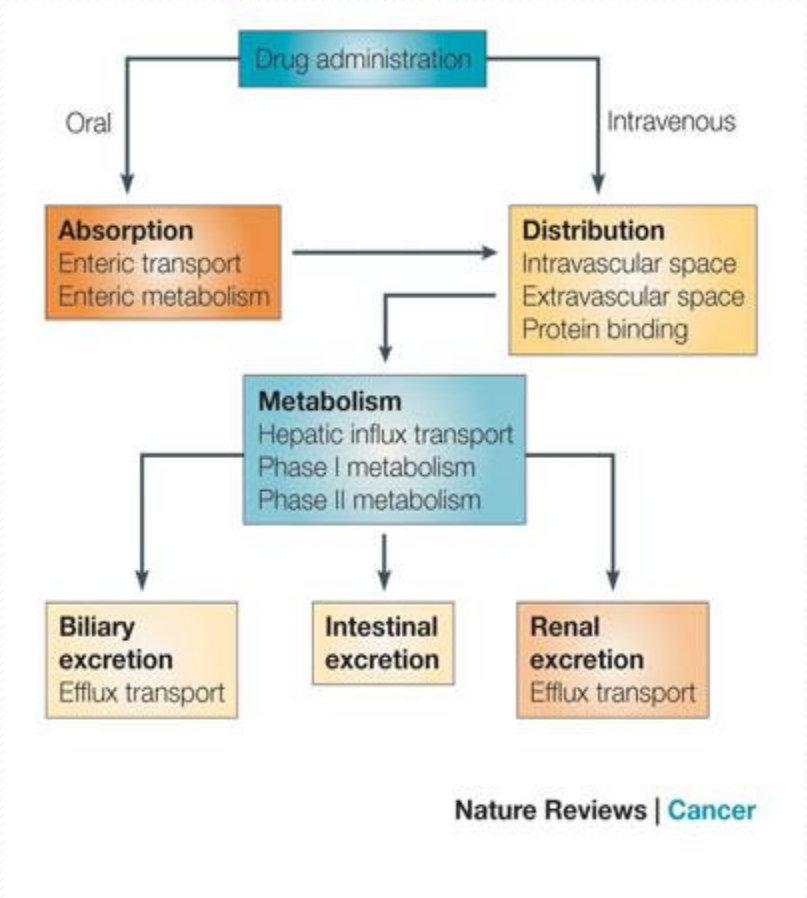
	CYP2D6
Caucasians	8.0%
Japanese	0.5%
Chinese	0.7%
U.S. Blacks	6.1%

Excretion

- Process by which a drug or its metabolites is eliminated from the body
- Main organ of elimination is the kidneys
- Other organ of excretion include the biliary system, GIT, skin and lungs

The process of drug disposition

- The process of drug disposition can be divided into four parts(absorption, disposition, metabolism and excretion)
- Each part has several steps within it. Inter-individual and intra-individual differences in these steps are potential sources of pharmacokinetic variability.



AGE-RELATED CHANGES THAT AFFECT ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION

Table 1 | **Age-related changes that affect absorption, distribution, metabolism and excretion**

Change	Impact on drug pharmacokinetics	References
Absorption		
Reduced gastric-acid secretion; reduced splanchnic blood flow; reduced gastrointestinal motility; concurrent use of many drugs (polypharmacy)	All can potentially reduce drug bioavailability. The multiple concomitant drugs taken by elderly patients can compete for binding sites on transporter proteins or change pH. Effects of age-related changes on absorption are unclear.	137–140
Distribution		
Increased proportion of body fat; reduced intracellular water; reduced plasma albumin; anaemia; polypharmacy	Between ages of 25 and 75 years, fat content increases from 15% to 30% of body weight and intracellular water is reduced from 42% to 33%, causing a reduction in Vd of water-soluble drugs and an increase in Vd of lipid-soluble drugs. Anaemia is a risk factor for increased toxicity of red-cell-bound drugs. A decrease of up to 15–20% in plasma albumin can increase the free fraction of drug.	141–145
Metabolism		
Reduced liver mass; reduced cytochrome P450 activity; polypharmacy	Autopsy studies indicate that the mass of the liver is reduced by 20–50% by 80 years of age, thereby decreasing the amount of metabolic enzymes. Phase I metabolism is reduced, with 30% less activity of several members of the P450 system in healthy older people compared with healthy younger people. Phase II metabolism is preserved.	145–147
Excretion		
Reduced hepatic blood flow; reduced renal blood flow; reduced GFR/CrCl; polypharmacy	Hepatic excretion of drugs can be negatively impacted by a reduction in blood flow to the liver. Loss of nephron mass with age is predictable, with a reduction in GFR by 1 ml/min for every year over the age of 40 years. A reduction in GFR is not reflected by an increase in serum creatinine, and calculated estimates of CrCl in the elderly might not be accurate.	148–150

CrCl, creatinine clearance; GFR, glomerular filtration rate; Vd, volume of distribution.

Samir D. Undevia, Gonzalo Gomez-Abuin & Mark J. RatainNature Reviews Cancer 5, 447-458 (June 2005)

THANK YOU

AMINOGLYCOSIDE TDM,,, EXERSICE

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Case Study #1

- FS is a 35 YO WM (70kg) with nosocomial pneumonia
- Current treatment includes gentamicin 80mg IV Q8 hours
- Serum concentrations ordered for 3rd dose

Case Study #1

- Labs: (Dose given at 0900)
  - Trough (0900) 0.5 mg/L
  - Peak (1000) 4 mg/L
  - SCr 1 mg/dL

Questions

- How do the peak and trough look versus what is desired?

Therapeutic Ranges:

Peak (gentamicin/tobramycin)

UTI/Synergy	4-6 mg/L
Bacteremia	5-7 mg/L
Pneumonia/Sepsis	7-9 mg/L
Osteomylitis	8-10 mg/L
Cystic Fibrosis	10-12 mg/L

Trough (gentamicin/tobramycin)

All indications	0.5-2 mg/L

Questions

- Labs: (Dose given at 0900)
  - Trough (0900) 0.5 mg/L (OK)
  - Peak (1000) 4 mg/L (Low)
  - SCr 1 mg/dL

- How do you correct the problem?

Calculate new dose to achieve:
Peak = 7 and trough = 1

Rules of Thumb

- Changes in peak concentrations are *usually* made with changes in <u>dose</u>

$$\text{Dose} = C_{max} \text{ X VD}$$

- Changes in trough concentrations are *usually* made with changes in <u>interval</u>

$$\text{Trough} = 1/\text{Interval}$$

Equation Definitions

- τ = Interval
- T' = time change between peak & trough

$$T' = \tau - (t_p - t_t)$$

- t = infusion time
- T = peak time from end of infusion

$$T = T_p - T_{eof}$$

eof = end of infusion

Step 1: Calculate K_e

Equation:

$$K_e = \frac{\text{Ln}\,(C_p / C_t)}{T'}$$

$$= \frac{\text{Ln}\,(4 / 0.5)}{7}$$

$$= 0.297\ hr^{-1}$$

Trough (0900) 0.5 mg/L
Dose (0900)
Peak (1000) 4 mg/L

$$T' = \tau - (t_p - t_t)$$

$$T' = 8 - (1) = 7$$

Step 2: Calculate $T_{1/2}$

Equation:

$$T_{1/2} = \frac{0.693}{K_e}$$

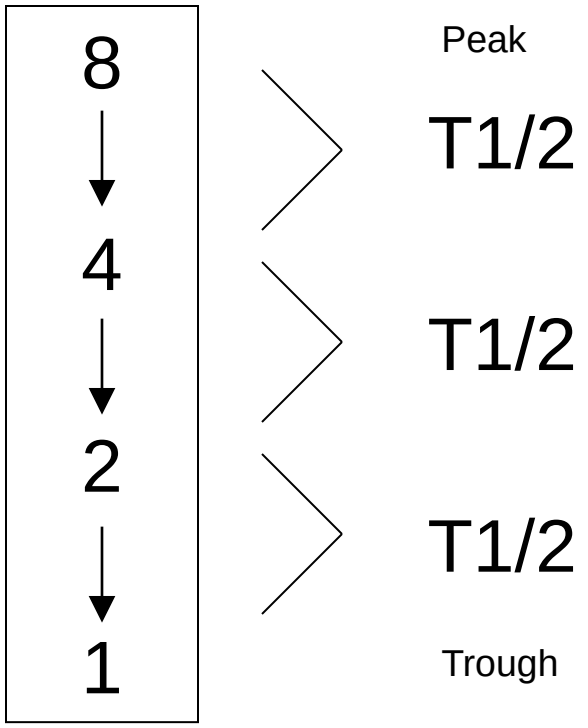
$$= \frac{0.693}{0.297}$$

$$= 2.33 \text{ hr}$$

Doublecheck:

Gent/Tobra τ roughly 3 X $T_{1/2}$

$\tau = 3 \times 2.33 = 7$ (~ 8 hours)



Step 3: Calculate C_{max}

Equation:

$$C_{max} = \frac{C_{pk}}{[e^{(-Ke \times T)}]}$$

$$= \frac{4}{[e^{(-0.297 \times 0.5)}]}$$

$$= 4.64 \text{ mg/L}$$

Step 4: Calculate Vd

Equation:

$$Vd = \frac{(Dose / t) \times [1-e^{(-Ke \times t)}]}{C_{max} \times K_e \times [1-e^{(-Ke \times \tau)}]}$$

$$= \frac{(80 / 0.5) \times [1-e^{(-0.297 \times 0.5)}]}{4.64 \times 0.297 \times [1-e^{(-0.297 \times 8)}]}$$

$$= 17.66 \text{ liters}$$

Step 4: Calculate Vd

Doublecheck:

Population normal Vd for aminoglycosides:

0.25 – 0.35 L/kg

(0.15 – 0.45 L/kg)

Calculate VD/kg:

17.66 L / 70 kg = 0.252 L/kg

Step 5: Calculate New τ

Equation:

$$\tau = \frac{\text{Ln}\left(C_{p\ \{desired\}} / C_{t\ \{desired\}}\right)}{K_e} + t$$

$$= \frac{\text{Ln}\,(7 / 1)}{0.297\ hr^{-1}} + 0.5$$

$$= 7.05 \text{ hours } (\sim 8 \text{ hours})$$

***NOTE: t is now presumed to be infused/drawn correctly, so it will always be 0.5 for gent/tobra**

Step 5: Calculate New τ

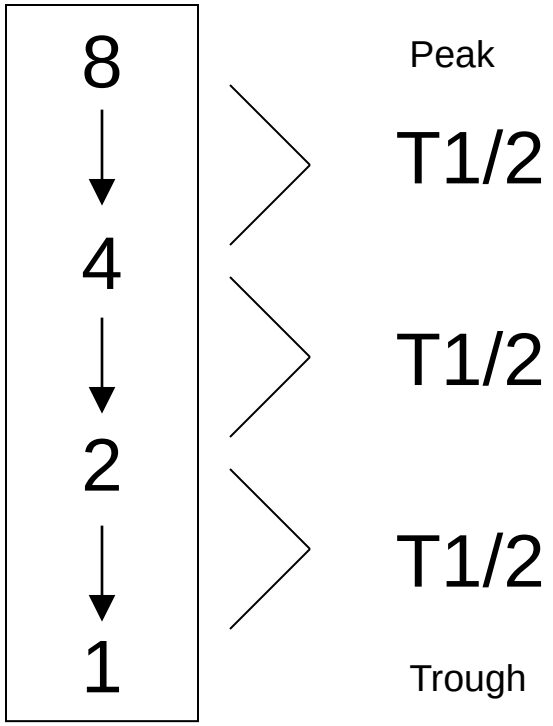
Doublecheck:

Gent/Tobra τ roughly 3 X $T_{1/2}$

τ = 3 x 2.33 = 7 (~ 8 hours)

Calculated:

$T_{1/2}$ = 7.05 hours (~ 8 hours)



Step 6: Calculate New Dose

Equation:

$$\text{Dose} = \frac{C_{pk\ \{desired\}} \times Vd \times K_e \times [1-e^{(-Ke \times \tau_{new})}]}{[1-e^{(-Ke \times t^*)}]} \times t$$

$$= \frac{7 \times 17.66 \times 0.297 \times [1-e^{(-0.297 \times 8)}]}{[1-e^{(-0.297 \times 0.5)}]} \times 0.5$$

$$= 120\text{mg}$$

***NOTE: t is now presumed to be infused/drawn correctly, so it will always be 0.5 for gent/tobra**

Rules of Thumb

- Changes in peak concentrations are *usually* made with changes in <u>dose</u>

$$\text{Dose} = C_{max} \text{ X VD}$$

- Changes in trough concentrations are *usually* made with changes in <u>interval</u>

$$\text{Trough} = 1/\text{Interval}$$

New Dose

120mg IV Q8h (↑ dose for ↑ peak)

Estimated Peak / Trough ~ 7 / 1

Satisfies goals - Write the note

Pharmacokinetics Note

9/26/01 Clinical Pharmacy re: Gentamicin Kinetics

1300

S: 35 YO WM diagnosed with nosocomial pneumonia.

O: Wt 70kg

SCr 1.0 mg/L

Other lab: Peak 4 mg/L (0900)

Trough 0.5 mg/L (1000)

Current Gentamicin dose 80mg IV Q8h

Pharmacokinetics Note

9/26/01 Clinical Pharmacy re: Gentamicin Kinetics

1300

A/P: Calculated kinetic parameters:

Ke = 0.297 hr^{-1}

$T_{1/2}$ = 2.33 hours

C_{max} = 4.64 mg/L

Vd = 17.66 L (0.25 L/kg)

Peak concentration falls short of desired goal of 7 mg/L. Would recommend changing the dose to 120mg IV Q8h for an estimated Peak/Trough of 7 and 1. Would also recommend re-checking serum concentrations with the 3rd new dose. Monitor I/O and SCr.

Keith Christensen, Pharm D

Clinical Pharmacokinetics of Aminoglycosides

Dr. Saif Khalid AlKhafaf
Lecturer , PhD in Pharmacology
College of Pharmacy

Aminoglycosides

1. Streptomycin → Little used except for TB
2. Gentamicin → Broad gram negative coverage
3. Tobramycin → Like gentamicin, but better activity against *Pseudomonas*
4. Netilmicin → Like gentamicin, but better activity against *Pseudomonas*
5. Amikacin → Often effective for bacteria resistant to gentamicin
6. Neomycin → Low resistance or toxicity

Antibacterial Spectrum

- **Aerobic gram -ve bacilli**

- ***Pseudomonas aeruginosa***

- **Gram +ve bacteria (used for synergy)**
Staphylococcus spp., Enterococcal spp.

- **Selected aminoglycosides have activity against: *Mycobacteria spp.*, *Yersinia pestis***

- **No activity against: hemophilus, anaerobes, pneumococcus, neisseria**

Clinical Use of Aminoglycosides

- Parenteral
  - -slow IV (1-2 hr) to avoid neuromuscular blockade
  - -synergistic with β-lactam antibiotics, but do not give in one IV* (drugs react, breaking down the β-lactams)
  - -Exception is use of oral neomycin to sterilize bowel for surgery
- Limited due to toxicity
  - - avoid use with other ototoxic drugs (e.g., ethacrynic acid)
  - •Generally used only for serious gram negative infections
  - •Third generation cephalosporin usually preferred
  - - For UTI, give bicarbonate to alkalinize urine

(* Chemical inactivation – conc., duration of exposure, temp, renal function)

Aminoglycosides - PK

- **Minimal** absorption after **oral** administration
- **Limited** tissue **distribution** due to polarity
- **Not metabolized**, excreted by the **kidney**
- **Rapid** absorption after **IM** administration

- highly **polar** basic compounds
- **insoluble** in lipids
- activity enhance by **alkaline** pH
- distributed highly in well perfuzed organs & ECFs
- do not pass through **meninges**
- do not penetrate the **eye**
- renal tissue **(10 – 50 x)** serum concentration

Serum Conc. Recommendations

	Gentamicin	Tobramycin	Amikacin	Netilmicin[a]
Peaks (μg/mL)				
Serious infections	6–8	6–8	20–25	6–8
Life-threatening infections	8–10	8–10	25–30	8–10
Troughs (μg/mL)				
Serious infections	0.5–1	0.5–1	1–4	0.5–1
Life-threatening infections	1–2	1–2	4–8	1–2

[a] Higher peak and trough values have also been suggested.

S/E……Nephrotoxicity

- Conditions such as sepsis, hypotension, and direct toxicity of aminoglycosides ***cannot*** be differentiated as causes of renal failure.
- It is rare for nephrotoxicity to occur in the first 5 days of therapy.
- Typical findings include: increased serum creatinine, increased BUN, proteinuria, urinary casts.

S/E……Ototoxicity

- Cranial nerve toxicity that includes auditory and vestibular dysfunction.
- Occurs in 2-10 % of patients.

Ototoxicity and Nephrotoxicity

Risk Factors Associated with Toxicity

Ototoxicity	Nephrotoxicity
Age	Age
Impaired renal function	Renal insufficiency
Dehydration	Elevated trough concentrations
Elevated trough concentrations	Elevated peak concentrations
Elevated peak concentrations	Total daily dose
Total daily dose	Cumulative dose
Cumulative dose	Concurrent nephrotoxic drugs
Concurrent ototoxic drugs	Prior aminoglycoside exposure
Prior aminoglycoside exposure	Hypovolemia
Dialysis	Gender
Duration of treatment	Duration of treatment
	Sepsis

Serum Concentration and Toxicity

- Peak concentrations for Gentimicin and tobramycin above 12 mcg/ml, Amikacin peak concentrations above 32 mcg/ml have been associated with higher risk of oto and nephrotoxicity.

- For gentimicin trough cp's of >2 mcg/ml have been associated with increased oto/nephrotoxicity

Concentration-efficacy relationships

- The pharmacodynamic properties of aminoglycosides are:
  - Concentration-**dependent** killing
  - **Significant** post-antibiotic effect
  - the Peak/MIC ratio is an important predictor of efficacy.
  - it is important to give a large enough dose to produce a peak level 8 to 10 ***times*** greater than the MIC

Pharmacokinetic parameters

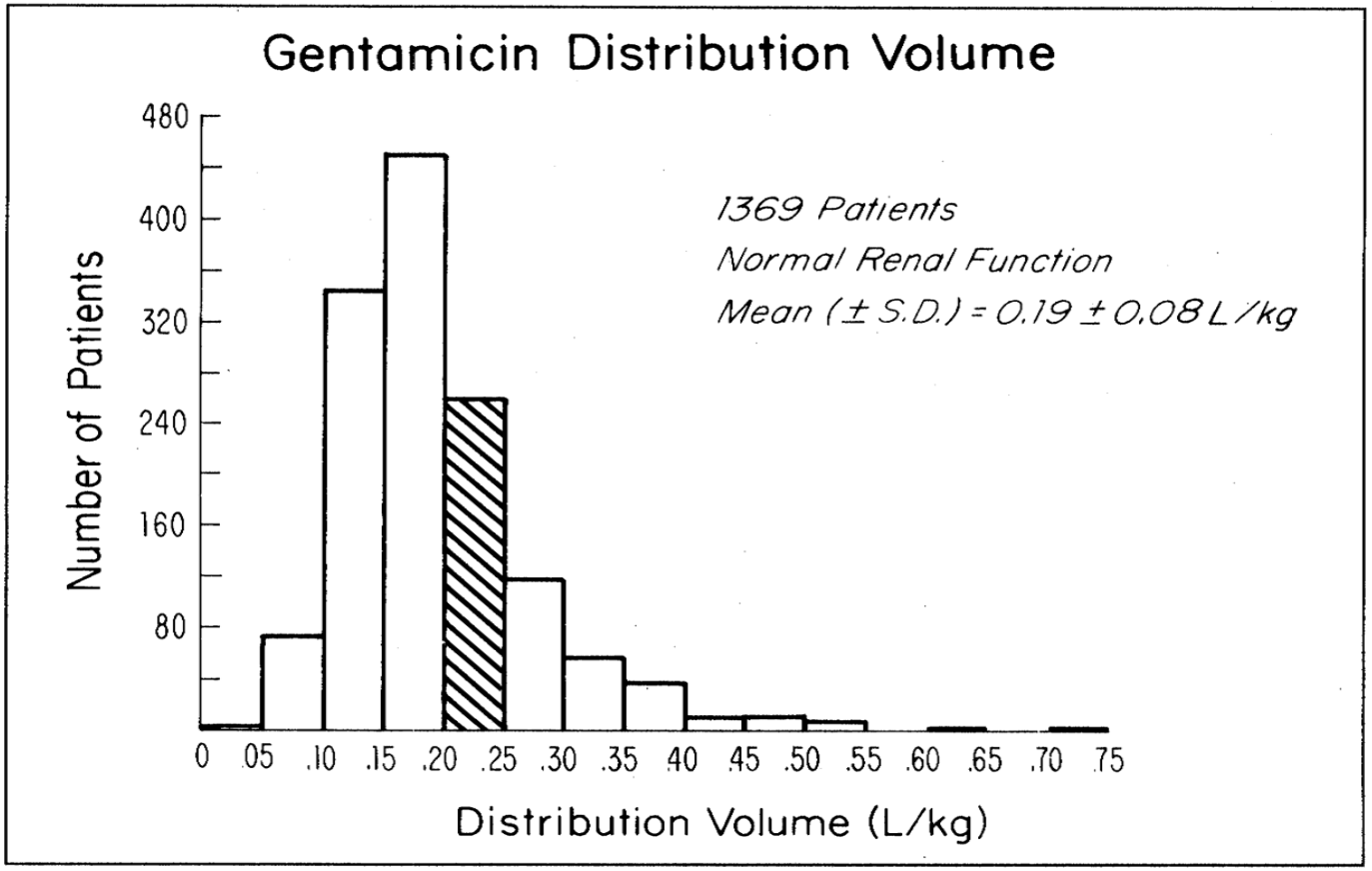
- When given by IV infusion over 30 minutes, aminoglycosides follow a **3-compartment pharmacokinetic model;**
  - Alpha (distribution), ß (elimination), and Gamma (tissue release).
  - When infused over one hour, the distribution phase is usually not observed.
  - The gamma phase begins approximately sixteen hours post infusion.
  - The amount released from tissue is very small, but does accumulate over time, contributing to AG toxicity.

- Although this model accurately represents the time course of AG serum levels, it cannot be used clinically because of its complexity. Therefore, the **simpler one compartment model is widely used**.

Volume of distribution

- The average Vd of AG's in otherwise healthy adults is 0.26 L/kg (range: 0.2-0.3). Although AG's do not distribute into adipose tissue, they do enter the extracellular fluid.
- Therefore, obese patients require a correction in the weight used for Vd calculation: **LBW + 40% of weight above LBW.**
- Patients with cystic fibrosis have a markedly increased Vd of 0.35 L/kg due to increases in extracellular fluid brought about by the disease process.
- Patients with ascites have additional extracellular fluid because of accumulation of ascitic fluid, which increases the Vd to approximately 0.32 L/kg.
- ICU patients may have a Vd 25-50% above normal.

Distribution

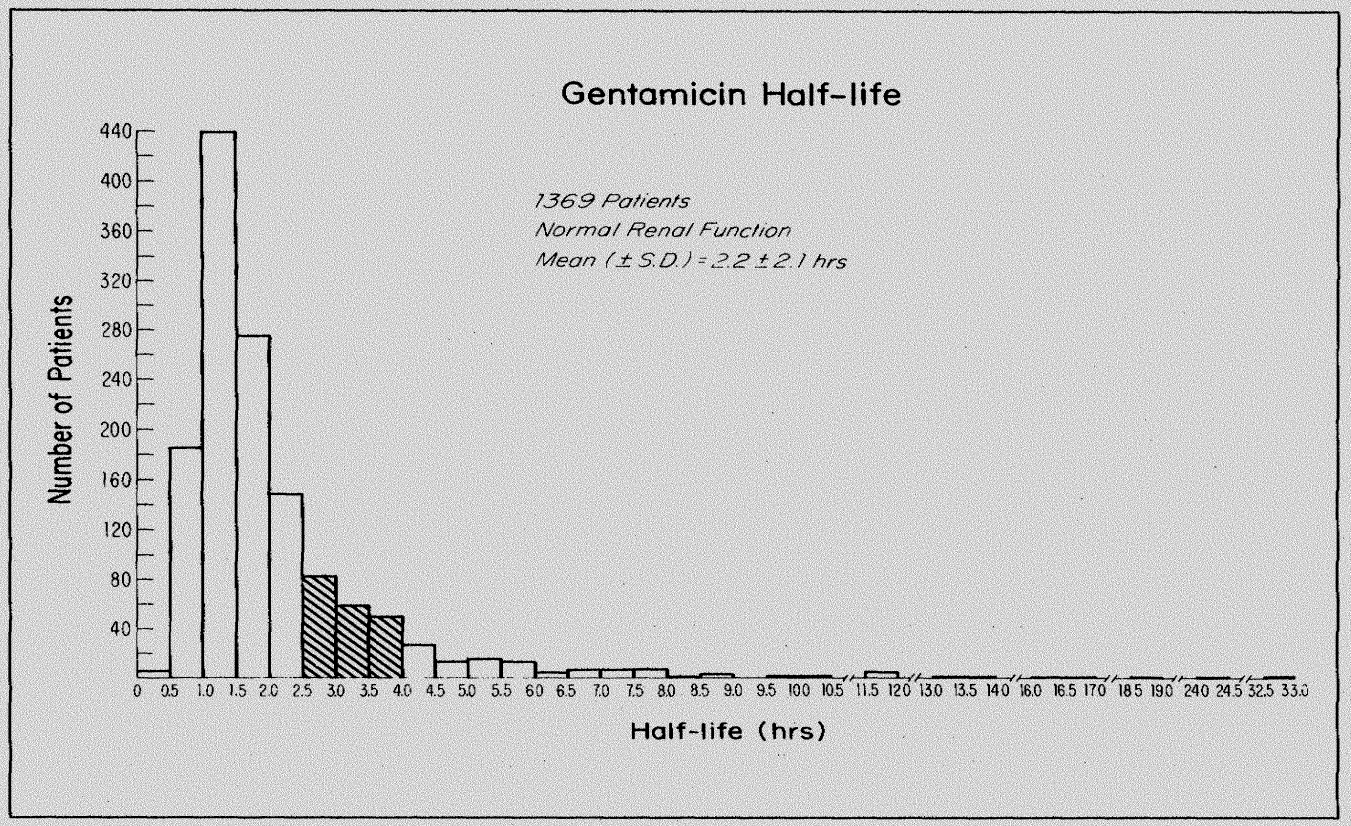


The distribution volume for gentamicin has been reported to be consistent from patient to patient and is thought to approximate the extracellular fluid compartment of 20% to 25% of body weight. Considerably more variation was noted in the distribution volume of gentamicin in these patients.

Elimination rate

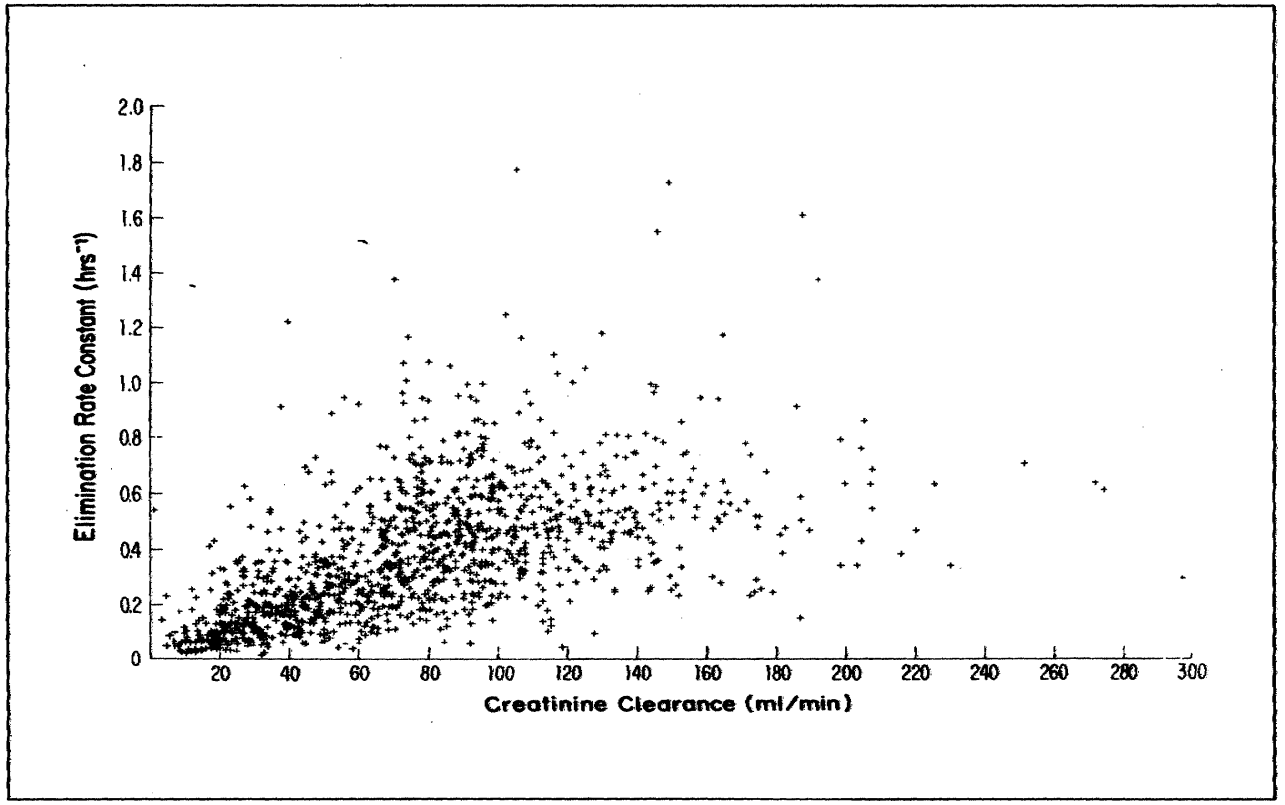
- AG elimination is closely correlated with creatinine clearance.
- Cystic fibrosis patients show a 50% increase in elimination rate.
- A major body burn increases the basal metabolic rate resulting in a marked increase in AG elimination.
- ICU patients are often hyper metabolic and therefore eliminate AG's more rapidly.

Excretion



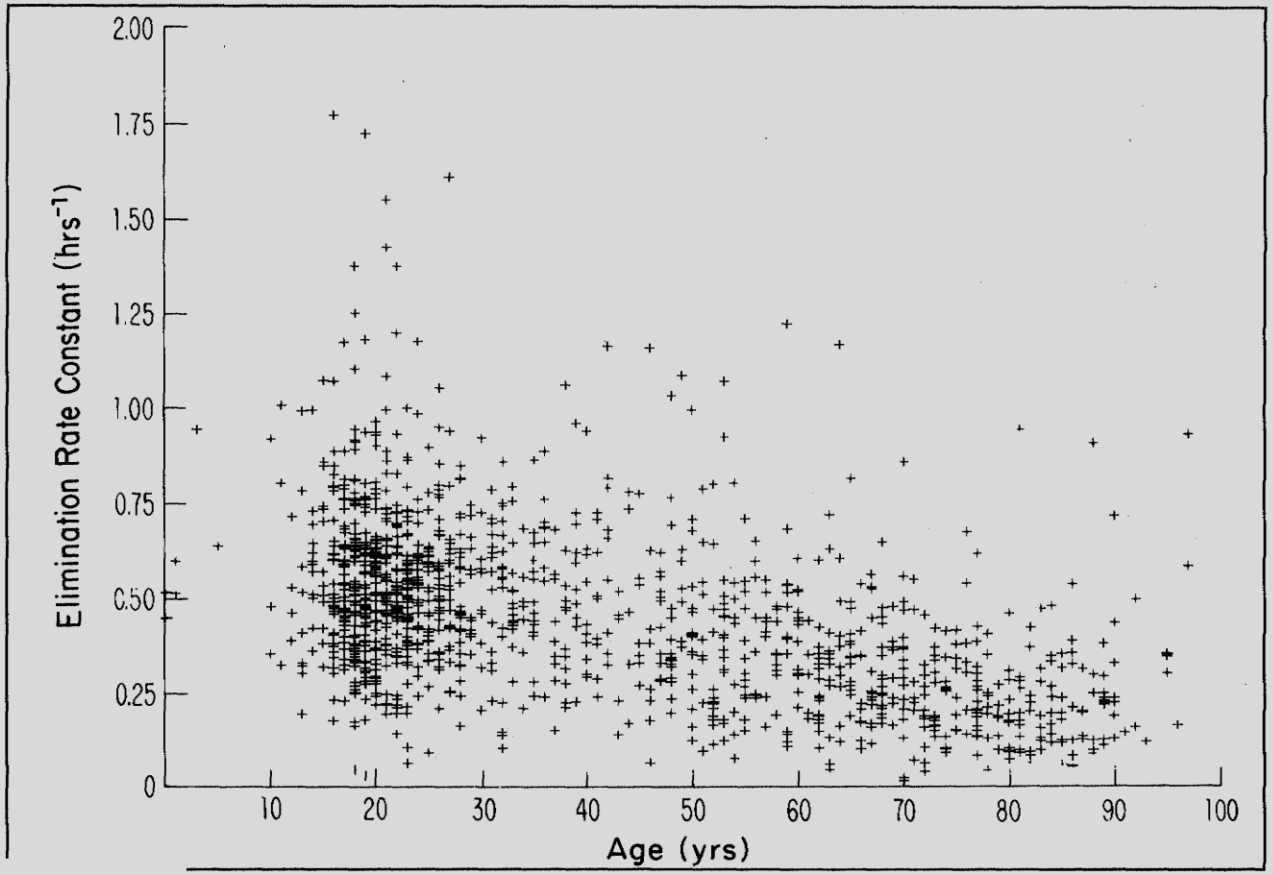
The half-life of gentamicin demonstrates a wide interpatient variation even in patients who have a normal serum creatinine. The majority of patients have a half-life less than the previously reported range of 2.5 to 4 hours. However, a substantial number of patients have prolonged elimination rates even though they have normal renal function tests as assessed by serum creatinine.

Renal Function



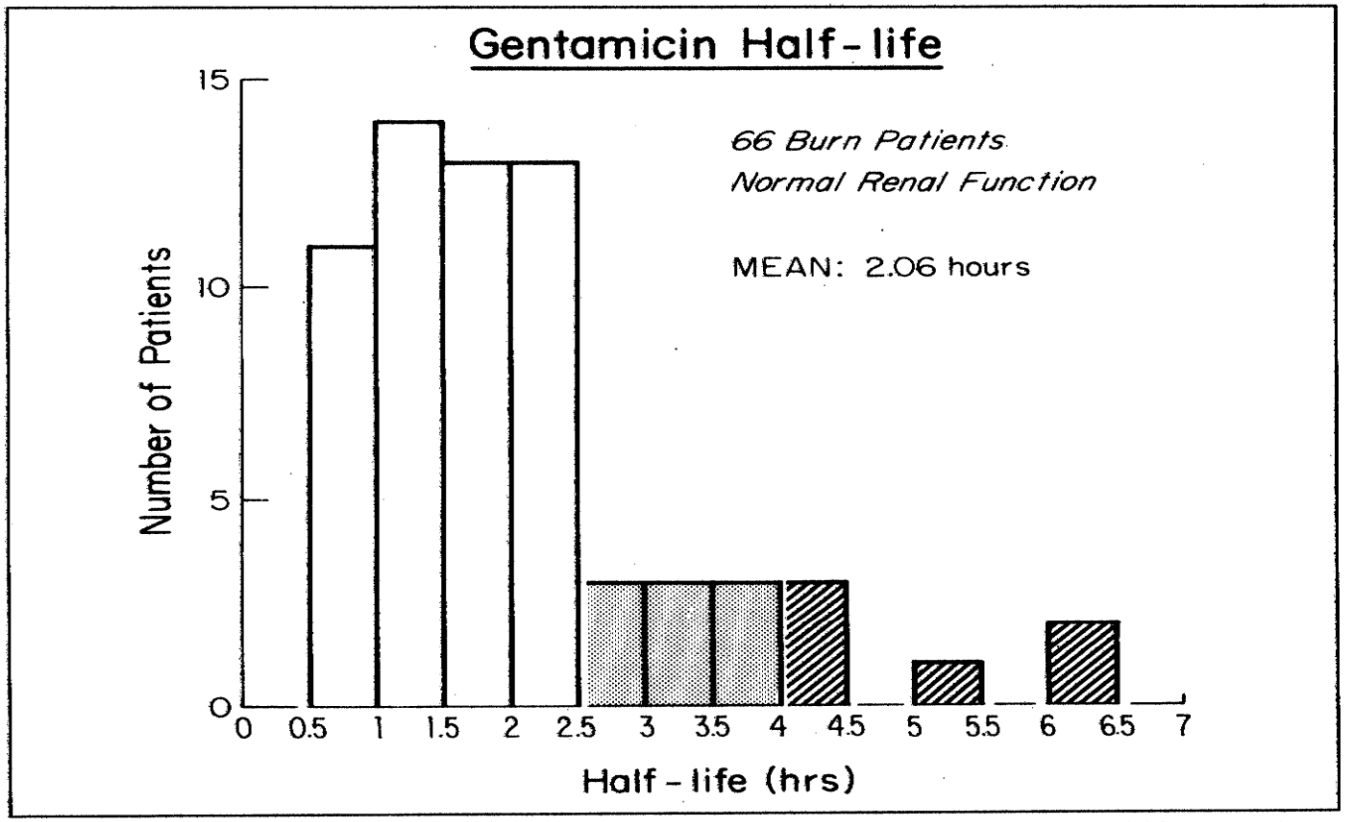
The relationship of gentamicin elimination rate constant and creatinine clearance is illustrated for 1640 patients. At any specific creatinine clearance, the elimination rate constant demonstrated at least a tenfold variation. The amount of variance (r^2) in the elimination rate constant explained by creatinine clearance was only 34%.

Age



The elimination rate constant of gentamicin continually decreased with increasing age in patients who had a normal serum creatinine (≤1.5 mg/dL). A substantial variation exists in this relationship.

Half life in Burn Patients



rapid rate of gentamicin elimination (half-life) was observed in 66 burn patients who had normal renal function

Other Factors Influencing Aminoglycoside Kinetics

- Age
- Fever
- Body Weight
- Gender
- Obstetric Patients
- Burn Patients
- Pediatric Patients
- Ascites

Monitoring parameters

- The following patient parameters should be monitored during aminoglycoside therapy:

  i. Aminoglycoside peak and trough levels

  Obtain levels 24 hours after initiating therapy, at steady state (approximately four half-lives), and every 2 to 3 days.

  ii. Urea and serum creatinine

  Measure every two days, or every day in unstable renal function.

Monitoring parameters

iii. Weight

Weigh patient every two to seven days.

iv. Urine output

Measure and monitor urine output daily

v. Baseline and weekly audiograms, and check for tinnitus or vertigo daily.

TDM: Aminoglycosides

- ***Monitoring is mandatory in ALL patients***
- ***AG accumulate in the renal cortex to levels 100-fold > plasma***

  >95% of AG are cleared by glomerular filtration

- **Desired peak serum concentrations**
  = 6.0 - 10 mg/L (Most)

- **Desired trough serum concentrations**
  = 0.5 – 2.0 mg/L (Most)

- **Due to large interpatient variability in the pharmacokinetics and potential ototoxicity and nephrotoxicity, serum concentrations should be monitored, especially in high-risk patients, those with renal impairment or who are given other ototoxic and/or nephrotoxic agents concurrently.**

Gentamicin – TDM

•Monitoring serum concentrations has been a challenge to clinicians due to the distributional characteristics of the drug.

•Assumption: first-order elimination from one-Compartment

•The peak concentration is drawn 30 minutes following the 30-minute intermittent intravenous infusion.

•ASSUMPTION: DISTRIBUTION IS COMPLETE WITH THIS SAMPLING STRATEGY.

Gentamicin – TDM

•Samples to determine trough concentration should be procured just prior to the third dose, often 0.5 hours . ASSUMPTION: STEADYSTATE ACHIEVED

•Monitoring trough concentrations alone is acceptable in otherwise normal healthy patients, following an initial set of peak and trough concentrations.

•For patients with fluctuating renal function, a pre-dose serum concentration and a series of post-dose serum concentrations should be obtained during the course of therapy.

Pharmaceutical Care for Aminoglycoside Therapy

1. Pre-Therapy

- Sign/symptom of infection
- Culture & sensitivity
- Renal function
- Complete blood count
- Urinalysis

2. On going Therapy

- Vital signs – BP,HR,RR, wt.
- Infusion rate, signs of phlebitis
- Renal function
- Signs of neuro/ ototoxicity
- Superinfection – bacteria/fungal

- diarrhea – mucus, bloody
- pseudomembranous colitis
- antibiotic-associated colitis

THANK YOU,,,,,,,,

Antiepileptics Drugs PK

SAIF KHALID ALKHAFAF
PHD. IN PHARMACOLOGY

PHENYTOIN

- Primarily used as an anticonvulsant.
- Phenytoin has been used for many years to treat children with partial and generalized tonic-clonic seizures.
- **Two major problems:**
  1. Binding of PHT to plasma protein is decreased in patients with renal failure or hypoalbuminemia.
  2. The metabolic capacity for PHT is limited

ADVERSE DRUG REACTION

1. Gingival hyperplasia
2. Folate deficiency
3. Peripheral neuropathy
4. Lateral nystagmus (>20mg/L)
5. Ataxia (>30mg/L)
6. Diminished mental capacity (>40mg/L)
7. Encephalopathy

Pharmacokinetic characteristics

- **Absorption**
  - Completely absorbed F = 1.0.
  - Injection /Capsule consist of the sodium salt (S = 0.92).
  - Chewable tablet /suspension contain the acid form (S = 1.0).
  - PO: Peak concentration time at 3 to 12 hours.
  - Insoluble in water, slow absorption.
  - The absorption of phenytoin is not first -order and non liner, and may be affected by food and antacids.

Distribution

- Approximately 90-95% of PHT bound to serum albumin.
- 5-10% is unbound and free to equilibrate with the tissues.
- In those diseases (renal and hepatic), a decrease in PPB of phenytoin and increase in the free fraction of drug and lead to increase in the clearance of phenytoin and the total concentration may be decrease.
- The Vd of phenytoin is about 0.6 to 0.8 L/Kg which is similar to that of total body water; obesity may increase the volume of distribution of phenytoin

Pharmacokinetic characteristics (cont')

- **Drug interactions**
  - Interaction with valproic acid (displacement and inhibition of CYP450):
    1. Phenytoin displaced from binding sites.
    2. Reduced (~50%) total concentration.
    3. Increased (9.6 – 15.5%) of the unbound PHT.

Metabolism and Elimenation

- Michealis and Menten demonstrated that enzyme have affinity capacity to metabolize substrate.
- When saturation occurs, change in metabolism of phenytoin will be occur from first-order (linear) process to a zero-order (non linear) process.
- Rate of metabolism (and/or excretion) is proportional to the plasma concentration.

Concentration	*t½ (hours)*
1	12.8
10	25.8
20	40.2
40	69.0

Metabolism and Elimenation

- Less than 5% of dose of phenytoin is excreted unchanged in the urine.
- Because phenytoin displays Michealis – Menten kinetic, the elimination is not linear and half – life is an inappropriate term.
- Half – life assume concentration – independent elimination.

$$D = Vmax \,.Cp \,/Km + Cp$$

Where:

- **D**: is the dose (mg/d).
- **Vmax:** is maximum rate of metabolism (mg/d).
- **Km**: is the serum concentration at which the rate of metabolism is half-maximal (ug/ml).
- **Cp**: is the serum concentration (ug/ml).

Key parameters

- **Target conc.** — **10 – 20 mg/L**
- **F** — **1.0**
- **S** — **0.92**
- **V_d** — **0.65 L/kg of body wt**
- **CL** — **- V_{max}** — **7.2 mg/kg/day**
  - **- K_m** — **4.4 mg/L**

Hypoalbuminemia correction

- **Hypoalbumin only:**

$$C_p^{normal} = \frac{C_p^{patient}}{0.9\,(Alb^{patient}/4.4) + 0.1}$$

- **Hypoalbumin with renal failure:**

$$C_p^{normal} = \frac{C_p^{patient}}{0.48(0.9)(Alb^{patient}/4.4) + 0.1}$$

*$Alb^{patient}$ in g/dL

Initiating/adjusting phenytoin dosage regimen

- **Michaelis-Menten Kinetics**

$$\text{Dose} = \frac{V_{max} C_{ave} \tau}{(K_m + C_{ave})\, SF} \quad \text{(mg/kg Q}\tau\text{H)}$$

$$R_o = \frac{V_{max} C_p}{K_m + C_p} \quad \text{(mg/kg/day)}$$

Initiating PHT regimen (using equation)

$$D = \frac{V_{max} C_p}{K_m + C_p} \quad \text{(mg/kg/day)}$$

$$D = \frac{7.2 \times 15}{4.4 + 15}$$

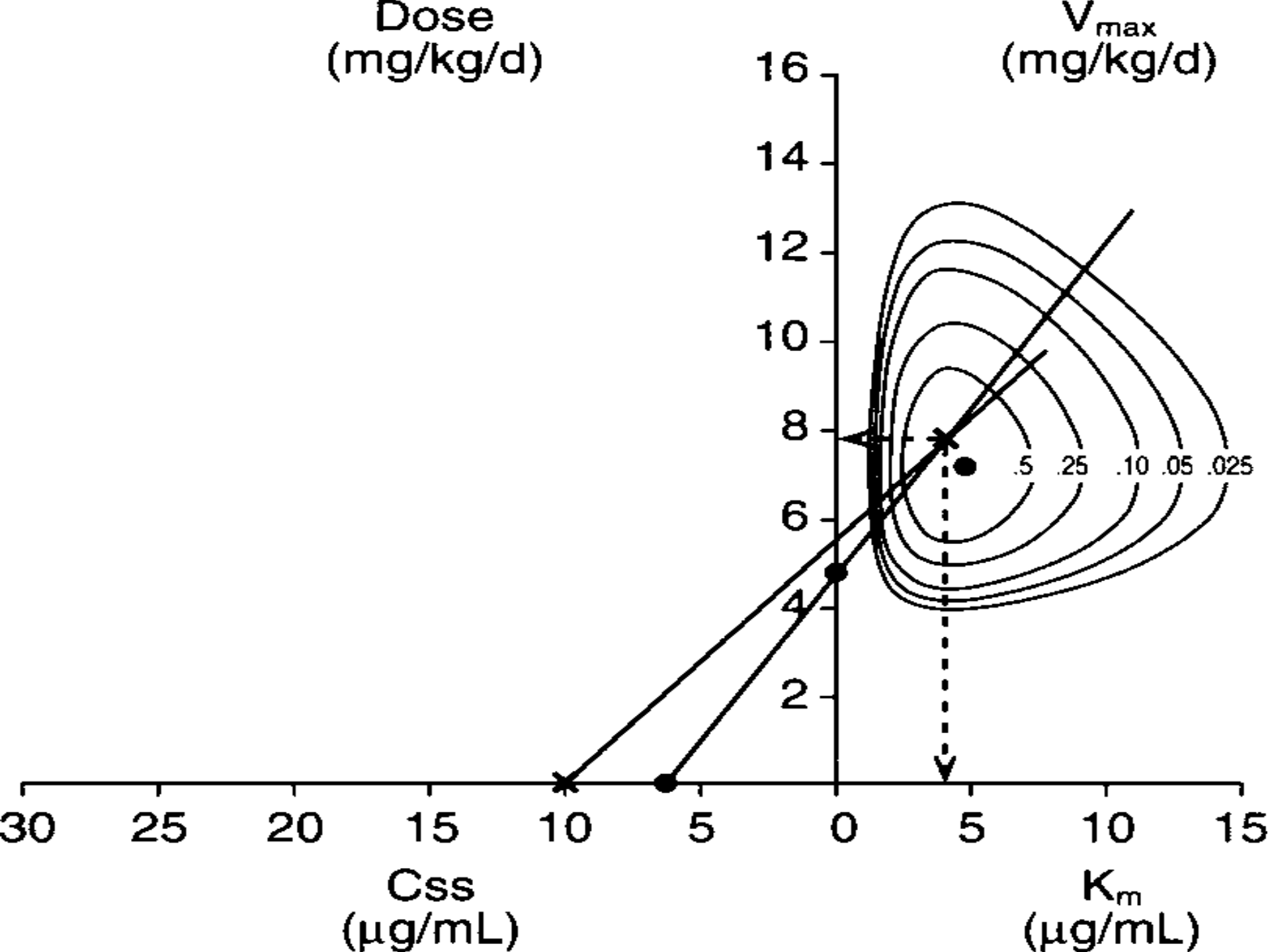
$$= 5.57 \text{ mg/kg/day}$$

Estimate **of Michaels-Menten parameters**

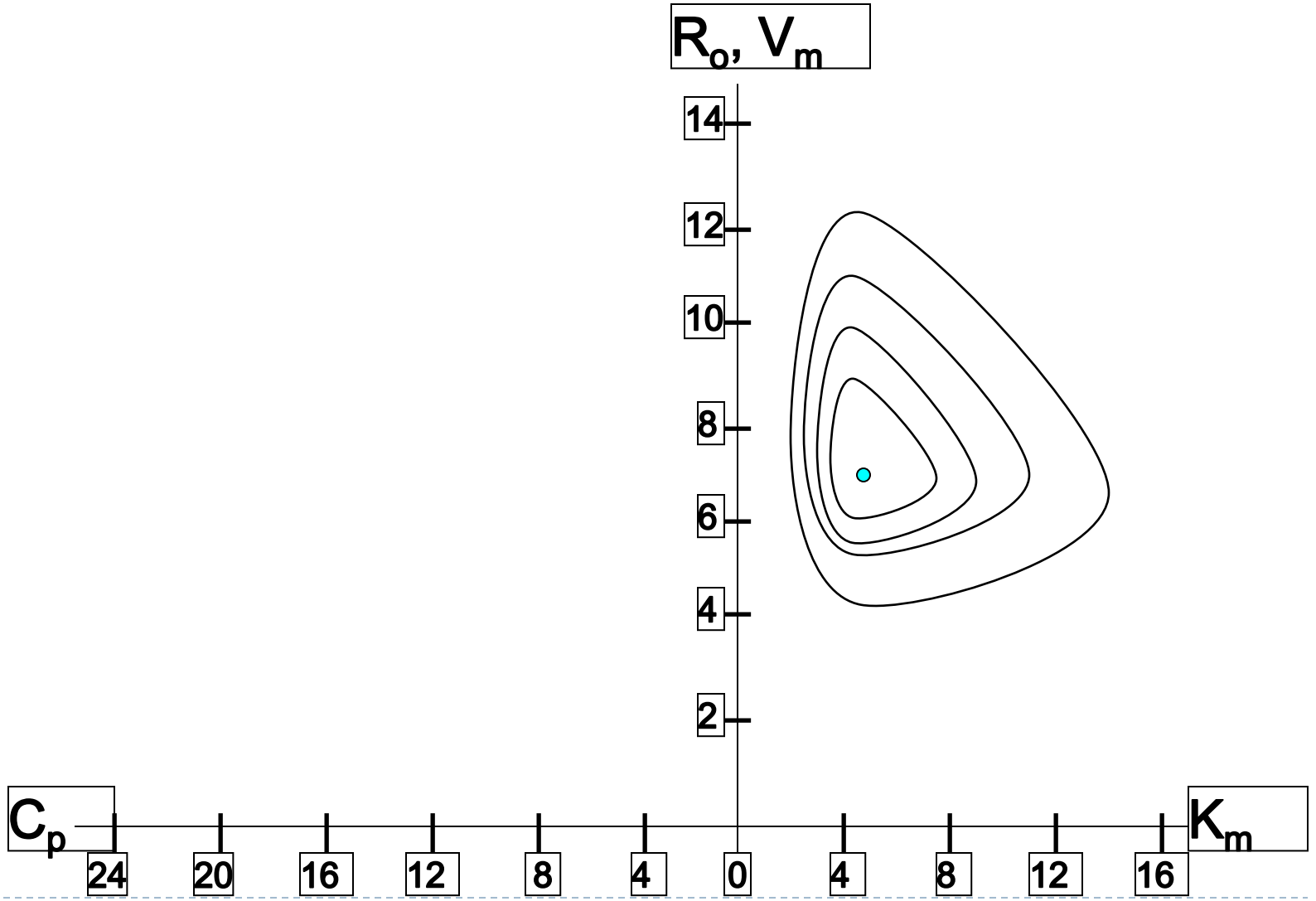
- Vm and Km are the pharmacokinetic parameters needed to estimate a maintenance dosage of phenytoin.
- We have three methods to estimate the pharmacokinetic parameters of phenytoin (Km and Vmax), we must be use the graph papers in this three methods:

A- Vozeh-Sheiner method (Orbit graph)

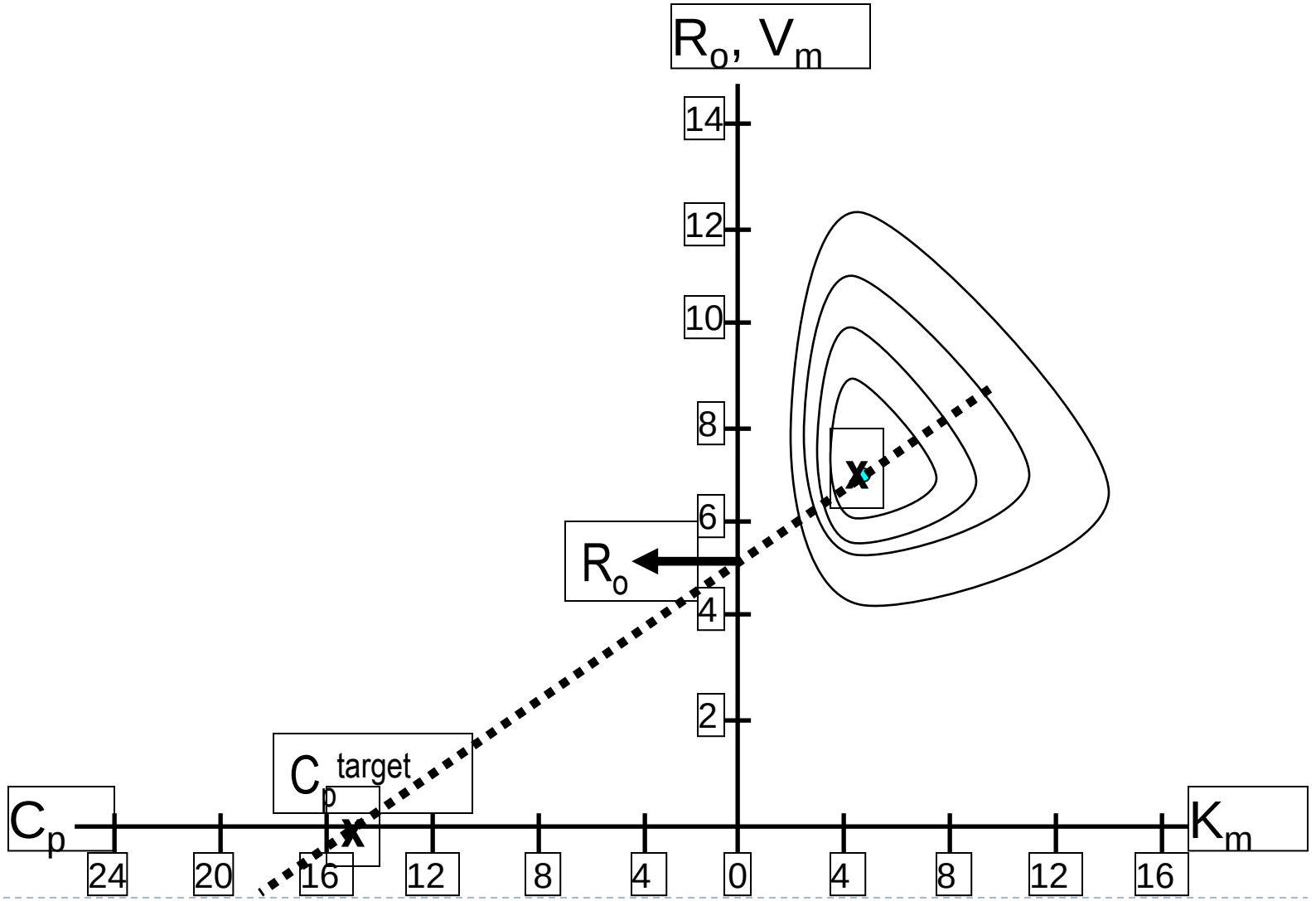
- We can estimate the parameters of phenytoin in this method by using one dose and one concentration.
- But we have two disadvantage that it use for adult and use for pediatric with limitation and we must be use the fraction of phenytoin salt (S=0.92 for capsule and injection, S=1 for suspension and chewable).


Dose
(mg/kg/d)
V_{max}
(mg/kg/d)
16
14
12
10
8
6
4
2
.5
.25
.10
.05
.025
30
25
20
15
10
5
0
5
10
15
Css
(µg/mL)
K_m
(µg/mL)

A- Vozeh-Sheiner method (Orbit graph)



1- INITIATING PHT REGIMEN
(USING ORBIT GRAPH)

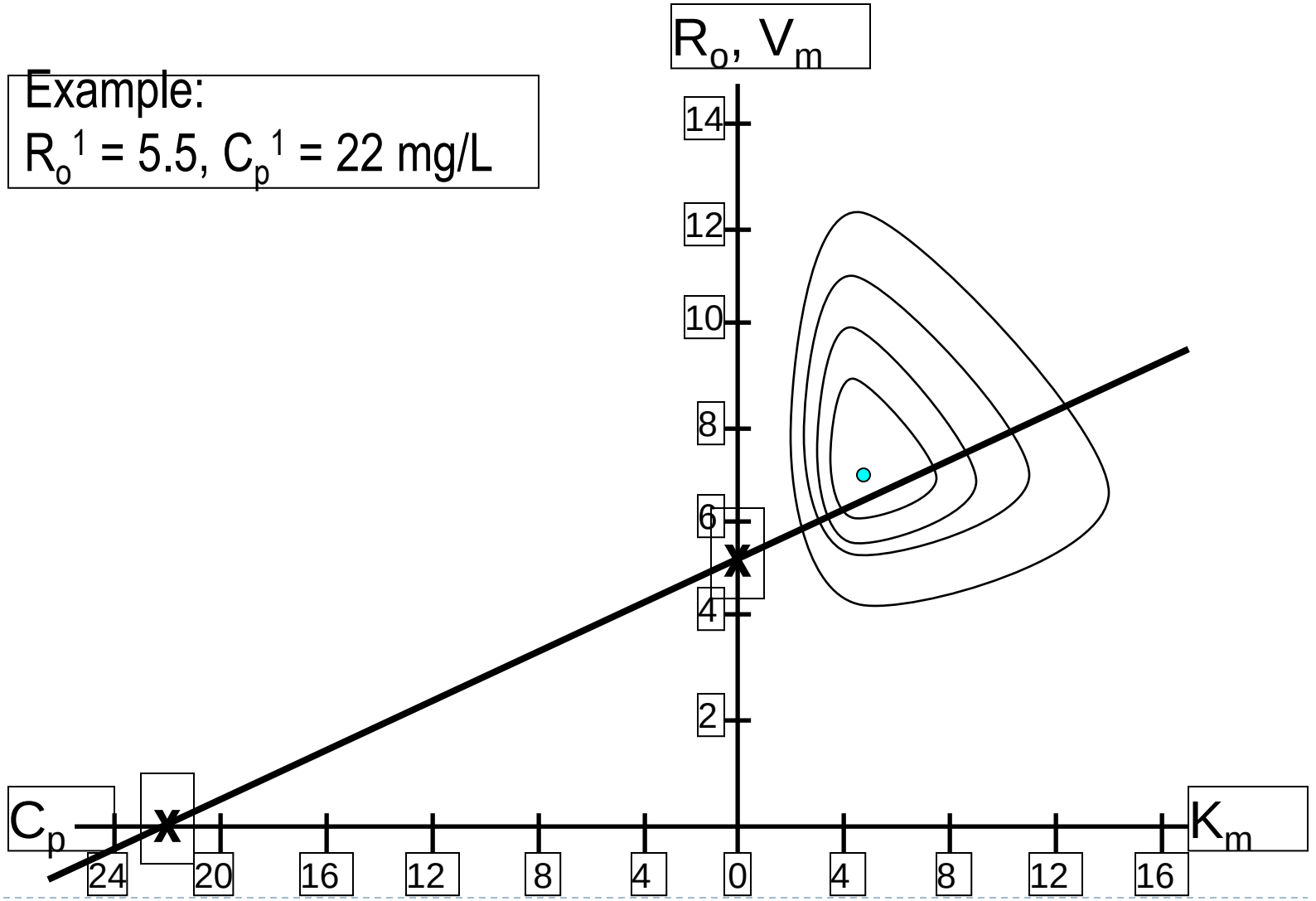


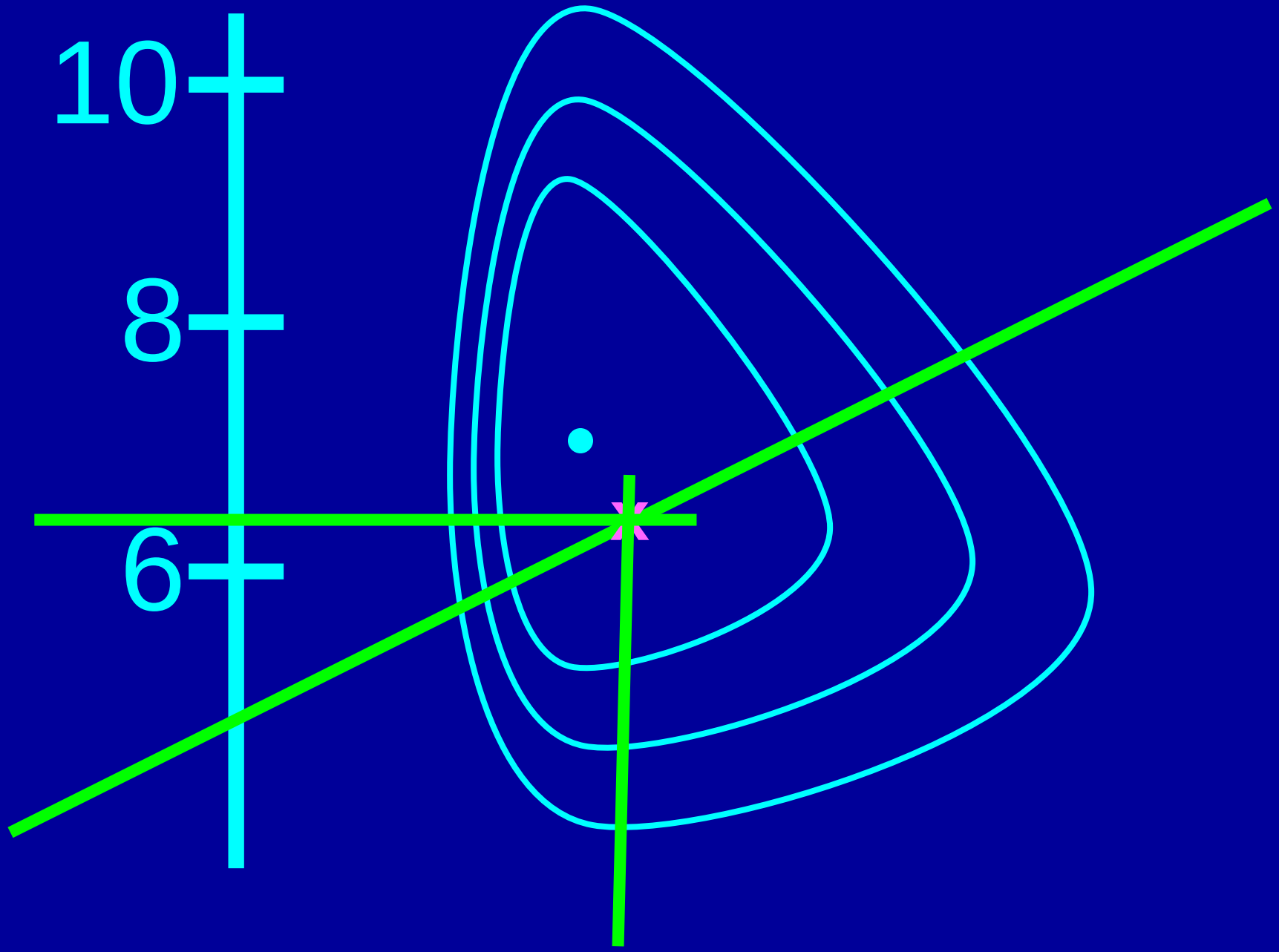
2- ADJUSTING PHT DOSAGE REGIMEN

(WITH ONE SERUM DRUG LEVEL – ORBIT GRAPH)

Example:

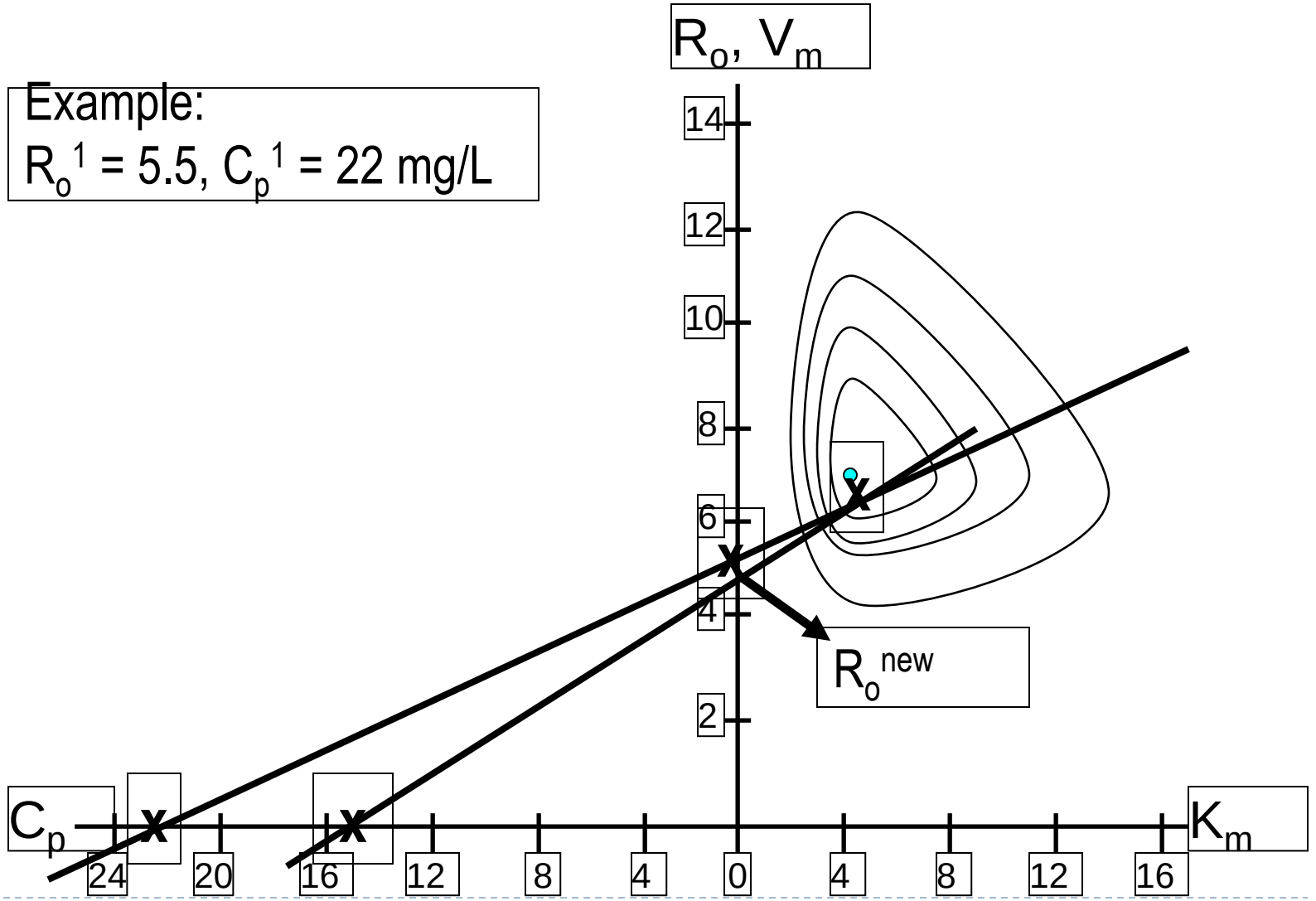
$R_o^1 = 5.5$, $C_p^1 = 22$ mg/L




10
8
6

3- ADJUSTING PHT DOSAGE REGIMEN

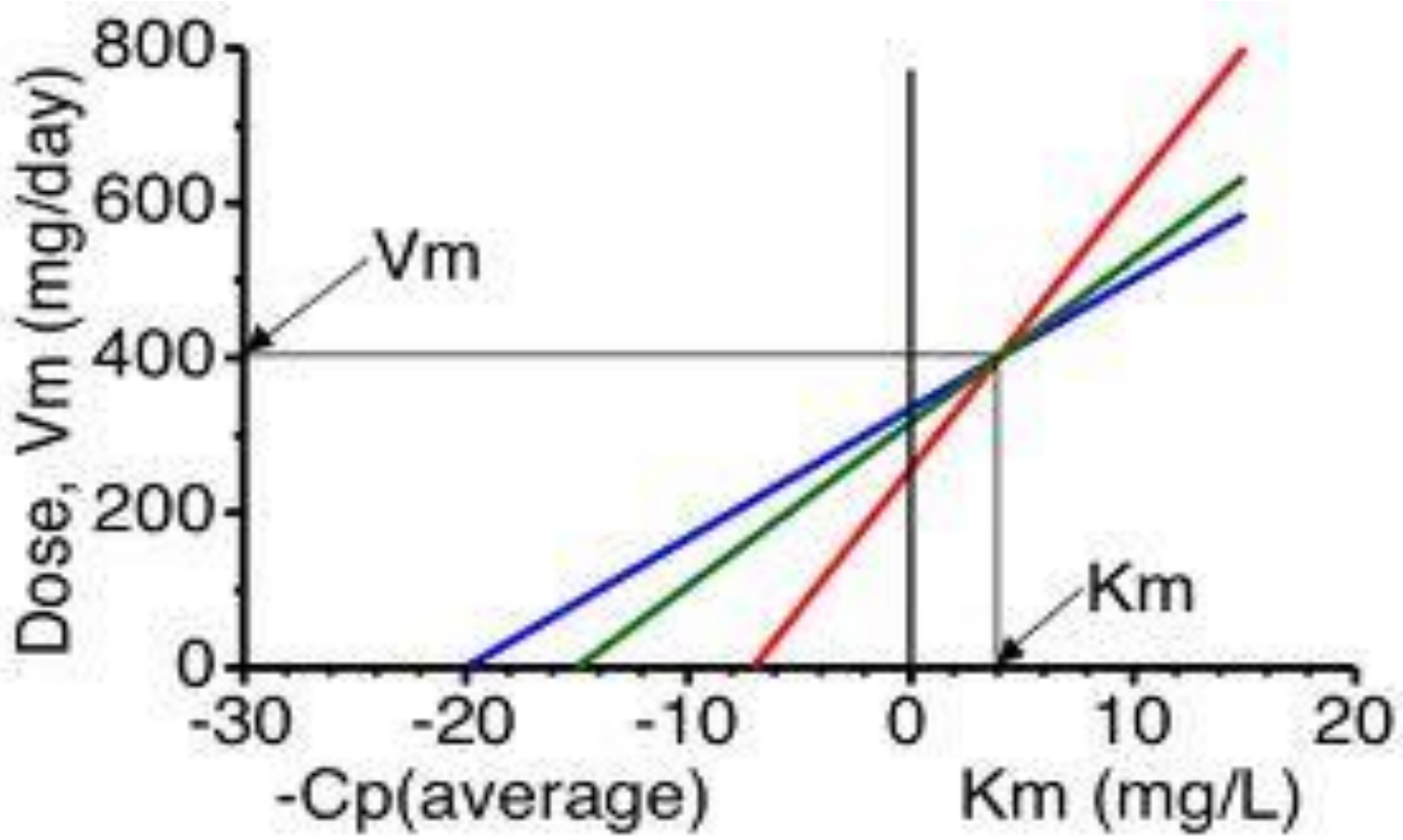
(WITH ONE SERUM DRUG LEVEL – ORBIT GRAPH)



B- Mullen method

- Similar to the orbit graph method but the population orbs denoting the Bayesian distribution of Km and Vmax parameters is omitted.
- And we must be use two doses and two concentration study-stat.

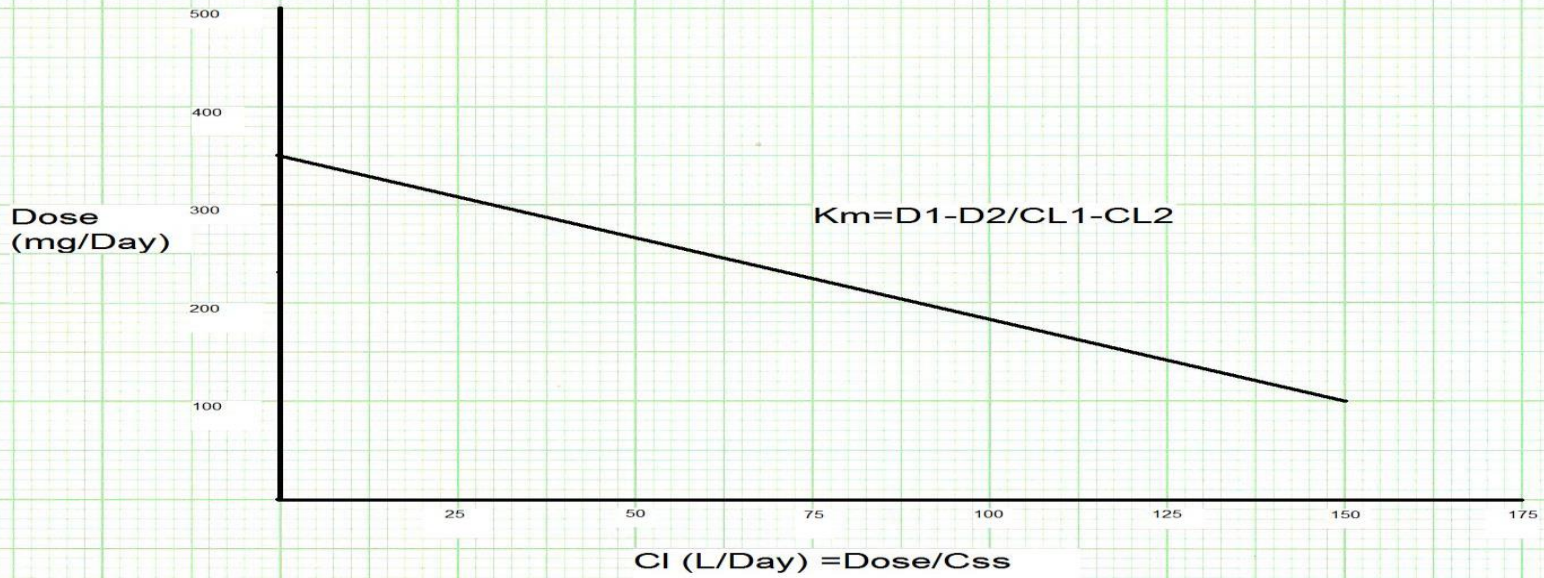
B- Mullen method



C- Ludden method

- This is the best method to estimate the parameters in children because this method use for adult and children, also we aren't need to multiple the doses by the fraction of phenytoin salt (S).

- But we need to two doses and two concentration study –stat to estimate the phenytoin pharmacokinetic parameters.



Ludden method

2mm Square 26cm x 20cm

ADJUSTING PHT DOSAGE REGIMEN

(WITH ONE SERUM DRUG LEVEL – EQUATION)

$$R_o = \frac{V_{max} C_p}{K_m + C_p}$$

$$V_{max}^{*} = \frac{R_o^{given} \left(K_m^{pop} + C_p^{achieved}\right)}{C_p^{achieved}}$$

$$R_o^{new} = \frac{V_{max}^{*} C_p^{target}}{K_m^{pop} + C_p^{target}} \quad \text{(mg/kg/day)}$$

ADJUSTING PHT DOSAGE REGIMEN

(WITH TWO SERUM DRUG LEVELS – EQUATION)

$$R_o^{1} = \frac{V_{max}^{*} C_p^{1}}{K_m + C_p^{1}}.$$

$$R_o^{2} = \frac{V_{max} C_p^{2}}{K_m^{*} + C_p^{2}}.$$

$$R_o^{new} = \frac{V_{max}^{*} \times C_p^{target}}{K_m^{*} + C_p^{target}}.$$

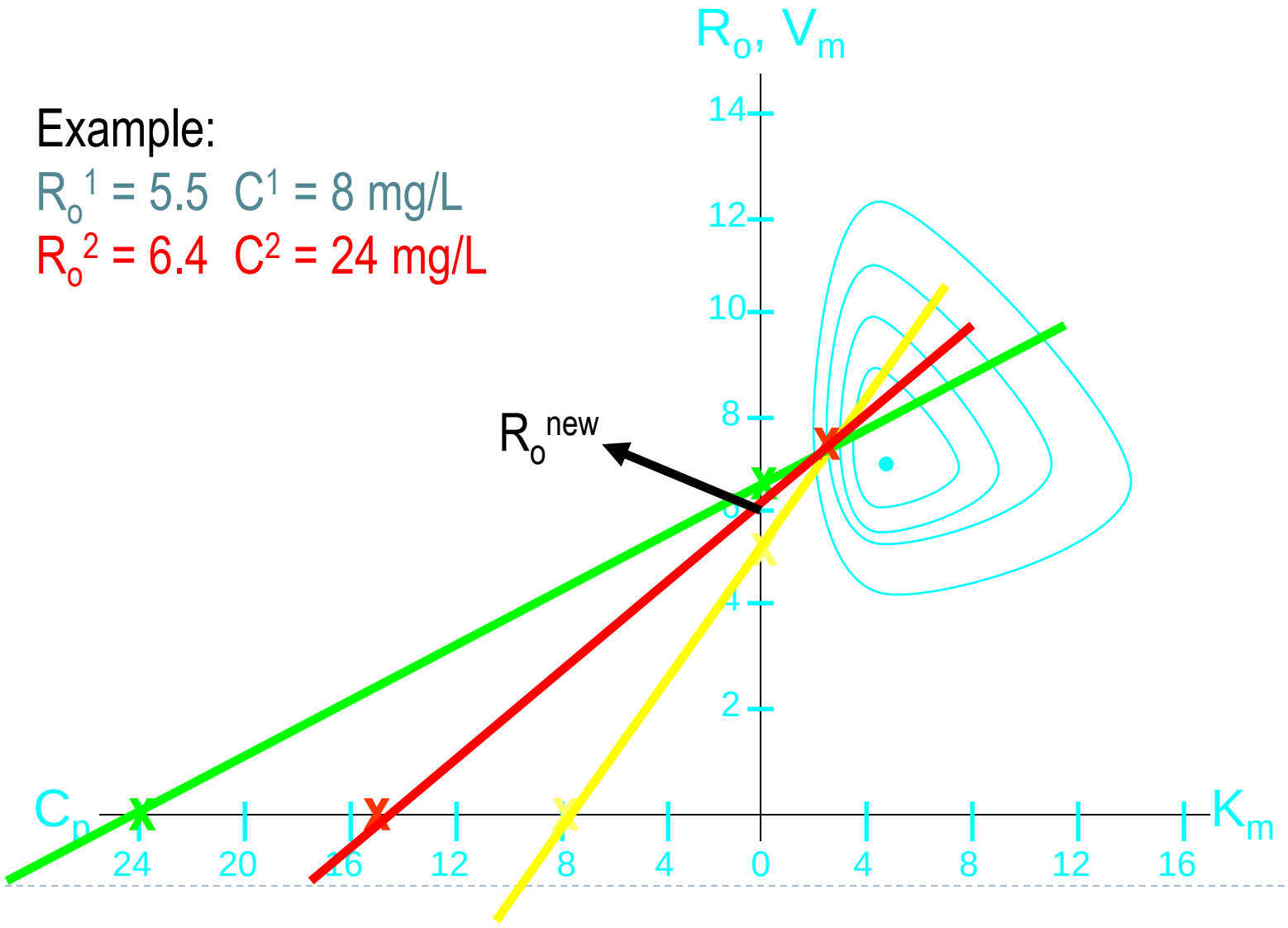
ADJUSTING PHT DOSAGE REGIMEN

(WITH TWO SERUM DRUG LEVELS – ORBIT GRAPH)

Example:

$R_o^1 = 5.5$ $C^1 = 8$ mg/L

$R_o^2 = 6.4$ $C^2 = 24$ mg/L



OTHER ANTIEPILEPTICS

VALPROIC ACID

- **Pharmacokinetic Characteristics**
  - Many formulation
  - Diurnal variation in absorption: night times AUC for enteric coated tablet was 32% lower than day times AUC.
  - CL_{VPA} increase by CBZ, PHB, PHT and PRI.
  - Metabolized to active metabolite: 4-ene VPA
  - Protein binding 90 – 95%

VALPROIC ACID (CONT')

- **Key Parameters**
  - Target concentration 50 – 100 mg/L
  - F 1.0
  - S 1.0
  - V_d ~0.2 L/kg
  - CL- Children 13 ml/kg/H
    - Adults 8 ml/kg/H
  - t½- Children 6 – 8 H
    - Adults 10 – 12 H

VALPROIC ACID (CONT')

- **Dose Requirement:**
  - Maintenance Dose

    Adults 10 – 45 mg/kg/day PO

    Children 10 – 60 mg/kg/day PO
- **Toxic Effects**
  - Gastric irritation, nausea, vomiting
  - Weight gain
  - Sedation, stupor, tremor
  - Thrombocytopenia
  - Hepatotoxicity, pancreatitis
  - Hyperammonemia

CARBAMAZEPINE

- Insoluble in water.
- Humidity will reduced dissolution.
- Autoinduction is concentration dependent: increase D_M and CL of unbound drug.

Time	*t½ (H)*
After initial dose	~35
After 3 – 4 weeks	~12

CARBAMAZEPINE (CONT')

- **Pharmacokinetic Characteristics**
  - Metabolized to active metabolite: CBZ epoxide
  - Drug interaction: CYP450 inhibitors eg. Erythromycin, Fluoxetine, Propoxyphene, VPA and Verapamil.
  - Bound to α-acid glycoprotein.
  - 1% excreted unchanged in the urine.

CARBAMAZEPINE (CONT')

- **Key Parameters**
  - Target concentration 4 – 12 mg/L
  - F 0.8
  - S 1.0
  - V_d 1.4 L/kg
  - CL- Monotherapy 0.064 L/kg/H
    - Polytherapy 0.1 L/kg/H
  - t½- Monotherapy 15 H
    - Polytherapy 10 H

CARBAMAZEPINE (CONT')

- **Dose Requirement:**
  - Anticonvulsant

    Adults 5 – 25 mg/kg/day PO

    Children 5 – 30 mg/kg/day PO
  - Trigeminal neuralgia

    Adults 3 – 20 mg/kg/day PO
- **Toxic Effects**
  - Diplopia
  - Hyponatremia, water intoxication
  - Seizure, Arrhythmias

DOSE ADJUSTMENT FOR VAPROIC ACID AND CARBAMAZEPINE

$$C_{ave}^{\infty} = \frac{D}{K_e V_d \tau}.$$

$$= \frac{D}{CL\ \tau}.$$

THANK YOU

Bioavailability (F) and Therapeutic Index (TI)

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Definitions

- **Pharmacokinetics** is the study of the time course of the drug concentration in the body, i.e., "what the body does to the drug".
- **Pharmacodynamics** is the study of the relationship of drug concentration to pharmacologic effects, i.e., "what the drug does to the body".
- **Therapeutic drug monitoring** is the measurement of the serum level of a drug and the coordination of this serum level with a therapeutic range.
- **The therapeutic range** is that range of serum drug concentrations which have been shown to be efficacious without causing toxicity in the majority of patients.

BIOAVAILABILITY

- The fraction of the dose of a drug (F) that enters the general circulatory system,

$$F = \frac{\text{amt. Of drug that enters systemic circul}}{\text{Dose administered}}$$

$$F = \frac{\text{AUC}}{\text{Dose}}$$

Bioavailability

- A concept for oral administration (Extravascular)
- I.V injection gives 100% bioavailability.
- Measures the rate and extent by which a drug reaches systemic circulation
- Fraction of unchanged drug that reaches systemic circulation

Factors that Affect Bioavailability

1. Biopharmaceutical factors
   - Dosage form
   - Physicochemical properties
2. Physiologic factors
   - Gastric motility
   - Pre-systemic metabolism
3. GIT contents – Food, drugs, fluid
4. Disease states

In general,

- Dissolution and absorption characteristics of the administered chemical form (e.g. salt, ester).
- The dosage form (e.g. tablet, capsule).
- The rout of administration.
- Stability of the active ingredient in the gastrointestinal(GI)tract.
- The extent of drug metabolism before reaching the systemic circulation.
  - Drug can be metabolized by GI bacteria, GI mucosa and by liver before reaching the systemic circulation.

In general,

- It is apparent that bioavailibity will depend on both how well drug is absorbed and how much escape being removed by the liver before reaching the systemic circulation.

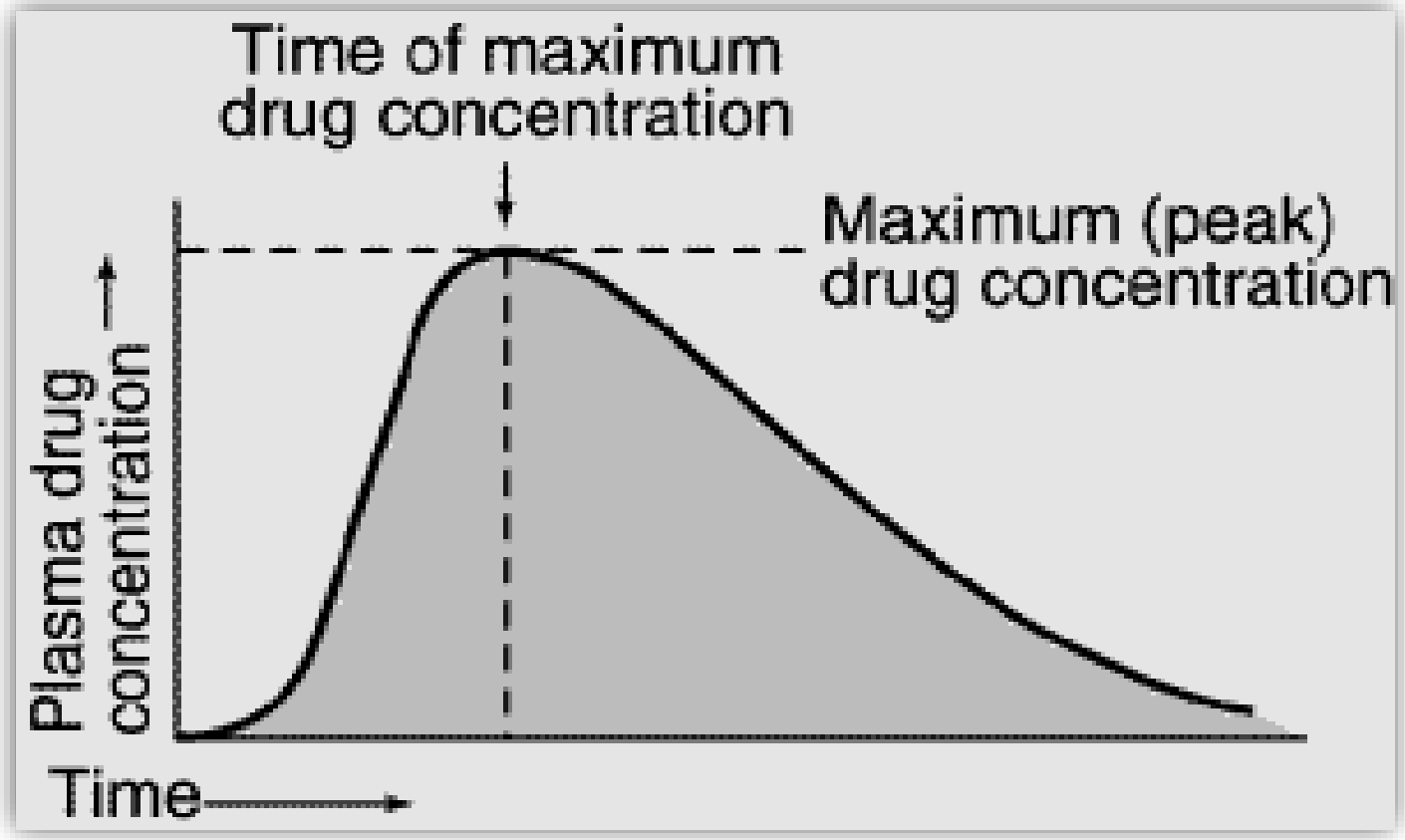
Bioavailability = *fraction absorbed + fraction escaping first pass clearance.*

- $F = f_g + f_H$

- Where the fraction of drug first pass clearance extraction by liver is (1-hepatic extraction ratio).

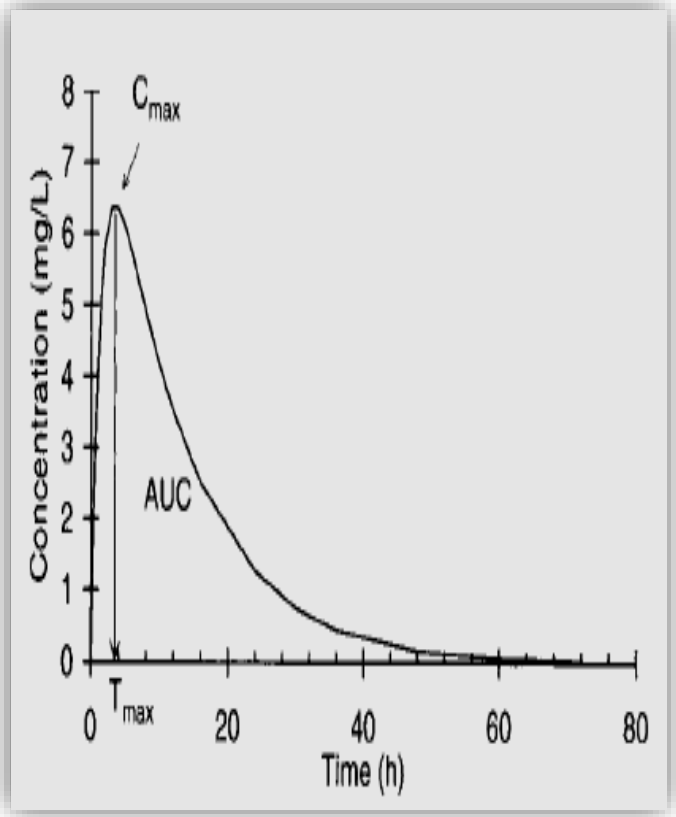
Plasma drug conc./Time

- Plasma data



Determinants of Bioavailability

- Calculated from comparison of the Area Under the Curve (AUC) relating plasma concentration to time for iv dosage compared with other route.
- AUC is the most reliable measure of bioavailability.
- It is directly proportional to the total amount of unchanged drug that reaches the systemic circulation.
  - *When the AUC, Cmax, and Tmax are the same within statistical limits for two dosage forms of the same drug, the dosage forms are considered to be* ***bioequivalent****.*



Calculation of bioavailability (F)

- The administered dose should be multiplied by a bioavailibity factor .

- *E.g. bioavailibity of Digoxin (Lanoxin) is estimated to be 0.7 for orally administered tablet(250 µg{0.25 mg} of Digoxin is given orally, the effective or absorbed dose can be calculated = dose x F).*

- Amount of drug absorbed or reaching the systemic circulation

$$= (F)(Dose)$$

$$= (0.7)(250\mu g) = 175\mu g$$

Dosage form

- Bioavailability can vary among different formulations and dosage forms of a drug.

$$\text{dose of new dosage form} = \frac{\text{amount of drug absorbed from current dosage form}}{F \text{ of new dosage form}}$$

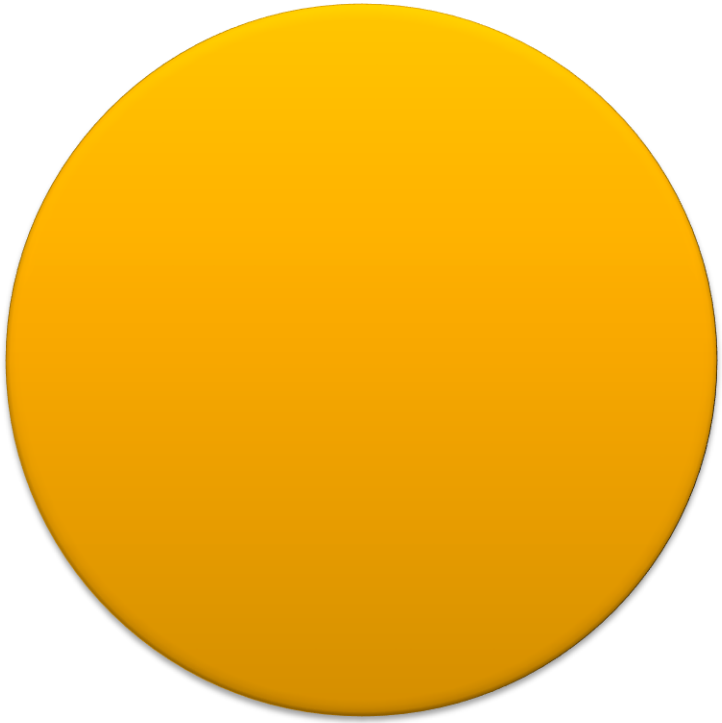
Chemical form(S)

- When salt or ester of a drug administered, the bioavailibity factor (F) should be multiplied by the fraction of the total molecular weight (S) that the active drug represents.
- *The amount of drug absorbed or reaching the systemic circulation = (S)(F)(Dose).*

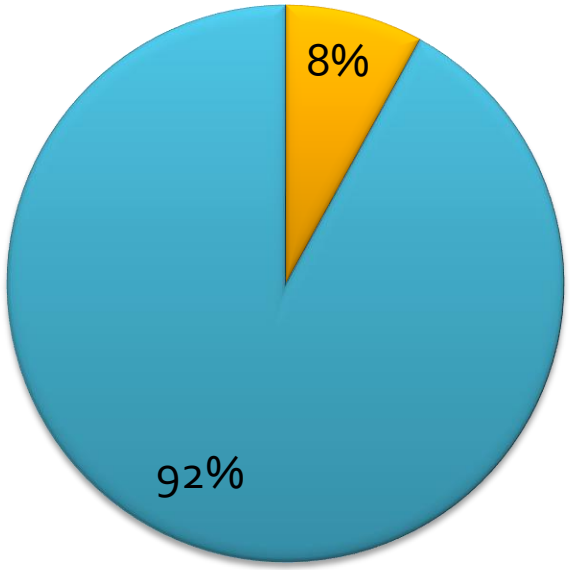
e.g. Aminophylline and Phynytoin.

- F&S *must be considered when drugs are administered by the oral rout*

The effect of the chemical drug form on bioavailability



300 mg phenytoin Sodium
(Sodium Salt of Phenytoin)



28 mg Sodium

272 mg Phenytoin

First pass effect

- Refers to metabolism by liver as the drug passes through the liver via the portal vein following absorption.
- The **first-pass effect** (also known as **first-pass metabolism** or **pre-systemic metabolism**) is a phenomenon of drug metabolism whereby the concentration of a drug is greatly reduced before it reaches the systemic circulation. It is the fraction of lost drug during the process of absorption which is generally related to the liver and gut wall.
- Notable drugs that experience a significant first-pass effect are Imipramine, Morphine, Propranolol, Buprenorphine, Diazepam, Midazolam, Demerol, Cimetidine, and Lidocaine.
- First pass effect can substantially decrease the amount of active drug reaching the systemic circulation and thus its bioavailability

Bioavailability

- Bioequivalence:
  - when two related drugs show comparable bioavailability

- Therapeutic Equivalence:
  - when two similar drugs have comparable efficacy and safety

Routes of Administration, Bioavailability, and General Characteristics

Route	Bioavailability (%)	Characteristics
Intravenous (IV)	100 (by definition)	most rapid onset
Intramuscular (IM)	75 to ≤ 100	large volumes often feasible; may be painful
Subcutaneous (SC)	75 to ≤ 100	smaller volumes than IM; may be painful; slower onset than IV or IM
Oral (PO)	5 to < 100	most convenient; first-pass effect may be significant
Rectal (PR)	30 to < 100	less first-pass effect than oral
Transdermal	80 to ≤ 100	usually very slow absorption; used for lack of first-pass effect; prolonged duration of action

ADMINSTRATION RATE(R_A)

- Is the average rate at which absorbed drug reach the systemic circulation :

$$RA = \frac{(S)(F)(Dose)}{\tau}$$

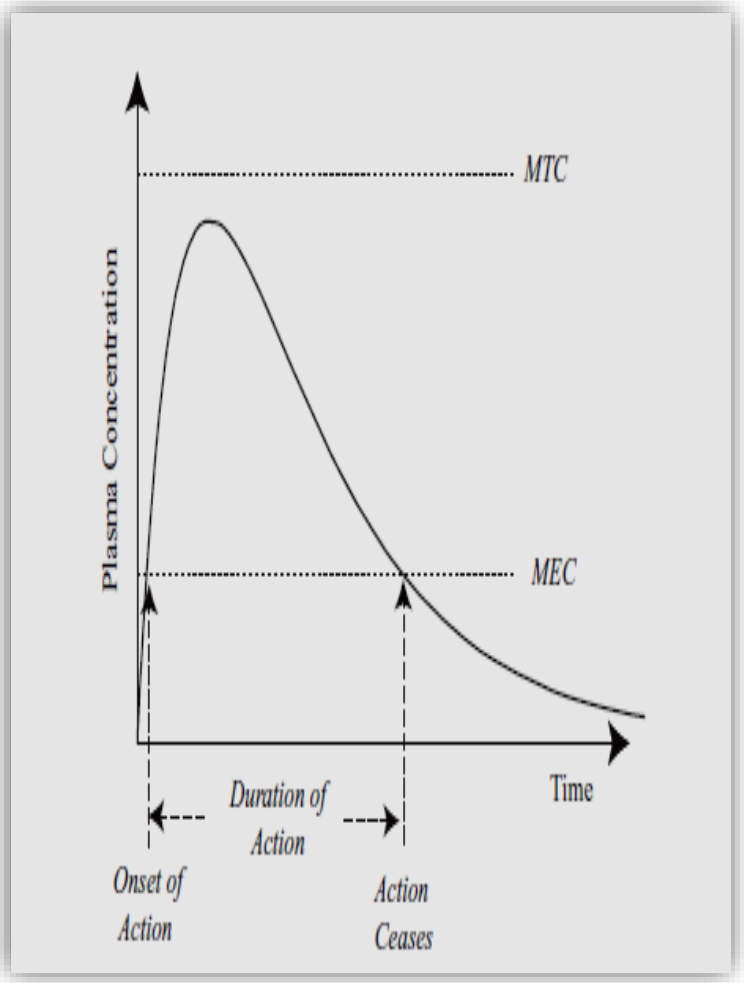
Problem: calculate the administration rate of Theophylline resulting from Aminophylline infused at rate of 40mg/hr?

Concept of therapeutic drug range

- Defined as the range of plasma concentrations that are associated with optimum response and minimal toxicity in most patients.
- Most commonly, the goal of therapy is to maintain drug concentrations within the therapeutic range at all times.
- Small number of drugs for which this is not desirable, such as certain antibiotics and drugs such as nitroglycerin, where tolerance develops with continuous exposure to the drug.

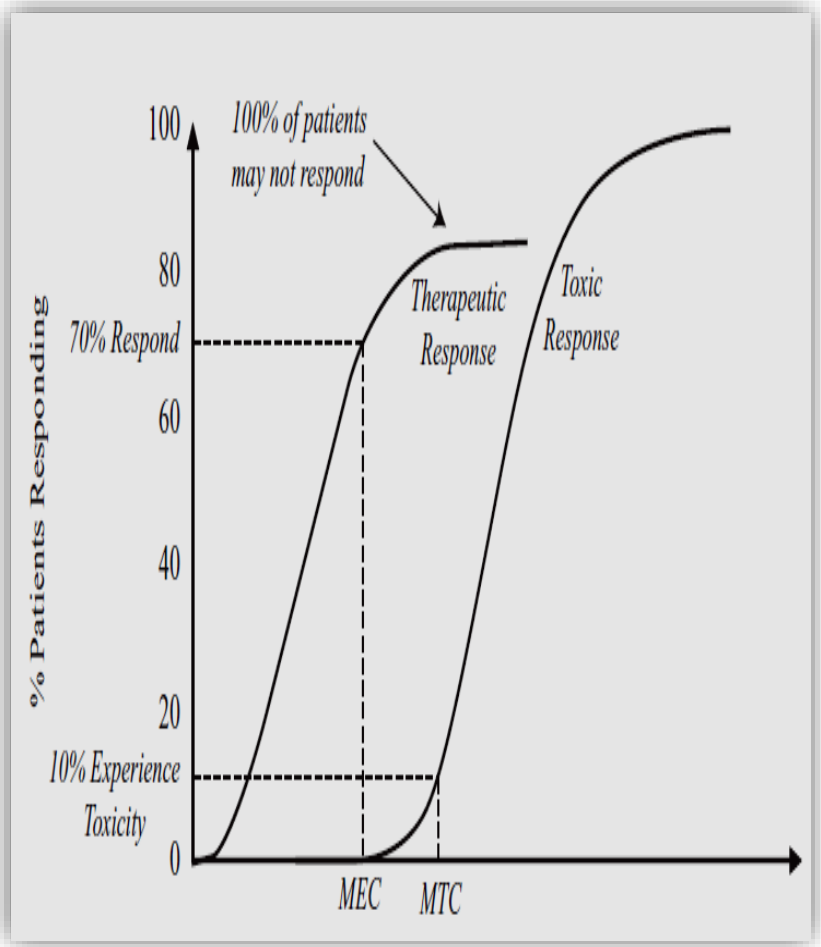
Therapeutic drug range

- **The minimum effective concentration** (MEC), the lower boundary for effective drug concentrations; plasma concentrations below the MEC have a high probability of being sub-therapeutic.
- **The maximum tolerated concentration** (MTC) is the upper boundary for optimum drug concentrations; plasma concentrations above the MTC have a high probability of producing adverse effects or toxicity.
- **The onset of action** of a drug, which may be estimated as the time it takes for plasma concentrations to reach the MEC.
- **The duration of action of a drug**, which may be estimated as the time during which plasma concentrations remain within the therapeutic range.



Therapeutic drug range

- The MEC and MTC are usually chosen at concentrations where a high percentage of patients experience a therapeutic effect and a small percentage of patients experience toxicity, respectively.
- The specific concentrations selected for the MEC and the MTC will depend on the margin of safety and the risk–benefit ratio acceptable for a given indication.



Therapeutic Index (TI) or Therapeutic Ratio.

- The therapeutic index or therapeutic ratio is a way to express the safety margin offered by a drug.
- It is the ratio of the dose of the drug that produces toxicity in 50% of patients to the dose of the drug that produces therapeutic response in 50% of patients:

$$TI = \frac{TD_{50}}{ED_{50}}$$

Factors Leading To Inter-individual Variation In Drug Concentration:

1. Variation in drug absorption.
2. Physiologic states (e.g. obesity, age extremes).
3. Disease states (e.g. renal and hepatic disease, cystic fibrosis).
4. Differences in metabolism and excretion.
5. Drug interactions.
6. Pharmaceutical formulation, route of administration, food.

Therapeutic range considerations

- Same drug but for different indications (e.g. Digoxin in AF, and CHF)
- When drug concentration doesn't give the desired response:
  1. Existence of **active metabolite** (e.g. Theophylline).
  2. Presence of **tolerance or resistance**.
  3. Single dose therapy.
  4. Time delay.
  5. Genetic influence or Gender.

TO BE CONTINUED !!!!!

Clearance (Cl)
Maintenance Dose (MD)
Elimination Constant (Ke)
Conc. (Max. and Min.)

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Clearance (CL)

- The intrinsic ability of the body or its organs of elimination (usually kidney & liver) to remove drug from the blood or plasma.
- The efficiency of irreversible elimination of a drug from the systemic circulation .
- It refer to the excretion of the unchanged drug into urine, gut contents, expired air, sweat, etc, and to the metabolic conversion of the drug into different chemical compound, predominantly in the liver.

$$CL_{TOTAL} = CL_{RENAL} + CL_{NONRENAL}$$

Clearance (CL)

- "*the volume of blood cleared of drug per unit of time*" .
- Clearance expressed as a volume per unit of time (*liter per hour or ml per minute*).
- It represents only the theoretical volume of blood or plasma which is completely cleared of drug in a given period .
  - The amount of drug removed depends on the plasma concentration of drug and the clearance.

Clearance (CL)

- At steady state, the rate of drug administration (R_A) and rate of drug elimination (R_E) must be equal.

$$R_A = R_E$$

- Drug clearance is constant if the drug is eliminated by first-order kinetics.
  - *Clearance (CL)can be best be thought of as the proportionally constant that makes the average steady state plasma drug level equal to the rate of drug administration (R_A):*

$$R_A = (CL)(Css\ ave)$$

  - $R_A = (S)(F)(Dose)/\tau$
  - Css ave is the average steady state drug constant.

$$CL = \frac{(S)(F)\left(DOSE/\tau\right)}{Css\ ave}$$

Clearance (CL)

$$CL = k_e . V_d$$

$$\mathrm{CL} = \frac{(\mathrm{S})(\mathrm{F})\left(\mathrm{DOSE}/\tau\right)}{\mathrm{Css\ ave}}$$

$$CL = \frac{(S)(F)(Dose)}{\tau \, . \, C_{ss\ av}}$$

Maintenance dose

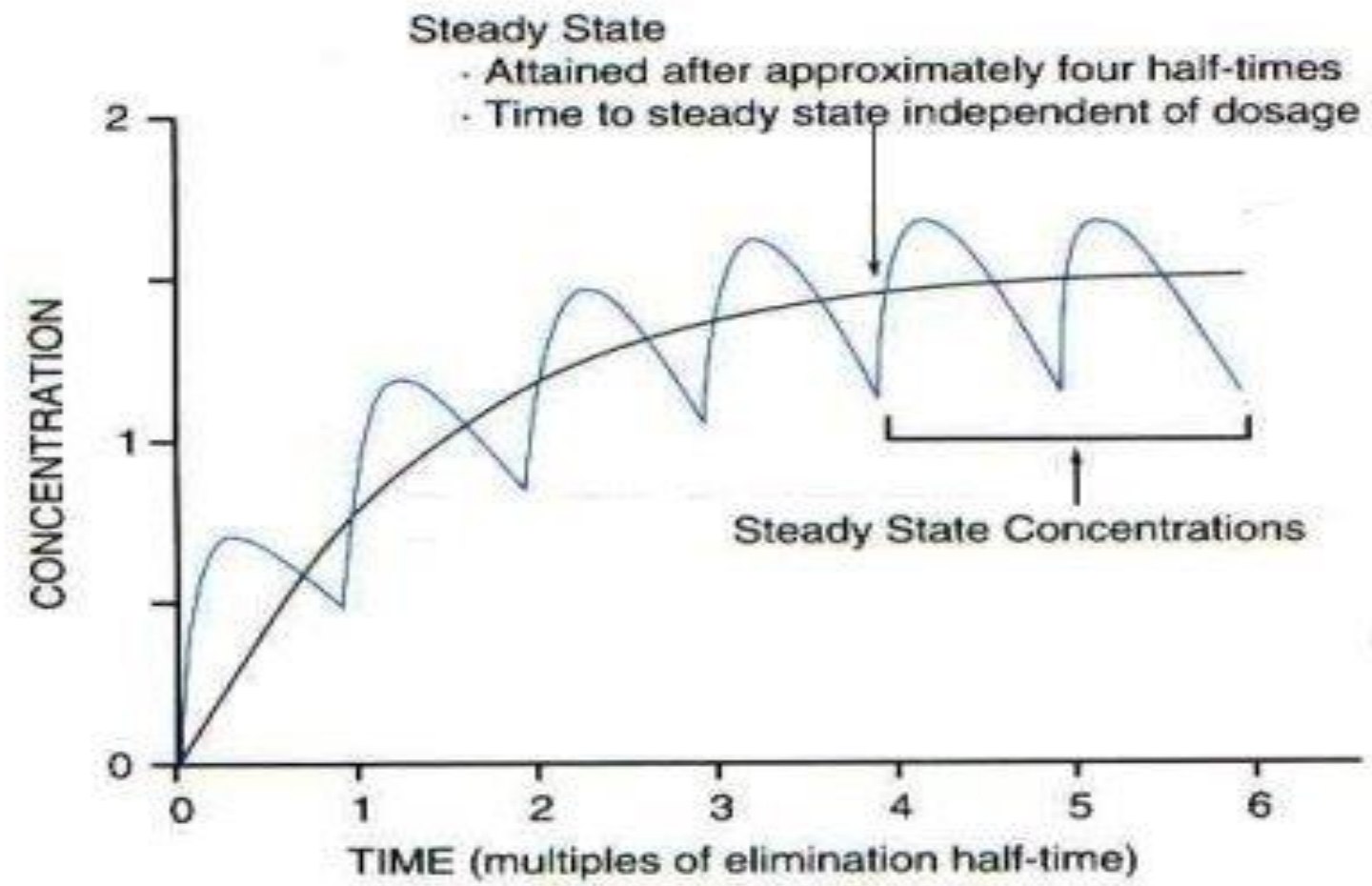
- ***Maintenance dose*:** the amount of a medication administered to maintain a desired level of the medication in the blood. Aiming to achieve the steady state.

- Clearance used to determine the maintenance dose required to achieve a target plasma conc. At steady state.
  - Steady state "*the situation at which the rate of drug administration is equal to the rate of drug elimination*".

Steady State

- The point where rate of drug availability equals rate of elimination.
- Constant drug concentration.
- Point where expect maximum drug effect
- Usually attained after 4-5 half lives.

Steady State



Maintenance Dose Calculation

- Maintenance Dose **(R_A) = CL x C_{SS} ave**
- CSS ave is the target average steady state drug concentration
- The units of CL are in L/hr or L/hr/kg
- Maintenance dose will be in mg/hr so for total daily dose will need multiplying by 24

Maintenance dose calculation

Maintenance Dose (R_A) = CL x C_{SS} ave

$$CL = \frac{(S)(F)\left(DOSE/\tau\right)}{Css\ ave}$$

$$MD = \frac{(CL)(CSSave)(\tau)}{(S)(F)}$$

Factors that alter clearance

1. Body weight
2. Body surface area
3. Cardiac output
4. Drug –drug interaction
5. Extraction ratio
6. Genetic
7. Hepatic function
8. Plasma protein binding
9. Renal function

Elimination Rate Constant (Ke) & Half-Life ($t_{1/2}$)

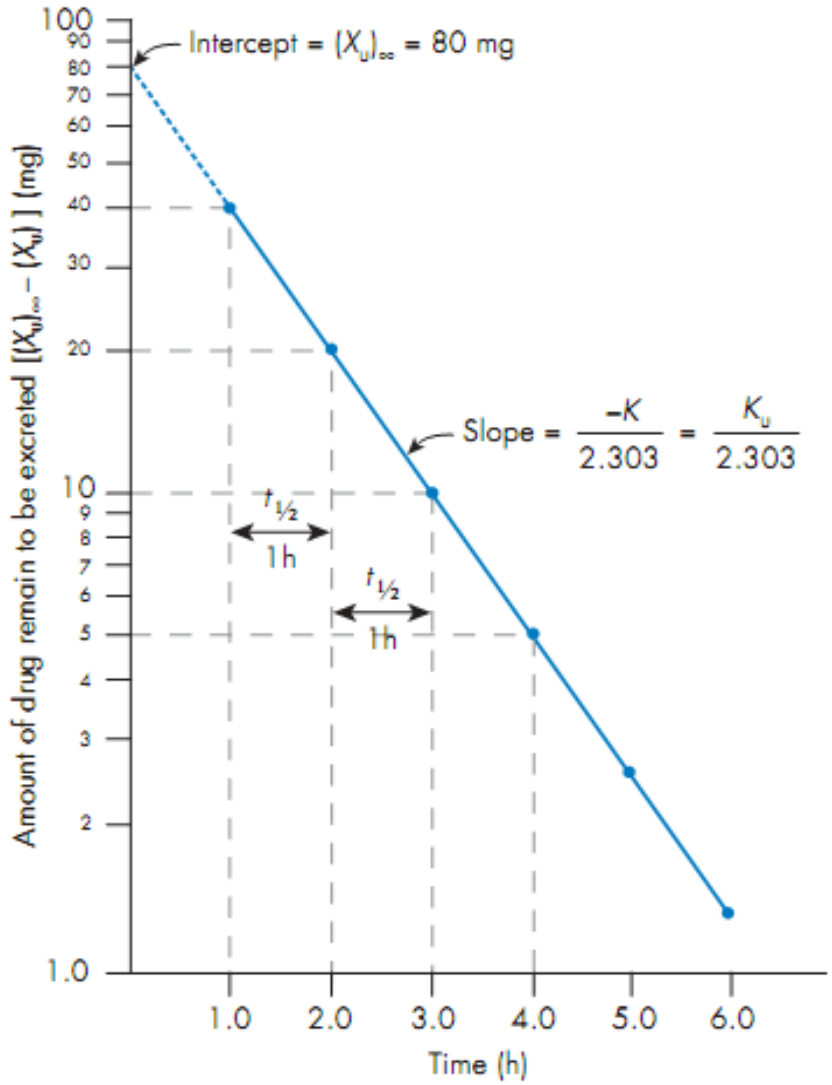
- Half-life is the time taken for the drug concentration to fall to half its original value

- The elimination rate constant (k_e) is the fraction of drug in the body which is removed per unit time.

Elimination Rate Constant (Ke) & Half-Life ($t_{1/2}$)

- ***First order kinetics*** : refers to process in which the amount or concentration of drug in the body diminishes logarithmically over time.
  - The amount of drug eliminated in a set amount of time is directly proportional to the amount of drug in the body.
  - The amount of drug eliminated over a certain time period increases as the amount of drug in the body increases; likewise, the amount of drug eliminated per unit of time decreases as the amount of drug in the body decreases.

Elimination rate constant (K_e)



- $C_2=(c_1)(e^{-kt})$
- $Ln(C_2/C_1)=-kt$
- $Ln(C_1/C_2)=kt$
- $Ln(C_1/C_2)/t = k$
- $K= ln(C_1/C_2)/t$

Elimination rate constant (K_e)

- Represents the fraction of drug eliminated per unit of time.
- Directly proportional to the serum drug concentration in 1st order kinetics.
- Dependant parameter; its value depends on volume of distribution and clearance.

$$k_e = \frac{0.693}{t_{1/2}}$$

$$k_e = \frac{CL}{V_d}$$

$$k_e = \frac{\ln\left[\frac{C_2}{C_1}\right]}{\Delta t}$$

Half-Life ($t_{1/2}$)

- $Cp_2 = Cp_1.e^{-kt}$
- **Logarithmic transform:**
  - $lnC_2 = lnC_1 - kt$
- **Elimination Half-Life:**
  - $t_{1/2} = ln2/k$
  - $t_{1/2} = 0.693/k$

Clinical Application of the Elimination Rate Constant (K)and Half-Life ($t_{1/2}$)

1. Estimating the time to reach steady state plasma concentrations after initiation or change in the maintenance dose.
2. Estimating the time required to eliminate all or a portion of the drug from the body once it is discontinued.
3. Prediction non steady-state plasma levels following the initiation of an infusion.
4. Prediction a steady-state plasma level from a non steady-state plasma level obtained at specific time following the initiation of an infusion

C_{max}

- Concentration of drug that occurs immediately after an IV dose, at the end of a dose infusion, or at a particular time after dose administration for a drug requiring absorption.

- $C_{max,ss}$: Css max= Δc/fraction of drug lost in τ

$$C_{\max} = \left(\frac{(S)(F)(Dose)}{V} \right) \left(\frac{1}{1 - e^{-kt}} \right)$$

$C_{ss\ min}$

- Drug concentration that occurs immediately before the next dose for drugs given intermittently in a multiple-dose fashion.
- For IV bolus

$$C_{\min,ss} = C_{\max,ss} . e^{-k_e \tau}$$

- For IV intermittent infusion

$$C_{\min,ss} = C_{\max,ss} . e^{-[k_e (\tau - t')]}$$

$C_{ss\ avg}$

- Average steady state concentration; the concentration measured approximately half way between the peak and trough or a drug administered long enough to be in steady state.

$$C_{ss,ave} = \frac{(S)(F)(Dose)}{Cl \times \tau}$$

TO BE CONTINUED !!!!!

“CREATININE CLEARANCE”

DR. SAIF KHALID ALKHAFAF

PHD. IN PHARMACOLOGY

Creatinine clearance (CL_{cr})

- Many drug eliminated partially or totally by the kidney.
- Accurate estimation of renal function is very important in designing drug therapy regimens .
- Creatinine clearnace determined by :
  1. Urine collection.
  2. Corresponding plasma sample .

Creatinine clearance

- Routine kidney function test include the measurement of :
  - Serum creatinine.
  - Creatinine clearance.
  - Serum urea.

- Both serum creatinine and creatinine clearance are used as kidney function tests to :
  1. Confirm the diagnosis of renal disease.
  2. Give an idea about the severity of the disease.
  3. Follow up the treatment.

Stages of CKD

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15 (or dialysis)

Advantage of creatinine clearance

1. Creatinine clearance is the most frequently used clearance test.
2. Investigation of patients with minor abnormalities of renal function.
3. Calculation of the initial doses of potentially toxic drugs that are eliminated.
4. Assessment of potential kidney donors.
5. It is endogenous substance derived from the turnover of creatine in muscle
6. Its daily production is relatively constant, (depends on total muscle mass, not protein diet).
7. It is removed from the body by renal excretion.

Disadvantage of creatinine clearance

1. Creatinine is actively secreted by the renal tubules, so, creatinine clearance is higher than the true Glomerular Filtration Rate (GFR) by 10-20%. (*This is significant only when the GFR is* ***<10 ml/min***).

2. Creatinine clearance requires three measurements:
    1. Urinary creatinine concentration
    2. Plasma creatinine concentration
    3. Accurately timed (24 hour) and measured urine collection

3. Each of these has an inherent imprecision that can affect the accuracy of the overall result.

Problems of creatinine clearance

- Routine measurement of creatinine clearances in patients has been fraught with problems:

1. Incomplete urine collections,
2. Serum creatinine concentrations obtained at incorrect times, collection time errors can produce erroneous measured creatinine clearance values.
3. Equations used in estimation of CL_{Cr} include: body weight or size, age, and gender.

Creatinine pharmacokinetics

- Creatinine is a waste product formed in muscle by creatine metabolism.
- Creatine is synthesized in liver, passes into the circulation and is taken up almost entirely by skeletal muscles for conversion to creatine phosphate, which serves as a storage form of energy in skeletal muscles.
- About 2% of total creatine is converted daily to creatinine so that the amount of creatinine produced is related to the total muscle mass.

Creatinine pharmacokinetics

- Its rate of formation (R_A) is primarily determined by individual muscle mass or lean body weight (varies).
- For any given individual, the rate of creatinine production is assumed constant.
- It is eliminated exclusively by renal glomerular filtration.
- Decrease in glomerular filtration rate (GFR) ultimately results in arise in the serum creatinine level until new steady state. (rate in = rate out)

Indirect measurement of creatinine clearance

- When only ***serum creatinine Cr_{sr}*** is available or if it is not be desirable to wait 24 hrs to measure ΔX_u (ΔX_u is the mass of creatinine excreted over time Δt,), the following formulae can be used to predict creatinine clearance. For *males and females* respectively:

$$CL_{Cr}\ (ml/min) = \frac{(140 - Age)\,Weight(kg)}{(72)(Cr_{sr}\ (mg/dl))}$$

$$CL_{Cr}\ (ml/min) = [0.85]\left[\frac{(140 - Age)\,Weight(kg)}{(72)(Cr_{sr}\ (mg/dl))}\right]$$

Renal Function Measurement

- GFR Estimation
  - Cockcroft-Gault equation

$$CL_{Cr}(ml/min) = \frac{(140-Age)(IBW(kg)}{(72)(Cr_{sr}\ (mg/dl))}$$

    - Multiply by 0.85 if female,
      - IBW: 50 kg + 2.3 kg/inch over 5 ft (male)
      - IBW: 45.5 kg + 2.3 kg/inch over 5 ft (female)
    - Adjusted Body Weight= IBW+0.4(TBW-IBW)

Evaluation creatinine clearnace: urine collections (*direct measurement*)

- One method of determining GFR from creatinine is to collect urine (usually for 24-hours) to determine the amount of creatinine that was removed from the blood over a given time interval.

- Creatinine clearance (CL_{Cr}) is calculated from the creatinine concentration in the collected urine sample (U_{Cr}), urine flow rate (V), and the plasma concentration (P_{Cr}).

Evaluation creatinine clearnace: urine collections (*direct measurement*)

- Since the product of urine concentration and urine flow rate yields creatinine excretion rate, which is the rate of removal from the blood, creatinine clearance is calculated as removal rate per min ($U_{Cr} \times V$) divided by the plasma creatinine concentration.

- This is commonly represented mathematically as

$$CL_{Cr} = \frac{U_{cr} \times V}{P_{Cr}}$$

Cont,

- Creatinine clearance is calculated from the formula:
  - (U_{Cr}) = urinary creatinine concentration (mg/dl)
  - (V), = urine flow rate [ml/min or (L/24 h)/1.44)
  - P_{Cr} = plasma creatinine concentration (mg/dl)

- Creatinine clearance is normally 60-120 ml/min,
- Creatinine clearance is lower in females and old age.
- The clearance formula is only valid for a steady state, i.e. when renal function is not changing rapidly

- Urine volume = 2000 ml /24 hours to convert it to ml/min we divide by 1440

Cont,

- Creatinine clearance
  - Can be calculated with 24 hour urine and a blood draw

$$CL_{Cr} = \frac{U_{Cr}\ (mg/dl) \times U_{volume}\ (ml)}{(S_{Cr}\ (mg/dl))\ (1440)}$$

Problem 1

- *Creatinine clearance is to be determined in a 55-year-old 65-kg female patient. Her urine was collected over a 24-h period, and the urinary concentration of creatinine determined. The patient's serum concentration of creatinine was measured at the beginning of the study. The data are as follows:*

  - *Collection period: 24 hrs*
  - *Volume of urine collected: 1050 ml*
  - *Urinary creatinine concentration: 1.14 mg/ml*
  - *Serum creatinine concentration: 1.0 mg/dl*

  Determine creatinine's clearance rate (ml/min)?

Summery

- In general, Creatinine clearance is the removal of Creatinine from the body. In renal physiology,
- Creatinine clearance (CL_{Cr}) is the volume of blood plasma that is cleared of Creatinine per unit time.
- Clinically, Creatinine clearance is a useful measure for estimating the glomerular filtration rate (GFR) of the kidneys.

To be continued !!!!!

CYCLOSPORIN
Pharmacokinetic

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PHD IN PHARMACOLOGY
COLLEGE OF PHARMACY

Indications & Dosages

- **Indications**
  - Systemic lupus erythematosus (SLE)
  - DOC for immunosuppression in organ transplant
  - Dermatitis and psoriasis
  - Other autoimmune diseases

- **Dosages**
  - Initial dose
    - 10mg/kg/day (oral)
    - 1-2mg/kg/day (IV)

ADME

- **Absorption**
  - Absorption ranged from 3%-60%
  - It may be taken with food or on an empty stomach, but you should try to be consistent (eg: always with food or always on an empty stomach).
  - DO NOT take cyclosporine with grapefruit or grapefruit juice as this may cause your blood levels of cyclosporine to increase. Orange juice has no effect on cyclosporine blood levels.

ADME (Concentrations)

- Desired blood concentration 100-450 ng/ml
- Min. effective concentration 100 ng/ml
- Potentially toxic concentration >600ng/ml
- Peak concentration measure after 1-8 hours of oral dose
- Cyclosporine absorption is incomplete and some what erratic, although a new microemulsion formulation improves its consistency and provides 20-30% bioavailability.

ADME

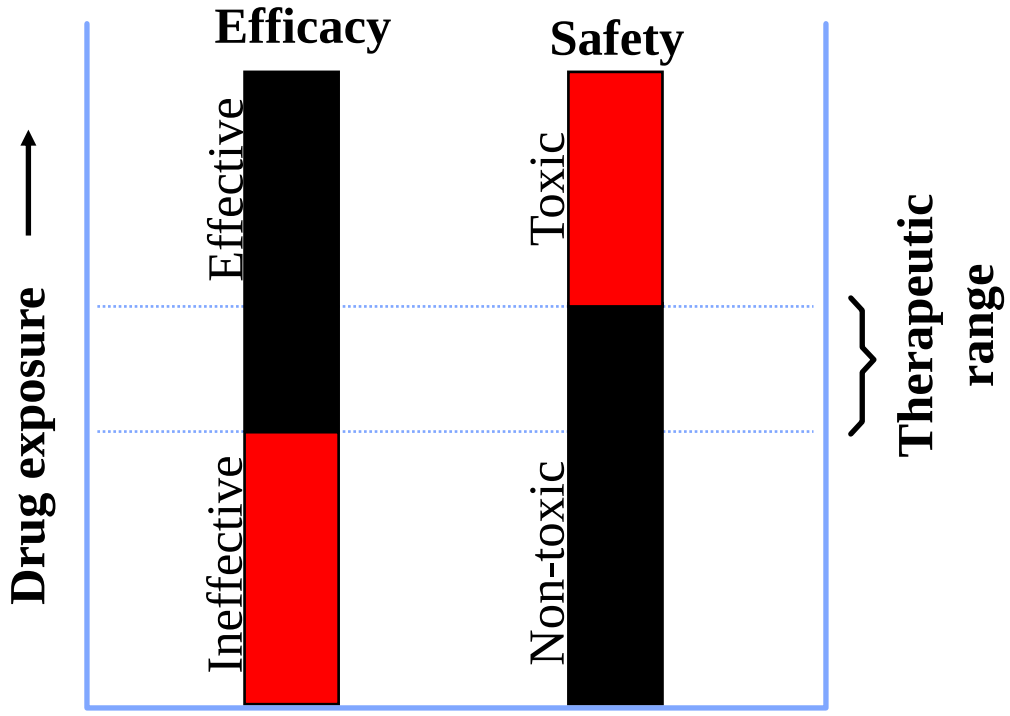
- **Distribution**
  - Highly lipid-soluble & distributed widely in the body
  - 98% bind to erythrocytes and plasma protein
  - Distribution is highly variable and influenced by lipoprotein concentration & composition
  - V_d ~ 4.1 L/kg (average)
  - T1/2 = 6-12 hours, therefore time to steady state = 2-3 days

ADME

- **Metabolism**
  - Extensively metabolized via cytochrome P450
  - Liver is the major site of elimination, thus would reduce clearance in hepatic insufficiency
- **Elimination**
  - Biliary is the major route
  - >44% of the dose appeared as CSA metabolite in bile
  - <1% excreted unchanged in urine

Cyclosporin exposure exhibits a narrow therapeutic range between efficacy and safety

A narrow therapeutic range drug is one which commonly exhibits adverse effects which limit use in doses close to those required for therapeutic effect



Adverse effects

- The principal adverse reactions of cyclosporine therapy are renal dysfunction, tremor, hirsutism, hyperkalemia, hepatotoxicity, hypertension, and gum hyperplasia.
- **Hypertension** which is usually **mild to moderate** may occur in 50% of patients following renal transplantation and in most cardiac transplant patients.
- **Rare adverse effects include**: anxiety, chest pain, constipation, depression, hair breaking, hematuria, joint pain, lethargy, mouth sores, MI, night sweats, pancreatitis, pruritus, swallowing difficulty, tingling, upper GI bleeding, visual disturbance, weakness, and wight loss.
- **Nephrotoxicity** increases when the drug is taken with diltiazem, potassium

Adverse effects

Adverse effects	Incidence (%)	Clinical comments
Renal dysfunction	28	Reversible
Hirsutism	25	-
Tremor	25	Dose-related
Hypertension	19	Not dose-related, require therapy
Gum hyperplasia	5	Maintain good oral hygiene

Rejection vs Nephrotoxicity

- **Nephrotoxicity** is often difficult to differentiate from renal **allograft rejection**

	Rejection	Nephrotoxicity
Serum creatinine	Sudden ↑	Gradual ↑
Temperature	Febrile	Non-febrile
CSA concentration	↓	High
Effect of dose reduction	No change/worsening of renal function	Improvement in function

TDM

- TDM is usually done immediately post-operation phase
- TDM repeat every 1-2 months
- Samples should represent trough levels (**C_0 monitoring**) & drawn at steady state 2-3 days after initiating/changing dose.

Limitations of trough conc. (C_0) monitoring

- C_0 does not accurately reflect inter-patient variability.
- C_0 is not an accurate predictor of clinical efficacy or events of acute rejection.
- Therefore, need another type of monitoring for CSA → the C_2 monitoring.
- AUC (area under curve) determine efficacy & safety

C_2 monitoring

- C2 is the best estimate of AUC of oral cyclosporine
- C2 monitoring is done 2-hour post dose and repeated every 2 hours until it reaches steady state
- **Advantages:**
  - Measured as AUC
  - Practical, simple & safe
  - Sensitive predictor of acute rejection & graft survival
  - Target **AUC_{0-4}** = 4400-5500ng/ml
- **Disadvantages:**
  - Cost
  - Require multiple blood samples

Major drug interactions

- ↑ **CSA metabolism**
  - Anticonvulsants – phenobarb, phenytoin
  - Rifampicin
- ↓ **CSA metabolism**
  - Erythromycin
  - Ketoconazole
  - Cimetidine
  - Grapefruit juice

Adjusting CSA dose

$$\textbf{New dose} = \frac{\textit{Css desired}}{\textit{Css current}} \times \textit{Current dose per day}$$

Conclusion

- Cyclosporin is a narrow therapeutic index drug whose high pharmacokinetic variability markedly influences clinical outcomes
- The first 4 hours post-dose are the period of highest inter-subject pharmacokinetic variability and greatest pharmacodynamic effects
- C_2 exhibits the highest single-point correlation with AUC_{0-4} in renal, liver, and paediatric renal and liver transplants using Neoral
- Achieving optimum C_2 target levels early (day 3-5) post-transplant appears to markedly reduce the risk of acute rejection

Thank you

Digoxin Pharmacokinetics

DR. SAIF KHALID ALKHAFAF
PHD. IN PHARMACOLOGY

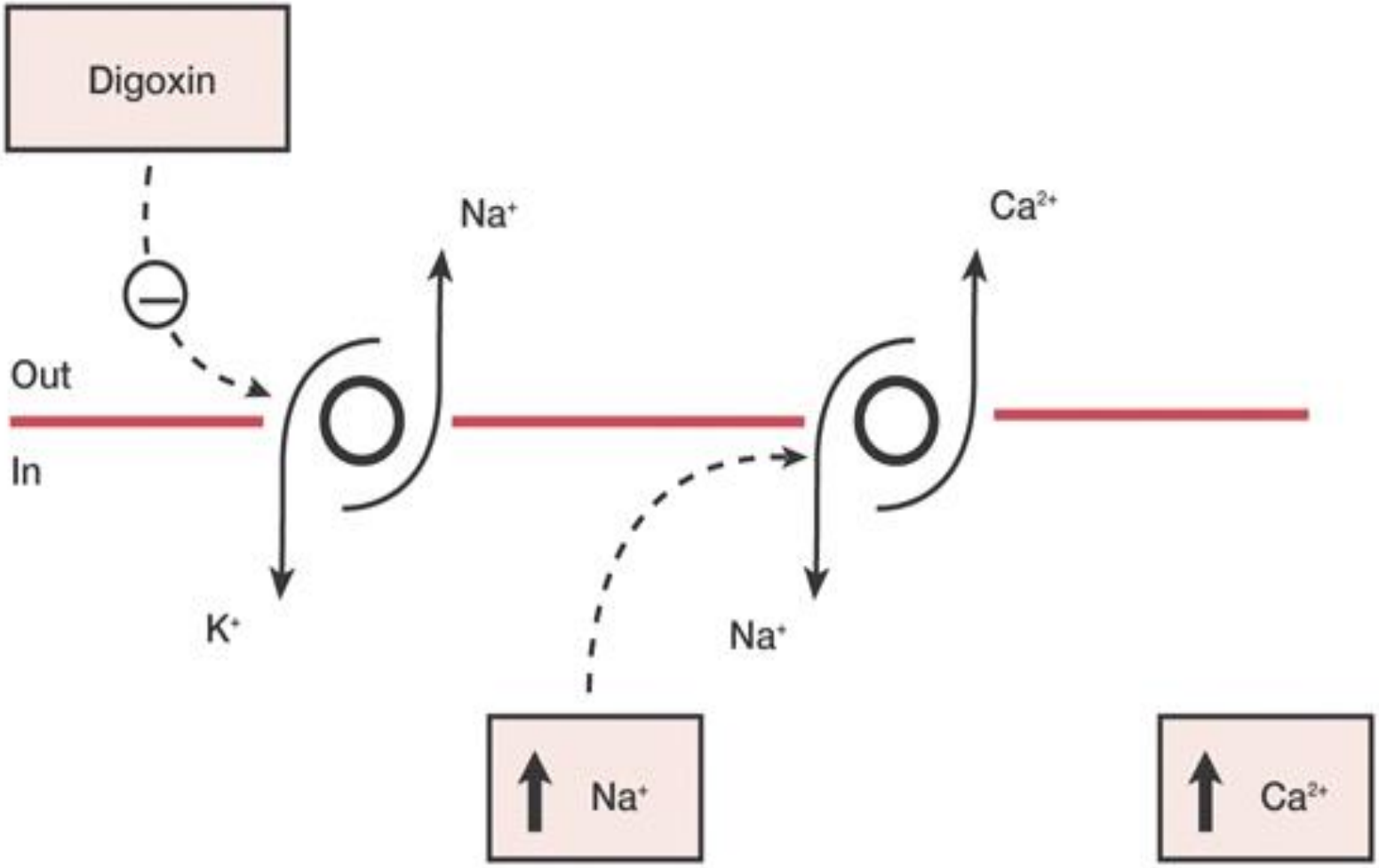
Introduction

- Digoxin: most commonly used digitalis preparation

- Digoxin is used for the treatment of congestive heart failure (CHF) because of its +ve inotropic effects on the myocardium and for the treatment of Atrial fibrillation because of its –ve chronotropic effects.

- Mechanism of action:
  - Inactivation of the Na^+K^+ATPase pump, then sodium-calcium exchanger increasing intracellular calcium.
  - Increases vagal tone.

MOA of Digoxin



Therapeutic concentrations

- The generally accepted therapeutic ranges for digoxin are:
  - Clinically beneficial inotropic effects of digoxin are generally achieved at steady-state serum concentrations of 0.5–1 ng/mL.
  - Chronotropic effects usually require higher digoxin steady-state serum concentrations of 0.8–1.5 ng/mL.
  - Because of pharmacodynamic variability, clinicians should consider these ranges as initial guidelines.

Toxic concentrations

- Steady-state digoxin serum concentrations above 2 ng/mL are associated with an increased incidence of adverse drug reactions.
- At digoxin concentrations of 2.5 ng/mL or above ~50% of all patients will exhibit some form of digoxin toxicity.
- Most digoxin side effects involve the gastointestinal tract, central nervous system, or cardiovascular system.

Side effects

- Gastrointestinal distress
- Dizziness
- Headache
- Weakness
- Syncope or coma
- Seizure
- Confusion
- Disorientation
- Delirium
- Hallucinations
- Visual changes (yellow-green halos)

Factors Enhancing Toxicity

- Decreased renal, hepatic, or thyroid function.
- Drugs
  - Antidysrhythmic, spironolactone, indomethacin, clarithromycin, erythromycin.
- Electrolyte abnormalities
  - Hypokalemia, hypomagnesemia, and hypercalcemia

Laboratory Evaluation

- Potassium level may be a better prognostic indicator in acute poisoning than the digoxin level.

- Digoxin level
  - Therapeutic levels 0.5 – 2.0 ng/µl
    - With signs of toxicity therapeutic level does not exclude toxicity
  - Acute exposures
    - Digoxin absorbed into the plasma then redistributed to the tissues
    - Serum levels most reliable at 6 hours

- Renal and hepatic function, and electrolytes must also be evaluated.

Digoxin dosing

- Digoxin is given as an intravenous injection or orally as a tablet, capsule, or elixir.
- When given intravenously, doses should be infused over at least 5–10 minutes.
- Average bioavailability constants (F) for the tablet, capsule, and elixir are 0.7, 0.9, and 0.8.
- Usual digoxin doses for adults are 250 μg/d (range: 125–500 μg/d) in patients with good renal function (creatinine clearance ≥80 mL/min).
- 125 μg every 2–3 days in patients with renal dysfunction (creatinine clearnace ≤15 mL/min).

Basic clinical pharmacokinetic parameters

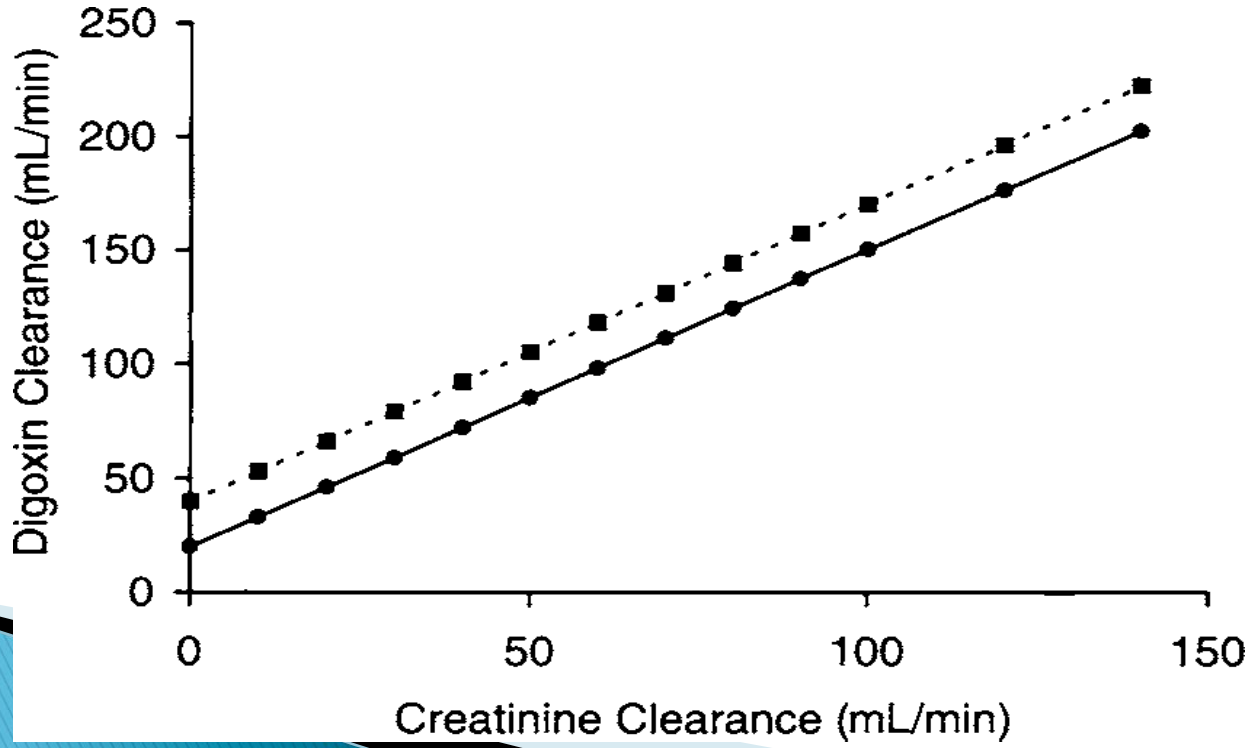
- 75% of digoxin elimination from the body is by the kidney and 25% is removed by hepatic metabolism.

- Adults with normal renal function (creatinine clearance ≥80 mL/min) have an average digoxin half-life of 36 hours (range: 24–48 hours) .

- Plasma protein binding is ~25% for digoxin.

Clearance

- Digoxin clearance is proportional to creatinine clearance for patients with [Cl = 1.303(CrCl) + 20] and without [Cl = 1.303(CrCl) + 40] **heart failure**. Nonrenal clearance is lower for patients with heart failure because reduced cardiac output results in decreased liver blood flow and digoxin hepatic clearance.



Volume of distribution

- Volume of distribution = 7 L/kg (range: 5–9 L/kg).

- For patients with **renal dysfunction** (creatinine clearance ≤30 mL/min), creatinine clearance should be used to provide an improved volume of distribution estimate (V in L) using the following formula:

$$V_d = 226 + [298 \times Cl_{cr} / 29.1 + Cl_{cr}] \times [Weight/70]$$

Interpreting blood drug levels

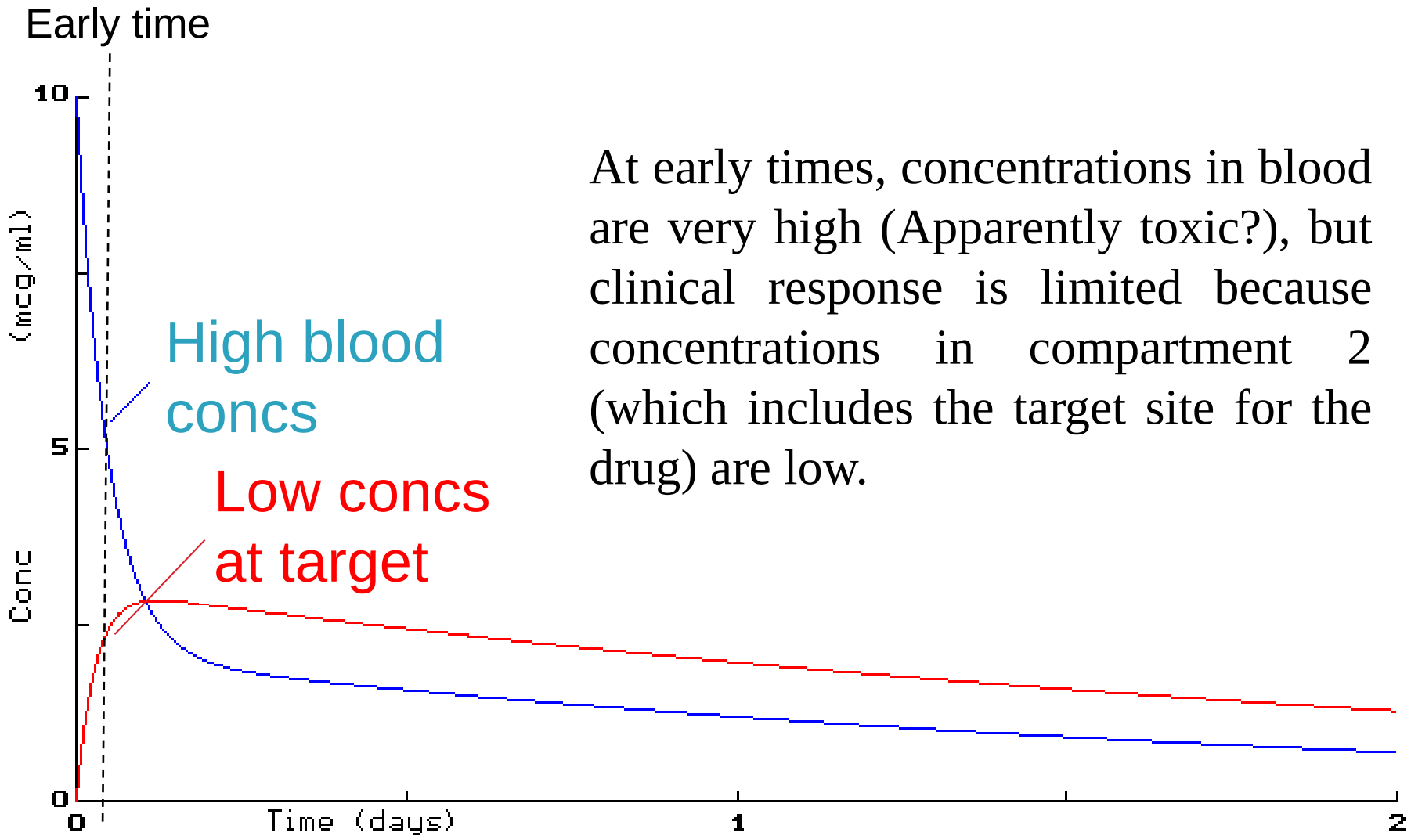
- Digoxin enters cardiac muscle slowly. So, for digoxin, cardiac muscle forms part of the second compartment.

- Digoxin acts on cardiac muscle. Clinical effect is therefore related to concentrations in compartment 2, not those in the blood (part of compartment 1).

- If blood samples are taken soon after dosing, the results are likely to be very misleading, as blood and cardiac muscle have not reached equilibrium.

- Usual rule is that, for digoxin, blood samples should not be taken less than 6 hours after dosing.

Interpreting blood drug levels



At early times, concentrations in blood are very high (Apparently toxic?), but clinical response is limited because concentrations in compartment 2 (which includes the target site for the drug) are low.

Exercise

- MJ is a 50-year-old, 70-kg (5 ft 10 in) male with atrial fibrillation for less than 24 hours. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute an intravenous digoxin dose for this patient to control ventricular rate.

1. Estimate creatinine clearance.

$CrCl_{est}$ = [(140 − age)BW] / (72 · SCr) =

[(140 − 50 y)70 kg] / (72 · 0.9 mg/dL)

$CrCl_{est}$ = 97 mL/min

2. Estimate clearance.

$Cl = 1.303\ (CrCl) + Cl_{NR}$ =

1.303(97 mL/min) + 40 mL/min =

167 mL/min

3. *Use average steady-state concentration equation to compute digoxin maintenance dose.*

$D/\tau = (Css \cdot Cl) / F$

$= (1.2\ \mu g/L \cdot 167\ mL/min \cdot 1440\ min/d) / (1 \cdot 1000\ mL/L)$

$= 288\ \mu g/d$, round to $250\ \mu g/d$

4. *Use loading dose equation to compute digoxin loading dose (if needed).*

$V = 7\ L/kg \cdot 70\ kg = 490\ L$

$LD = (Css \cdot V) / F$

$= (1.2\ \mu g/L \cdot 490\ L) / 1 = 588\ \mu g$ rounded to $500\ \mu g$

Thank you

Lithium Pharmacokinetics

DR. SAIF ALKHAFAF

PHD IN PHARMACOLOGY

Introduction

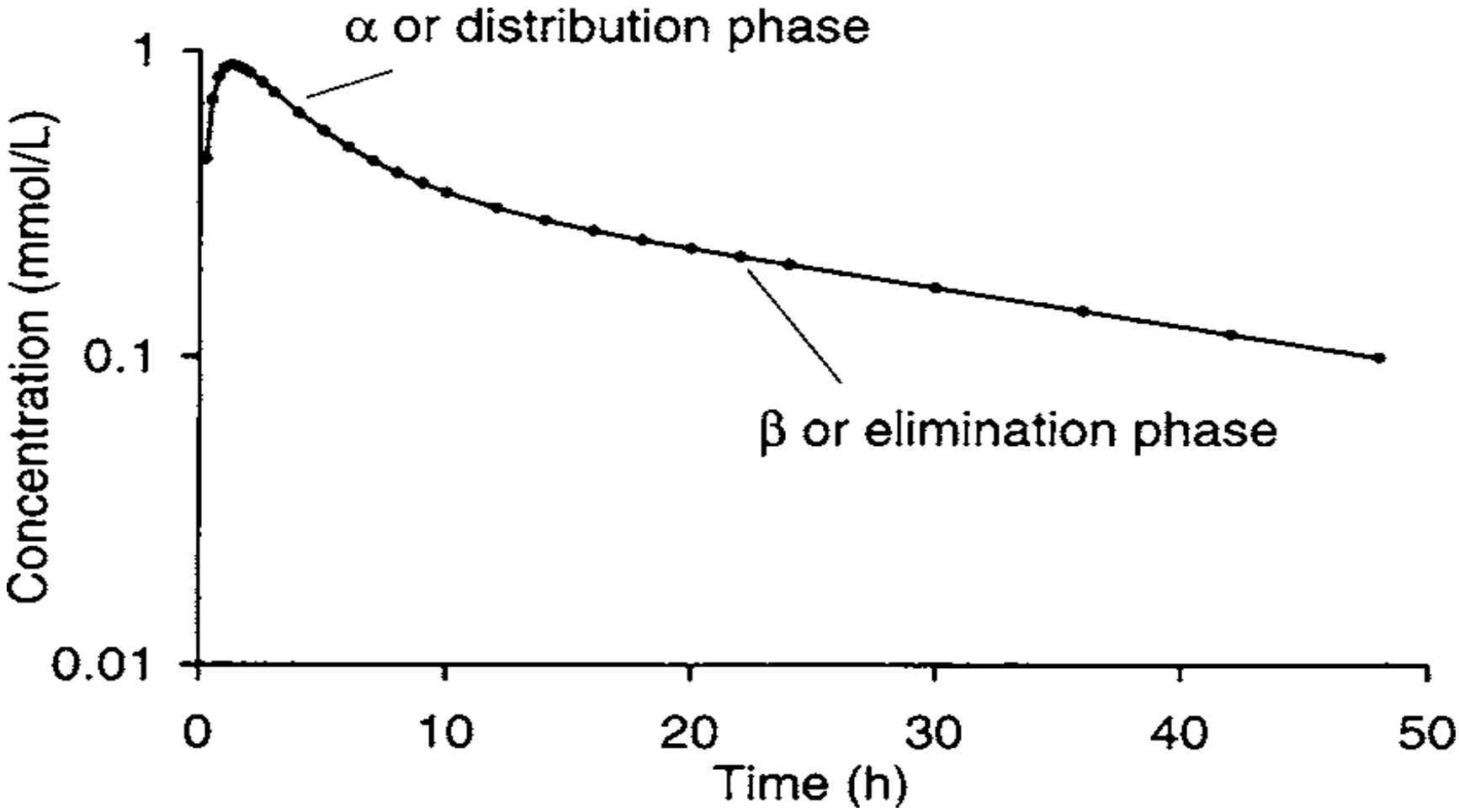
- Lithium is an alkali metal that is administered as a monovalent cation (Li+) for the treatment of bipolar disorder.
- In the United States, orally administered carbonate and citrate salts of lithium are available.
- This drug has been used in psychiatric medicine since the 1940s.
- Among the current theories are competition with other cations at receptor and tissue sites:
  - Dopamine-receptor supersensitivity blockage.
  - Decreased stimulation of β-receptor.

Therapeutic concentrations

- The general therapeutic range for lithium is 0.6–1.5 mmol/L.
- Because lithium is a monovalent cation, the therapeutic range expressed in mEq/L is identical to these values (i.e. 0.6–1.5 mEq/L).
- For long-term maintenance use, the usual desired range is 0.6–0.8 mmol/L.
- For individuals with acute mania, a minimum lithium concentration of 0.8 mmol/L is usually recommended. The usual desired range for these individuals is 0.8–1 mmol/L.

Therapeutic concentrations

- After oral administration, lithium concentrations follow a complex concentration/time curve that is best described using multicompartment models.
- Maximum serum concentrations occur 2–3 hours after the dose is given.
- After the peak concentration is achieved. the distribution phase lasts for 6–10 hours, followed by the elimination phase.
- Because of the long distribution phase, lithium serum concentrations used for dosage adjustment purposes should be obtained no sooner than 12 hours after dosage administration.


α or distribution phase
β or elimination phase
Concentration (mmol/L)
1
0.1
0.01
0
10
20
30
40
50
Time (h)

Toxic concentrations and side effects

- At lithium serum concentrations within the upper end of the therapeutic range (1.2–1.5 mmol/L), the following adverse effects can be noted in patients: decreased memory and concentration, fine hand tremor.
- At concentrations just above the therapeutic range (1.5–3 mmol/L), slurred speech, nystagmus, blurred vision, tinnitus, hand tremors, and muscle fasciculation may occur in patients.
- If concentrations exceed 3 mmol/L, severe toxicity occurs with seizures, irreversible brain damage, hypotension, respiratory and cardiovascular complications, stupor, coma, and death.
- At toxic lithium concentrations, lithium can cause a nonspecific decrease in glomerular filtration which, in turn, decreases lithium clearance.
- Lithium concentrations above 3.5–4 mmol/L may require hemodialysis to remove the drug as quickly as possible.

Clinical monitoring parameters

- Before initiating lithium therapy, patients should undergo a complete physical exam and a general serum chemistry panel (serum creatinine), complete blood cell count with differential, thyroid function tests, and urinalysis (including osmolality and specific gravity) should be obtained.
- For patients with renal dysfunction (measured 24-hour creatinine clearance) or baseline cardiac disease (electrocardiogram).
- Lithium serum concentrations should be measured every 12 hours for twice daily dosing.
- Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized.
- During lithium maintenance therapy, steady-state lithium serum concentrations should be repeated every 3–6 months.

Basic Clinical Pharmacokinetic Parameters

- Lithium is eliminated almost completely (>95%) unchanged in the urine.
- 60–80% of the amount filtered is reabsorbed by the proximal tubule of the nephron.
- Lithium eliminated in the saliva, sweat, and feces accounts for less than 5% of the administered dose.
- Lithium carbonate capsules (150, 300, 600 mg) and tablets (rapid release: 300 mg; sustained release: 300, 450 mg) are available.
- Oral bioavailability is good for all lithium salts and dosage forms and equals 100%.
- The typical dose of lithium carbonate is 900–2400 mg/d in adult patients with normal renal function.
- Adults with normal renal function (creatinine clearance >80 mL/min) have an average elimination half-life of 24 hours, volume of distribution equal to 0.9 L/kg, and clearance of 20 mL/min for lithium.

Drug-Drug intraction

- Thiazide diuretics cause sodium and water depletion, which leads to increased sodium reabsorption in the proximal tubule of the kidney as a compensatory mechanism. Since lithium is reabsorbed by the same mechanisms as sodium, lithium reabsorption increases and lithium clearance decreases by 40–50% during treatment with thiazide diuretics.
- Because of this, many clinicians favor the use of a loop diuretic, with careful monitoring of adverse effects and lithium serum concentrations.
- NSAID-induced decrease in renal blood flow via inhibition of prostaglandins, also decrease lithium clearance and increase lithium concentrations.
- Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been reported to inhibit the elimination of lithium by an undefined mechanism.
- Theophylline increases the lithium clearance/creatinine clearance ratio by as much as 58% resulting in an average decrease of 21% in steady-state lithium concentrations.

كيفية حساب الـ Dose

initial dosage determination methods

1- pharmacokinetic dosing method
2- Literature-based recommended dosing
3- Test dose methods

Exercise

MJ is a 50-year-old, 70-kg (5 ft 10 in) male with bipolar disease. He is not currently experiencing an episode of acute mania. His serum creatinine is 0.9 mg/dL. Compute an oral lithium dose for this patient for maintenance therapy.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$\text{CrClest} = [(140 - \text{age})\text{BW}]/(72 \times \text{SCr}) = [(140 - 50\ \text{y})70\ \text{kg}]/(72 \times 0.9\ \text{mg/dL})$$

$$\text{CrClest} = 97\ \text{mL/min}$$

2. *Estimate clearance.*

The drug clearance versus creatinine clearance relationship is used to estimate the lithium clearance for this patient:

$$\text{Cl} = 0.288(\text{CrCl}) = 0.288(97\ \text{mL/min}) = 27.9\ \text{L/d}$$

3. *Use average steady-state concentration equation to compute lithium maintenance dose.*

For a patient requiring maintenance therapy for bipolar disease the desired lithium concentration would be 0.6–0.8 mmol/L. A serum concentration equal to 0.6 mmol/L will be chosen for this patient, and oral lithium carbonate will be used (F = 1, 8.12 mmol Li+/ 300 mg of lithium carbonate).

$D/\tau = (Css \times Cl) / F = (0.6 \text{ mmol/L} \times 27.9 \text{ L/d}) / 1 = 16.7 \text{ mmol/d}$

D/τ = (300-mg lithium carbonate/8.12 mmol Li+) 16.7 mmol/d = 617 mg/d, rounded to 600 mg/d of lithium carbonate.

This dose would be given as 300 mg of lithium carbonate every 12 hours.

سؤال رقم 1 من أسئلة الجابتر

PG is a 67-year-old, 72-kg (6 ft 1 in, serum creatinine = 1.2 mg/dL) male with bipolar disease requiring maintenance therapy with oral lithium. Suggest an initial lithium carbonate dosage regimen designed to achieve a steady-state lithium concentration equal to 0.6 mmol/L.

Pharmacokinetic Dosing Method

1- حساب الـ CrCl: -

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$CrCl_{est} = [(140 - age)BW]/(72 \cdot SCr)$

$= [(140 - 67\ y)72\ kg] / (72 \cdot 1.2\ mg/dL)$

$CrCl_{est} = 61\ mL/min$

2- حساب الـ Cl of Lithium: -

1- حساب الـ CrCl: -

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$CrCl_{est} = [(140 - age)\ BW]/(72 \cdot SCr)$

$= [(140 - 67\ y)72\ kg] / (72 \cdot 1.2\ mg/dL)$

$CrCl_{est} = 61\ mL/min$

2- حساب الـ Cl of Lithium: -

$Cl = 0.288(CrCl)$

$= 0.288(61\ mL/min)$

$= 17.6\ L/d$

3- أقوم بتحديد الـ Css:-

أعطاها بالسؤال ومقدارها 0.6 mmol/L

4- أقوم الان بحساب الـDose:-

For a patient requiring maintenance therapy for bipolar disease the desired lithium concentration would be 0.6–0.8 mmol/L. A serum concentration equal to 0.6 mmol/L will be chosen for this patient, and oral lithium carbonate will be used (F = 1, 8.12 mmol Li+/300 mg of lithium carbonate).

$D/\tau = (Css \cdot Cl) / F$
$= (0.6\ mmol/L \cdot 17.6\ L/d) / 1$
$= 10.6\ mmol/d$

$D/\tau = (300\ mg\ lithium\ carbonate/8.12\ mmol\ Li+)\ 10.6\ mmol/d$
$= 392\ mg/d$

Rounded to 450 mg/d of lithium carbonate. This dose would be given as 150 mg of lithium carbonate in the morning and 300 mg of lithium carbonate in the evening.

سؤال رقم 3 من أسئلة الجابتر

DU is a 21-year-old, 70-kg (5 ft 9 in, serum creatinine = 0.8 mg/dL) female with bipolar disease who requires therapy with lithium. She is currently experiencing an episode of acute mania. Suggest an initial lithium carbonate dosage regimen designed to achieve a steady-state lithium concentration equal to 0.8 mmol/L.

Pharmacokinetic Dosing Method

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = \{[(140 - age)BW]/(72 \cdot SCr)\} \cdot 0.85$$

$$= \{[(140 - 21\ y)70\ kg]/(72 \cdot 0.8\ mg/dL)\} \cdot 0.85$$

$$= 123\ mL/min$$

.

The drug clearance versus creatinine clearance relationship for a patient with acute mania is used to estimate the lithium clearance for this patient:

Pharmacokinetic Dosing Method

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$CrCl_{est} = \{[(140 - age)BW]/(72 \cdot SCr)\} \cdot 0.85$

$= \{[(140 - 21\ y)70\ kg]/(72 \cdot 0.8\ mg/dL)\} \cdot 0.85$

$= 123\ mL/min$

.

The drug clearance versus creatinine clearance relationship for a patient with acute mania is used to estimate the lithium clearance for this patient:

$Cl = 0.432(CrCl)$

$= 0.432(123\ mL/min)$

$= 53.1\ L/d$

.

For a patient requiring therapy for the acute mania phase of bipolar disease the desired lithium concentration would be 0.8–1 mmol/L. A serum concentration equal to 0.8 mmol/L was chosen for this patient هو نطانيا بالمسأله, and oral lithium carbonate will be used (F = 1, 8.12 mmol Li+/300 mg of lithium carbonate).

For a patient requiring therapy for the acute mania phase of bipolar disease the desired lithium concentration would be 0.8–1 mmol/L. A serum concentration equal to 0.8 mmol/L was chosen for this patient هو نطانيا بالمسأله, and oral lithium carbonate will be used (F = 1, 8.12 mmol Li+/300 mg of lithium carbonate).

$$D/\tau = (Css \cdot Cl) / F$$
$$= (0.8 \text{ mmol/L} \cdot 53.1 \text{ L/d}) / 1$$
$$= 42.5 \text{ mmol/d}$$

D/τ = (300 mg lithium carbonate/8.12 mmol Li+) 42.5 mmol/d
= 1570 mg/d, rounded to 1500 mg/d of lithium carbonate. This dose would be given as 600 mg of lithium carbonate at 0800 H and 2000 H and 300 mg of lithium carbonate at 1400 H.

ثاني طريقة سنتحدث عنها الان هي طريقه تسمي بـ

Literature Based Recommended Method

- For the treatment of acute mania, initial doses are usually 900–1200 mg/d of lithium carbonate.
- If the drug is being used for bipolar disease prophylaxis, an initial dose of 600 mg/d lithium carbonate is recommended.
- If creatinine clearance is 10–50 mL/min, the prescribed initial dose is 50–75% of that recommended for patients with normal renal function.
- For creatinine clearance values below 10 mL/min, the prescribed dose should be 25–50% of the usual dose in patients with good renal function. Recommended doses for children and adolescents with normal renal function are 15–60 mg/kg/d and 600–1800 mg/d, respectively, with doses administered three to four times daily.

PG is a 67-year-old, 72-kg (6 ft 1 in, serum creatinine = 1.2 mg/dL) male with bipolar disease requiring maintenance therapy with oral lithium. Suggest an initial lithium carbonate dosage regimen designed to achieve a steady-state lithium concentration equal to 0.6 mmol/L.

Literature-Based Recommended Dosing

1. *Estimate creatinine clearance.*
This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:
$CrCl_{est} = [(140 - age)BW]/(72 \cdot SCr) = [(140 - 67\ y)72\ kg]/(72 \cdot 1.2\ mg/dL)$
$CrCl_{est} = 61\ mL/min$

2. *Choose lithium dose based on disease states and conditions present in the patient.*
The patient requires prophylactic lithium therapy for bipolar disease, and has good renal function. A lithium carbonate dose of 600 mg/d, given as 300 mg every 12 hours, is recommended as the initial amount. The dosage rate will be increased 300–600 mg/d every 2–3 days as needed to provide adequate therapeutic effect, avoid adverse effects, and produce therapeutic lithium steady-state concentrations.

use of lithium serum concentrations to alter dosages

$$D_{new}/Css_{new} = D_{old}/Css_{old}$$

or

$$D_{new} = (Css_{new}/Css_{old})\, D_{old}$$

السؤال الرابع من أسئلة جابتر

Patient DU (please see problem 3) was prescribed lithium carbonate ***600 mg orally at 0800 H, 1400 H, and 2000 H.*** The current 12-hour postdose steady-state lithium concentration equals 0.6 mmol/L. Compute a new oral lithium dose that will provide a steady-state concentration of 1 mmol/L.

السؤال الرابع من أسئلة جابتر

Patient DU (please see problem 3) was prescribed lithium carbonate ***600 mg orally at 0800 H, 1400 H, and 2000 H.*** The current 12-hour postdose steady-state lithium concentration equals 0.6 mmol/L. Compute a new oral lithium dose that will provide a steady-state concentration of 1 mmol/L.

بالسؤال اعطى جرعة الليثيوم كل 6 ساعات.. واني عندي الـ Time intervalهي يوم واحد.. إذا الجرعة هي 1800 خلال يوم واحد.

$D_{new} = (Css_{new}/Css_{old})\ D_{old}$
$= (1\ mmol/L / 0.6\ mmol/L)$ 1800 mg/d
= 3000 mg/d, round to 2700 mg/d
The patient would be administered 900 mg of lithium carbonate at 0800 H, 1400 H, and 2000 H.

Thank you

PEDIATRIC PHARMACOKINETICS

DR. OMER Q. B. AL-LELA

ASSISTANT PROF. IN CLINICAL PHARMACY, PHD

MPS ASSOCIATION MEMBER

ISPOR, ISOP MEMBER

PEDIATRIC PHARMACOKINETICS

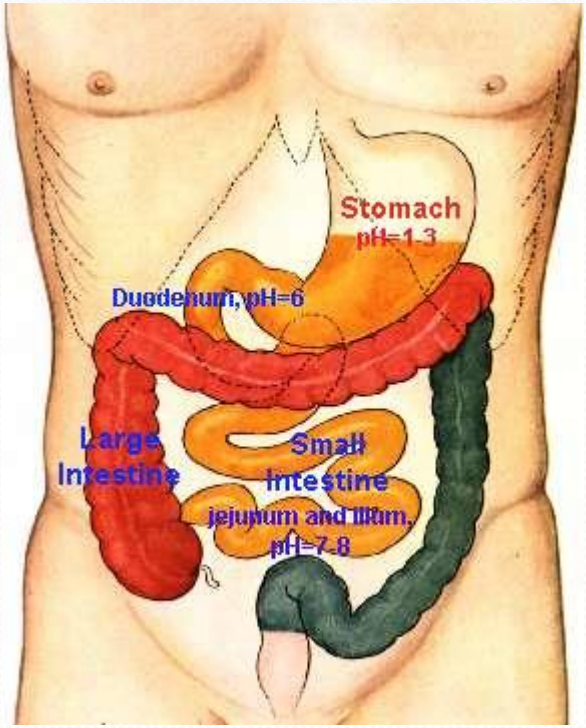
- Pediatrics growth
  - Neonate – newborn until 1 month of age
  - Premature neonate – newborn less than 36 weeks gestation
  - Low birth weight neonate – newborn less than 2 kg birth weight
  - Infant – pediatric of 1 – 12 months of age
  - Children – pediatric more than 12 months to adolescence

Pediatric has more immature organ function – hence reduce the ability to handle drugs

When I grow up, I want to be Double Mac

PEDIATRIC PHARMACOKINETICS

- Absorption
  - Oral absorption
    - Gastric pH – neonate gastric pH is neutral
      - Immature parietal cells
      - Reach adult value at 2 – 7 years old
      - Affect the stability of acid labile drugs
      - Increases the absorption of oral acid labile drugs
      - Low digestion of proteins



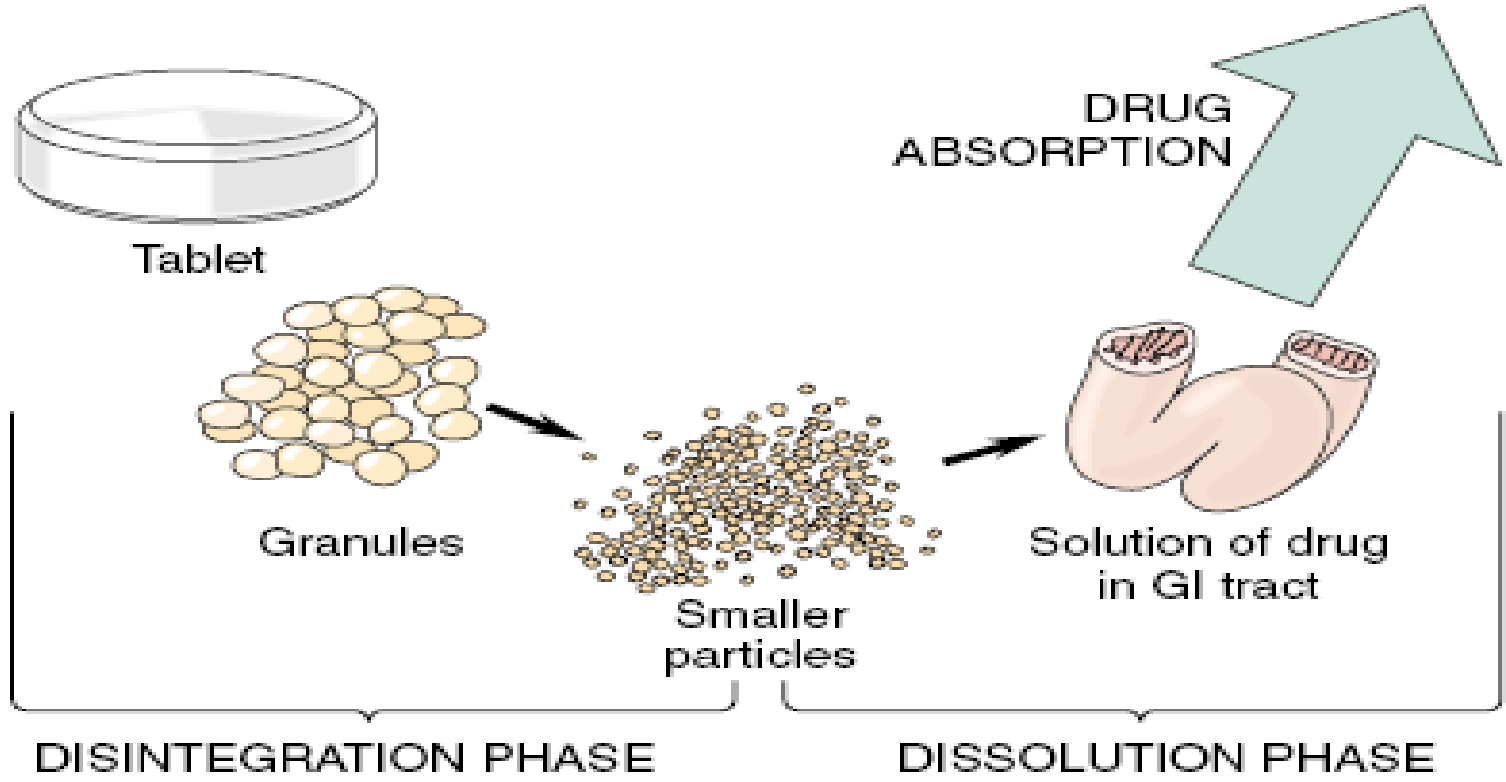
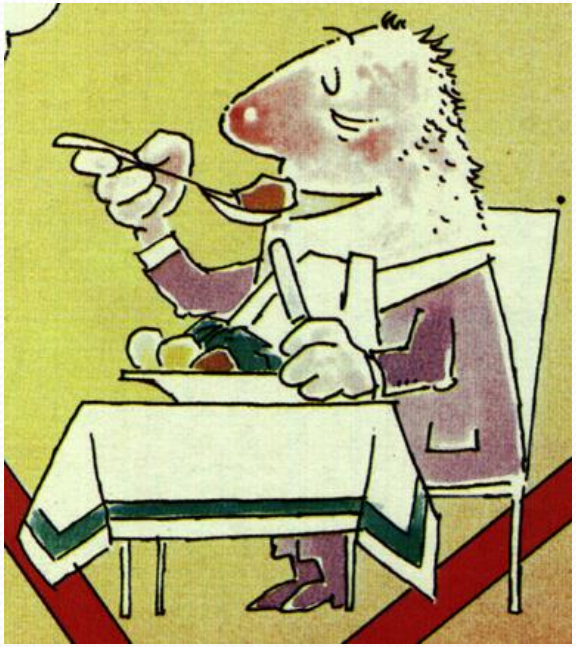


Figure 29-1 Phases of Solid Drug Absorption

PEDIATRIC PHARMACOKINETICS



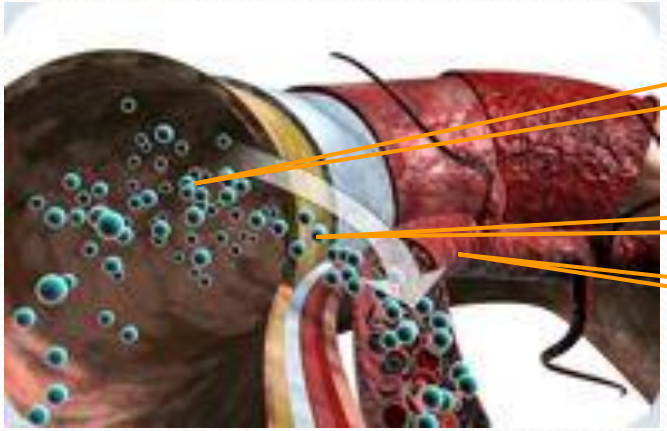
- Gastric emptying time (GET)
  - Slower than adult GET
  - Reach adult values at 1 year old
  - Increase the rate of acid labile drugs decomposition

PEDIATRIC PHARMACOKINETICS

- **Intestinal** motility
  - Slower than adult
  - Reach adult values after 1 year of age
  - Increase time for absorption
  - Increase passive absorption
  - Disease increases intestinal motility will affect the rate of absorption

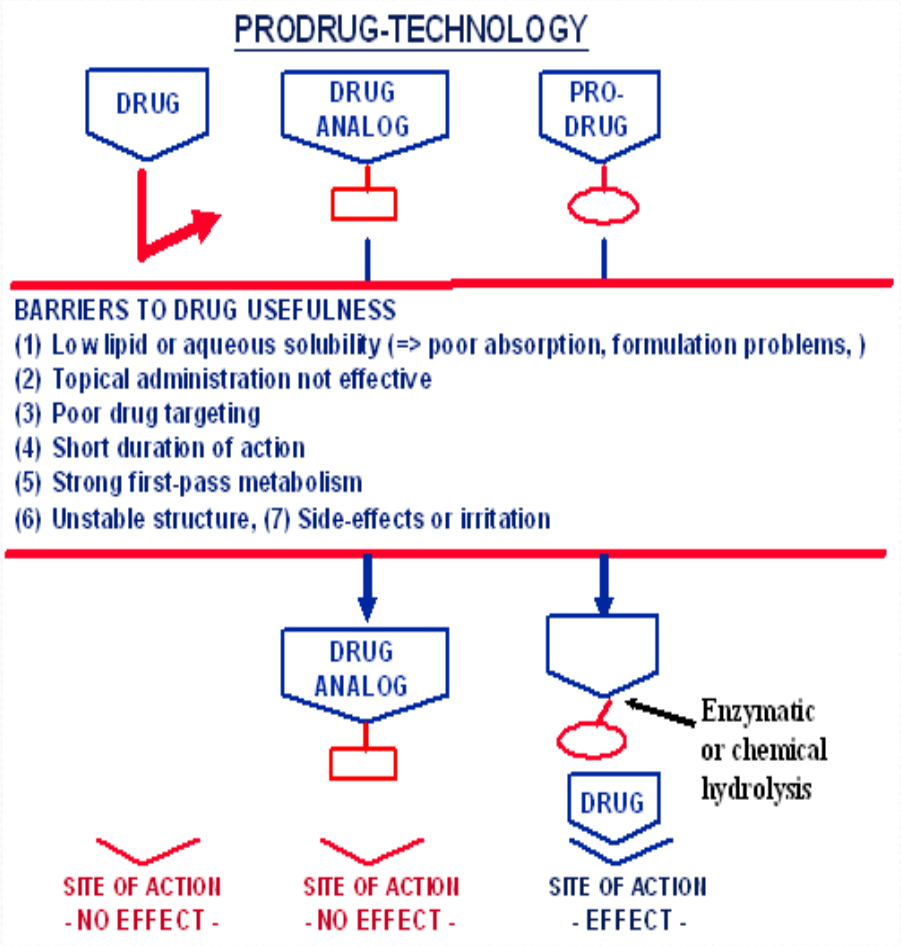
PEDIATRIC PHARMACOKINETICS

- **Mesenteric** perfusion
  - Low mesenteric perfusion secondary to limited mesenteric blood vessel
  - Lower concentration gradient between intestine and blood vessel
  - Reduce passive absorption



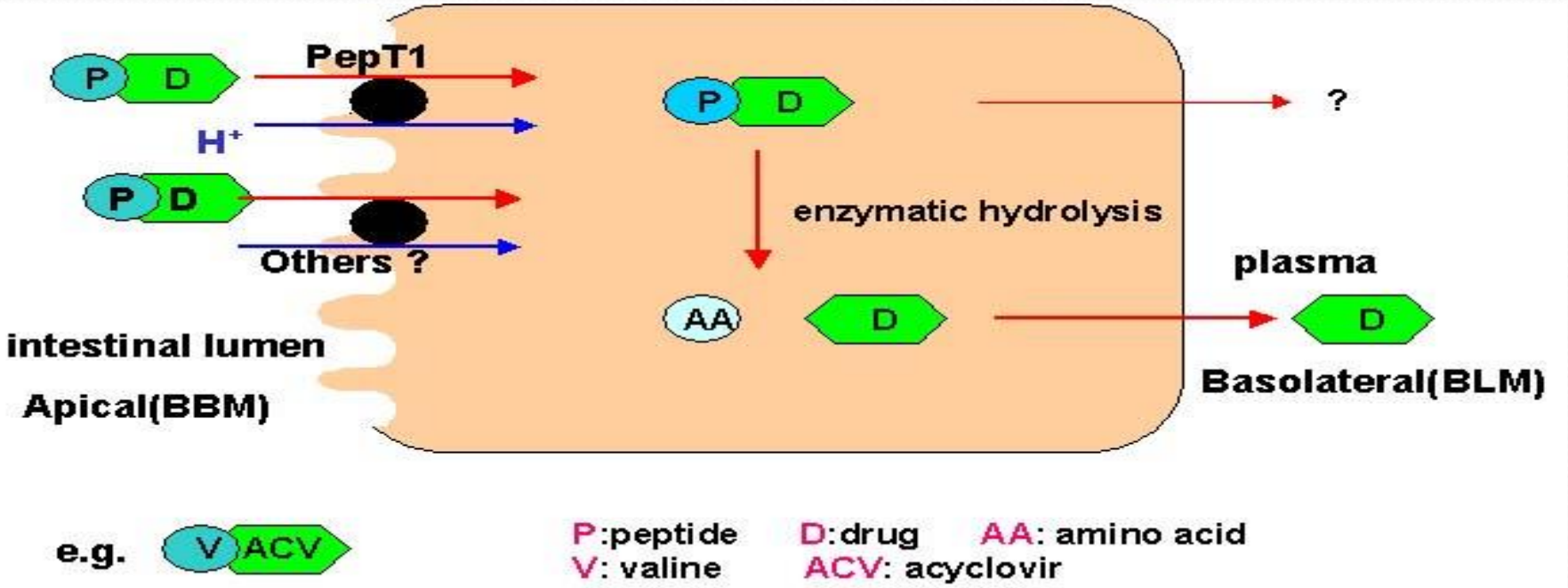
PEDIATRIC PHARMACOKINETICS

- **Enzyme**
  - The amount of GIT enzymes is inadequate
    - Volume
    - Types
  - Reduce the activation of pro drugs – decrease absorption
  - Low bile acid – reduce fat and fat soluble vitamins absorption (ADEK)



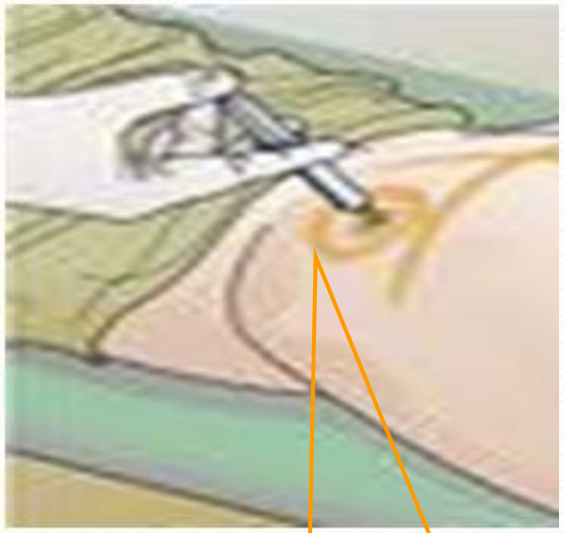
PEDIATRIC PHARMACOKINETICS

- Active absorption
  - Low / absent of protein carriers
  - Inefficient active transport
  - Low absorption of drugs requires active transport



PEDIATRIC PHARMACOKINETICS

- Non-oral absorption (IV, IM, SQ, Otic, Gutte, topical)
  - SQ and IM absorption are unpredictable and affected by
    - Hydration status
    - Blood flow
    - Vasomotor system

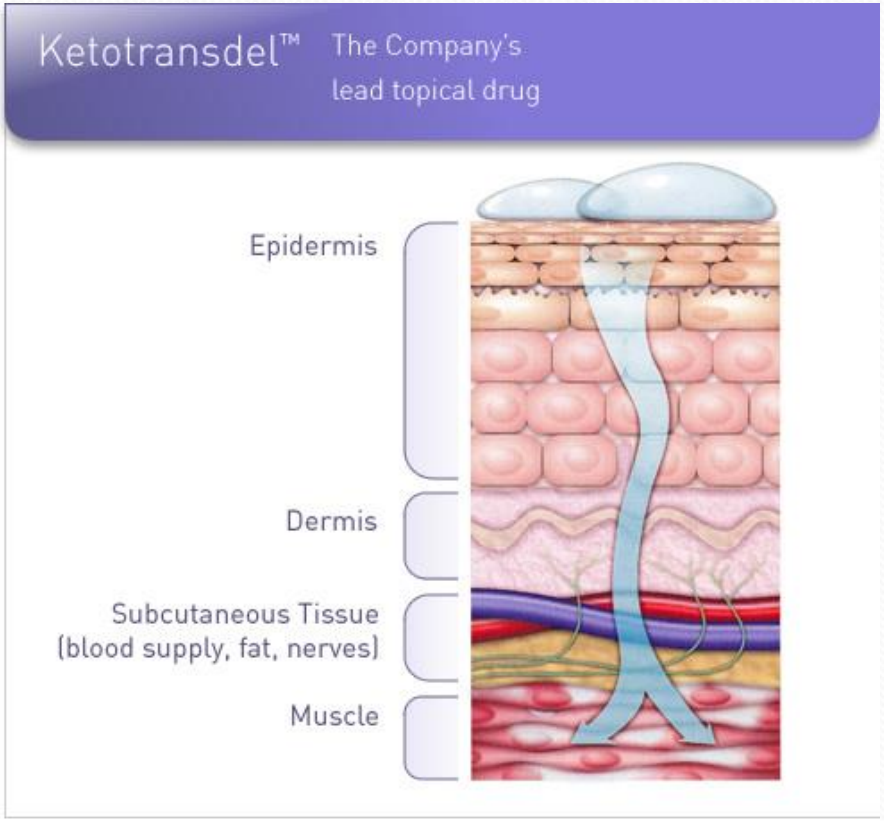


PEDIATRIC PHARMACOKINETICS

- **Rectal** absorption
  - Erratic and slower than adult but increase with age
  - Less blood vessel to the rectum
  - Convenience route in pediatric
  - Solution is better suppository
  - Fat soluble drugs have better absorption i.e. diazepam, clonazepam, theophylline

PEDIATRIC PHARMACOKINETICS

- **Topical**
  - Topical absorption is better than adult
  - Rate decreases with the reduction in TBW
  - May cause toxicities of topical drugs



PEDIATRIC PHARMACOKINETICS

- **Eye** drop
  - Absorption is better than adult
  - High hydration of the eyes
  - Thin stratum corneum

PEDIATRIC PHARMACOKINETICS

- **Volume distribution**
  - Depend on the TBW, PP, and body fat
  - TBW is higher in neonates and decreases with age – reach adult value at teenage
    - Water soluble drugs has higher Vd
  - Body fat is about 16% in neonate and reach adult value at 13 – 16 yo
    - Fat soluble drugs has lower Vd
  - Membrane Permeability of fat soluble drug is higher - increases the risk of toxicity

PEDIATRIC PHARMACOKINETICS

- **Volume distribution**
  - Protein plasma is lower than adult (80%) and reach adult value at 1 yo
  - Biding affinity is only 2/3 of adult albumin
    - Increase free drugs in neonate
  - Endogenous protein binding competitor such as bilirubin displaces drugs from binding site

PEDIATRIC PHARMACOKINETICS

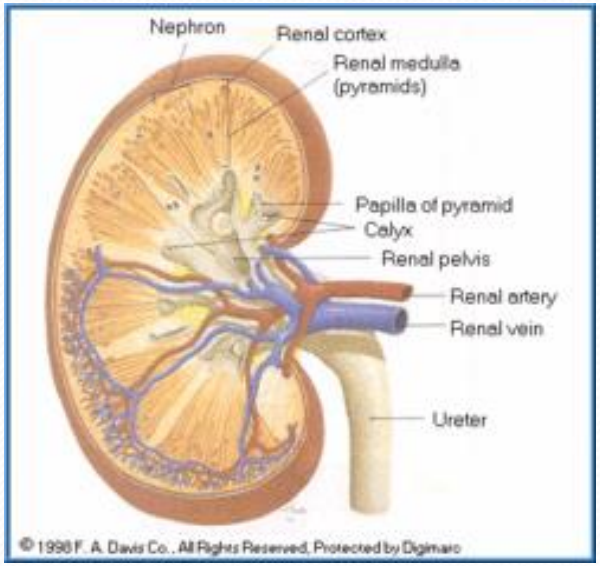
- **Metabolism**
  - All metabolic pathways are available in newborn but the capacity is lower than adult
  - Oxidation and reduction capacity is at 20 – 70% and reach adult value at 6 months and exceeding adult value up to teenage
  - Conjugation will reach adult value at 2-3 yo
  - Liver blood flow, carrier protein and uptake capacity are low and reach adult value at 1 yo

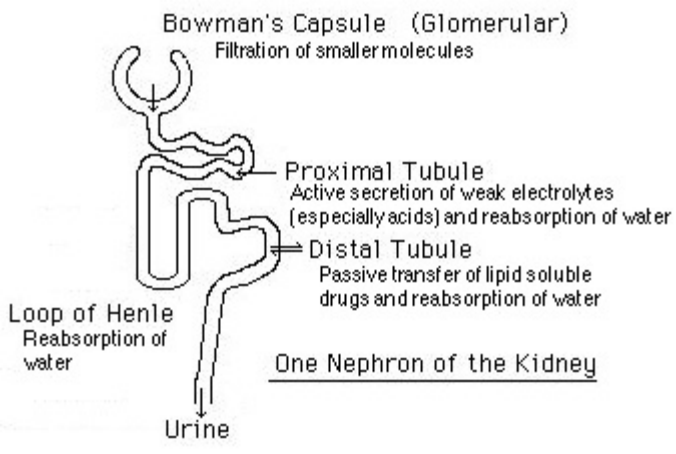
PEDIATRIC PHARMACOKINETICS

- **Metabolism**
  - Low liver blood flow influences the metabolism of high liver uptake
  - Immature billiary system - reduce metabolism and elimination
  - The use of liver enzymes inducer drugs will change the rate of hepatic metabolism

PEDIATRIC PHARMACOKINETICS

- **Excretion**
  - Total renal excretion is about 40% of adult
  - Glomerular filtration increases with the increase in renal blood flow – adult values is attained at 1 yo
  - Tubular secretion – slower than adult due to shorter tubules and low protein carrier
  - Tubular reabsorption is a passive process and depend to the pH of urine. Neonate urinary pH is about neutral and reabsorption of weak acid is slower than adult.





summary

- **Preterm newborn infants**; unique spectrum of diseases, rapid development and differences in their body functions, unique response to treatment, requirements for forms of medications that can be safely administered given their especially small size.)
- **Term newborn infants** (0 to 27 days); volumes of distribution may be different than those in older pediatric patients, blood-brain barrier is not fully mature. Oral absorption may be less predictable, hepatic and renal clearance mechanisms are immature and rapidly changing.
- **Infants and toddlers** (28 days to 23 months); Elimination of drugs from the body may exceed that in adults. Considerable variability in response to medication, because the development does not occur at the same rate in all children.
- **Children** (2 to 11 years); large variation and variability in development. Onset of puberty is highly variable and heralds a time of accelerated growth and marked changes which may alter response to medications and doses required.
- **Adolescents** (12 to 16-18 years (dependent on region)); Rapid growth and continued neurocognitive development. Increasing independance and responsibility; willingness to take medication may become a problem

Six Rights of Pediatric Medication Administration

- RIGHT patient
- RIGHT medication
- RIGHT dose
- RIGHT route
- RIGHT time
- RIGHT documentation

Pediatric Drug Therapy

- Dosage is calculated based on body weight
- Appropriate route of administration
- Suitable dosage form
- Adequate quantity

Pediatric Drug Therapy

- Color preference
  - Strawberry
  - Orange
- Taste preference
  - Strawberry
  - Orange
  - Sweet

Do not add medication into feeding bottle

Route of Pediatric drug administration

Accuracy of the dose is the primary problem in pediatric oral dose

Medication Administration at School

- Pediatric with chronic diseases may need to take their medication during school hours
- Medication administration at school need supervision from qualified personal
- Student should be allowed to bring their medication to school
- All prescription medication shall be kept in a container properly labeled with the child's name, the name of the medication, and the dosage, time and frequency to be given.
- All non-prescription medication shall be in the original container, properly labeled with the child's name and instructions for administration.

Medication Administration at School

- The school will not be responsible to provide medication to students
- It is the responsibility of the parent to ensure that proper medication is brought to school.
- Parents are responsible to inform the school's authority if their children need a chronic drug therapy


thank you

THERAPEUTIC DRUG MONITORING (TDM)

DR. SAIF KHALID ALKHAFAF

PHD. IN PHARMACOLOGY

INTRODUCTION

- In ***pharmacotherapy***, many medications are used without monitoring of blood levels, as their dosage can generally be varied according to need, clinical response showed by that patient.

- ***Insufficient levels*** will lead to under treatment or resistance.

- ***Excessive levels*** can lead to toxicity and tissue damage. hence there is need of TDM.

TDM

- Therapeutic drug monitoring is a branch of Clinical Pharmacy that specializes in the measurement of medication levels in blood.
- Its main focus is on drugs with a narrow therapeutic range.
- TDM = drug measurements in biological fluids.
- TDM was introduced in India in the mid and late 1980s

OBJECTIVES OF TDM

1. To achieve optimal drug therapy
2. To achieve desired pharmacological effect of drug within shortest period of time with no toxicity
3. To monitor SDC for clinical response
4. To benefit the patient medically & economically by reducing hospital stay And drug related toxicity.

MAJOR INDICATIONS FOR TDM

- Indications for TDM can be summarized as follows:

1. Low therapeutic index
2. Poorly defined clinical end point
3. Non compliance
4. Therapeutic failure
5. Wide variation in the metabolism of drugs
6. Major organ failure
7. Prevention of adverse drug effects

TDM IS UNNECESSARY WHEN

1. Clinical outcome is unrelated either to dose or to plasma concentration
2. The pharmacological effects can be clinically quantified
3. Drugs with wide therapeutic range such as beta blockers and calcium channel blockers.

CLINICAL USEFULNESS OF TDM

1. MAXIMIZING EFFICACY

- Epileptic pt. vs Phenytoin
- Burn pt. vs Gentamicin
- Asthmatic pt. vs Theophylline
- Life-saving in serious situations

CLINICAL USEFULNESS OF TDM

2. AVOIDING TOXICITY

- Overdose
- Differentiate adverse effects from disease states: Digoxin toxicity vs ventricular arrhythmias
- Altered pharmacokinetics

CLINICAL USEFULNESS OF TDM

3. IDENTIFYING THERAPEUTIC FAILURE

- Non-compliance
- Subtherapeutic dose
- Bioavailability problem
- Malabsorption
- Drug interactions

CLINICAL USEFULNESS OF TDM

4. HOSPITAL

- Reduce hospital congestion
- Increase quality of Rx and service
- Economic consideration

-Personnel: research, promotion & self esteem

- Medico-legal aspects

CLINICAL USEFULNESS OF TDM

5. PATIENT CARE

- Decrease duration of stay in hospital
- Receive safer and more effective Rx
- More economic
- Increased productivity
- Improve quality of life (QOL).

MAJOR CAUSES OF UNEXPECTED SERUM CONCENTRATION IN PATIENTS

The most important causes of unexpected serum concentrations are

- non compliance,
- inappropriate dosage,
- malabsorption,
- Poor bioavailability,
- drug interactions,
- hepatic or renal Disease
- altered protein binding
- and genetic factors.

LINEAR KINETICS

- If these factors can not be eliminated,
- A dosage adjustment is required for drugs with linear kinetics the following formulae may be used:

$$\text{new dose} = \text{old dose} \times \frac{\text{desired drug conc}}{\text{old drug conc}}$$

COMMON DRUGS IN TDM

1. Cardio active drugs : amiodarone, digoxin, digitoxin disopyramide, lignocaine, procainamide, propranolol and quinidine
2. Antibiotics : gentamycin, vancomycin, amikacin and tobramycin
3. Antidepressants : lithium and tricyclic antidepressants
4. Antiepileptic drugs : Phenytoin, phenobarbitone, carbamazepine, Valproic acid
5. Bronchodilators : theophylline
6. Cancer chemotherapy : methotrexate
7. Immunosuppressives : cyclosporine

Amikacin	**20–30 mcg/mL**
Carbamazepine	4–12 mcg/mL
Digoxin	1–2 ng/mL
Gentamicin	5–10 mcg/mL
Lidocaine	1–5 mcg/mL
Lithium	0.6–1.2 mEq/L
Phenytoin	10–20 mcg/mL
Procainamide	4–10 mcg/mL
Quinidine	1–4 mcg/mL
Theophylline	10–20 mcg/mL
Tobramycin	5–10 mcg/mL
Valproic acid	50–100 mcg/mL
Vancomycin	20–40 mcg/mL

THERAPEUTIC RANGE FOR COMMONLY MONITORED DRUGS

REQUEST FORM OF TDM

Patient Name..... Date..... HN.....
Age..... Sex..... Wt..... Ht.....
Ward.....Ordered by..... Phone No.....
DRUG LEVEL REQUESTED.....
REASON FOR REQUEST :
( ) Suspected toxicity ( ) Compliance
( ) Therapeutic confirmation ( ) Absence of therapeutic response
Please indicate when level is needed :
( ) within 24 h ( ) within 1-2 h ( ) stat ( ) others.....
TIME AND DATE OF LAST DOSE :
Date..... Route : IV, IM, SC, PO, Others.....
Time..... Dose..... Freq.....
THIS DRUG LEVEL IS FOR : SAMPLING TIME :
( ) Trough or predose level Date..... Time.....
( ) Peak level Date..... Time.....
DOES THE PATIENT HAVE ORGAN-SYSTEM DAMAGE ?
( ) Renal ( ) Hepatic ( ) Cardiac ( ) GI ( ) Endocrine ( ) Others.....
OTHER DRUG(S) PATIENT IS TAKING :.....
DRUG LEVEL & USUAL THERAPEUTIC RANGE.....
INTERPRETATION.....
.....
Date..... Technologist..... Time.....

STAGES IN TDM

1. Selection of proper Analytical Method.
2. Proper periods of sampling for Analysis
3. Establish relationship between SDC with therapeutic efficacy and/or toxicity of drug

TDM ASSAY METHODOLOGIES

1. **Enzyme multiplied immunoassay technique (EMIT)**: highly automated, rapid turnaround,many assays available, homogenous, moderate sensitivity but poor stability of alibration curve

2. **Enzyme-linked immunosorbent assay (ELISA)**: highly automated, rapid turnaround, moderate sensitivity but few assays available, heterogenous.

3. **Radioimmunoassay (RIA)**: high sensitivity but long turnaround,many interferences, heterogenous, radiation hazards

TDM ASSAY METHODOLOGIES

4. **Fluorescence polarization immunoassay FPIA**: highly automated, rapid turnaround, many assays available, stability of reagents and calibration curves, but moderate sensitivity.

5. **High-performance liquid chromatography HPLC**: highest sensitivity, most assays available, least expensive but long turnaround, requires highly trained personnel

TYPES OF ASSAY REQUIRED

1. Total drug conc.
2. Free drug conc.
3. Metabolites

TIMING OF SAMPLE COLLECTION

- The importance of proper timing of a sample is ***not*** given sufficient attention while ordering measurement of a plasma concentration.
- The best sampling time is in the ***pre-dose*** or through phase just prior to a maintenance dose, when a drug is administered by multiple oral doses.
- This principle is important for digitalis which is administered on a ***once daily*** basis in the morning.
- For drugs with a ***long half life*** such a phenytoin at least 4 to 5 half lives must elapse before a sample is taken.

SAMPLE TIMING FOR SOME IMPORTANT DRUGS:

- ***Phenytoin***: Since phenytoin has a long half life a single daily dose may be employed and so the timing of sampling is 4-5 ***t1/2***.
- ***Carbamazepine***: Its half life may be as long as 48 h following a single dose. A concentration taken just after a dose together with a peak level ***three hours later*** is ideal.
- ***Digoxin***: The measurement must be made ***at least six hours after*** a dose to avoid inappropriate high levels.
- ***Theophylline***: This drug has a narrow therapeutic index and timing of sampling is not critical if the patient is receiving one of the slow release formulations.
- ***Gentamicin***: Pre dose peak; ***0.5 hr after*** i.v. and ***1 hr after*** i.m. administration.

FACTORS TO BE CONSIDERED IN TDM

1-DOSAGE REGIMEN:

- It is one of the factors to be considered while interpreting TDM data.

- It is important to know the duration of drug therapy, dosage and when the last dosage was taken.

2-ACTIVE METABOLITE:

- Many drugs are biotransformed into compounds that are pharmacologically active.
- When evaluating the therapeutic effect of such drugs, the relative contributions of all active substances present in the serum must be integrated.
- e.g. imipramine is biotransformed to the active metabolite – desipramine.

3-EFFECT OF DISEASE STATES:

- Acute or chronic disease alters drug clearance patterns.
- Thus drug concentrations may be elevated or depressed depending on the pathophysiology of the system involved.
- e.g., liver disease impairs the clearance of drugs, dependent upon conversion to more water soluble compounds.

4-FREE DRUG MONITORING:

- Development of new filtration devices (equilibrium dialysis, ultrafiltration, ultracentrifugation) has made it possible to measure free unbound drug levels in serum.

- The **advantages** are that the free concentrations is independent of changes in plasma binding and is the pharmacologically active concentration.

- The **disadvantages** are that it is time consuming, expensive and therapeutic ranges do not yet exist for many drugs.

5-EFFECT OF AGE:

- Variability in response to drugs occurs at extremes of age.
- Elderly patients are more sensitive to the CNS depressant effect of drugs but are less sensitive to cardiovascular effects of propranolol.
- On the other hand young children are more sensitive to CNS depression effects of morphine.

PROBLEMS OF TDM SERVICE

1. Hospital personnel do not know the existence of TDM service
2. Physicians do not understand the principles, benefits, and the limitations of TDM service
3. Inappropriate sampling times
4. Do not state the indication of TDM
5. Insufficient patient's history and other necessary data
6. No consultation when problems arise

THANK YOU

Theophylline Pharmacokinetics

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Introduction

- Theophylline is a methylxanthine compound.
- It is used for the treatment of asthma, chronic obstructive pulmonary disease (COPD), and premature apnea.
- The bronchodilatory effects of theophylline are useful primarily for patients with asthma because bronchospasm is a key component of asthma.

Therapeutic concentrations

- The generally accepted therapeutic ranges for theophylline are:
  - 10–20 μg/mL for the treatment of asthma or COPD.
  - 6–13 μg/mL for the treatment of premature apnea.
  - Clinical response to theophylline concentrations between 5–15 μg/mL

- Theophylline therapy must be individualized for each patient in order to achieve optimal responses and minimal side effects.

Toxic concentrations and side effects

- In the upper end of the therapeutic range (>15 μg/mL) some patients will experience minor caffeine-like side effects include nausea, vomiting, dyspepsia, insomnia, nervousness, and headache.
- 20–30 μg/mL can cause various tachyarrhythmias including sinus tachycardia.
- 40 μg/mL, serious life-threatening adverse effects including ventricular arrhythmias or seizures can occur.

Clinical monitoring parameters

- Forced expiratory volume over 1 second (FEV1) should be measured on a regular basis for asthmatic patients.
- Peak-flow meter monitoring can be routinely performed by these individuals at home.
- Successful bronchodilator therapy will increase both of these values.
- Other spirometric tests useful for patients with COPD include vital capacity (VC), total lung capacity (TLC), forced vital capacity (FVC).

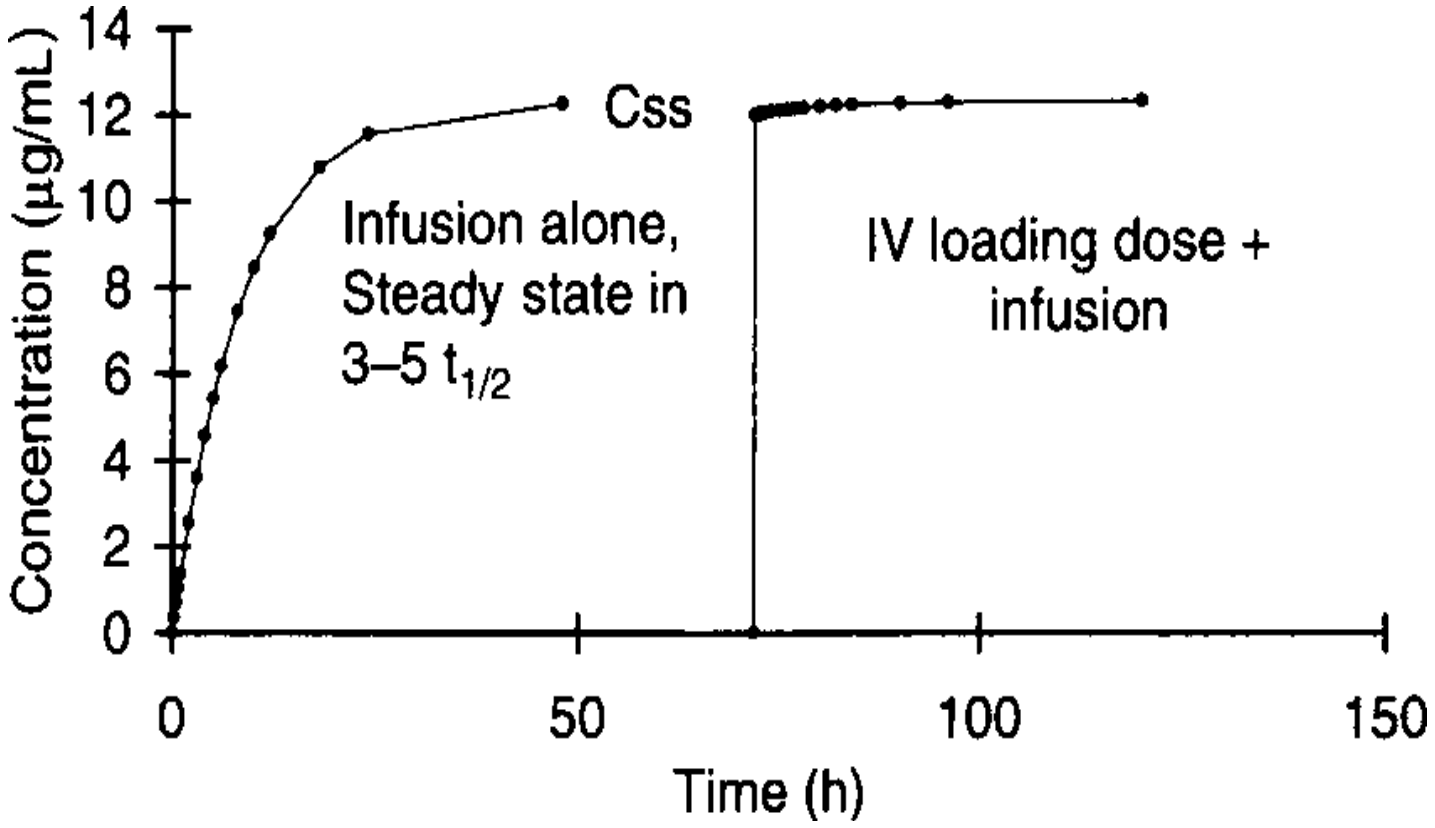
Loading Dose

- When intravenous theophylline is administered to a patient as a continuous infusion, it will take 3–5 half lives for serum theophylline concentrations to reach steady-state levels. Because of this, maximal drug response will take time to achieve.

- To hasten onset of drug action, loading doses are given to attain effective theophylline concentrations immediately.

- (LD in milligrams): LD = C_{ss} x V

Loading Dose
vs.
Infusion Dose



Basic Clinical Pharmacokinetic Parameters

- Theophylline is primarily eliminated by hepatic metabolism (>90%).
- About 10% of a theophylline dose is recovered in the urine as unchanged.
- Theophylline plasma protein binding is only 40%.
- Volume of distribution (V_d) = 0.48L/Kg ≈0.5L/Kg.
- Half-time ($t_{1/2}$) value depend on disease status and condition.

Basic Clinical Pharmacokinetic Parameters

Disease status and condition	Half time ($t_{1/2}$)
Adult + normal liver function	8 hrs
Adult + tobacco smoker	5 hrs
Adult + hepatic disease	24 hrs
Elderly > 65 yrs	12 hrs
Children 1-9 yrs	3.5 hrs

Basic Clinical Pharmacokinetic Parameters

- Theophylline and aminophylline are available for intravenous injection and oral use.

- Three different forms of theophylline are available (S):
  1. Aminophylline anhydrous is contains about 85% theophylline
  2. Aminophylline dihydrate contains about 80% theophylline.
  3. Oxtriphylline is contains about 65% theophylline.

- The oral bioavailability (F) of all three theophylline-based drugs is very good and generally equals 100%.

Exercise

OI is a 60-year-old, 85-kg (6 ft 1 in) male with emphysema who requires therapy with oral theophylline. He has liver cirrhosis and normal cardiac function.

Suggest an initial theophylline or aminophylline dosage regimen designed to achieve a steady-state theophylline concentration equal to 10 μg/mL.

1. Estimate half-life and elimination rate constant

- Patients with severe liver disease have highly variable theophylline pharmacokinetics and dosage requirements. Hepatic disease destroys liver parenchyma where hepatic drug–metabolizing enzymes are contained, and the expected theophylline half-life ($t_{1/2}$) is 24 hours.

- The elimination rate constant is computed using the following formula:

$$k = 0.693/t_{1/2} = 0.693/24\ h = 0.029\ h^{-1}$$

2. Estimate volume of distribution and clearance.

- The patient is not obese, so the estimated theophylline volume of distribution will be based on actual body weight:

$$V = 0.5 \text{ L/kg} \times 85 \text{ kg} = 43 \text{ L}.$$

- Estimated theophylline clearance is computed by taking the product of the volume of distribution and the elimination rate constant:

$$Cl = kV = 0.029 \text{ h}^{-1} \times 43 \text{ L} = 1.25 \text{ L/h}.$$

3. Compute dosage regimen.

- Oral sustained-release theophylline tablets will be prescribed to this patient (F = 1, S = 1).

- The initial dosage interval (τ) will be set to 12 hours.

- The dosage equation for oral theophylline is:

$$D = (Css \times Cl \times \tau)/(F \times S) =$$

$$(10\ mg/L \times 1.25\ L/h \times 12\ h) / (1 \times 1) =$$

150 mg every 12 hours.

Sampling time

- A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives.
- Since the patient is expected to have a half-life equal to 24 hours, the theophylline steady-state concentration could be obtained anytime after the fifth day of dosing (5 half-lives = 5 x 24 h = 120 h or 5 days).
- Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Thank you

VANCOMYCIN

PHARMACOKINETICS

DR. SAIF KHALID ALKHAFAF

PHD. IN PHARMACOLOGY

Introduction

- A glycopeptide antibiotic.
- Approved for use by FDA (USA) in 1958.
- Used for severe G+ve infections due to organisms that are resistant to other antibiotics.
- Active against Methicillin- Resistant Staphylococcus aureus (MRSA) and ampicillin-resistant enterococci.

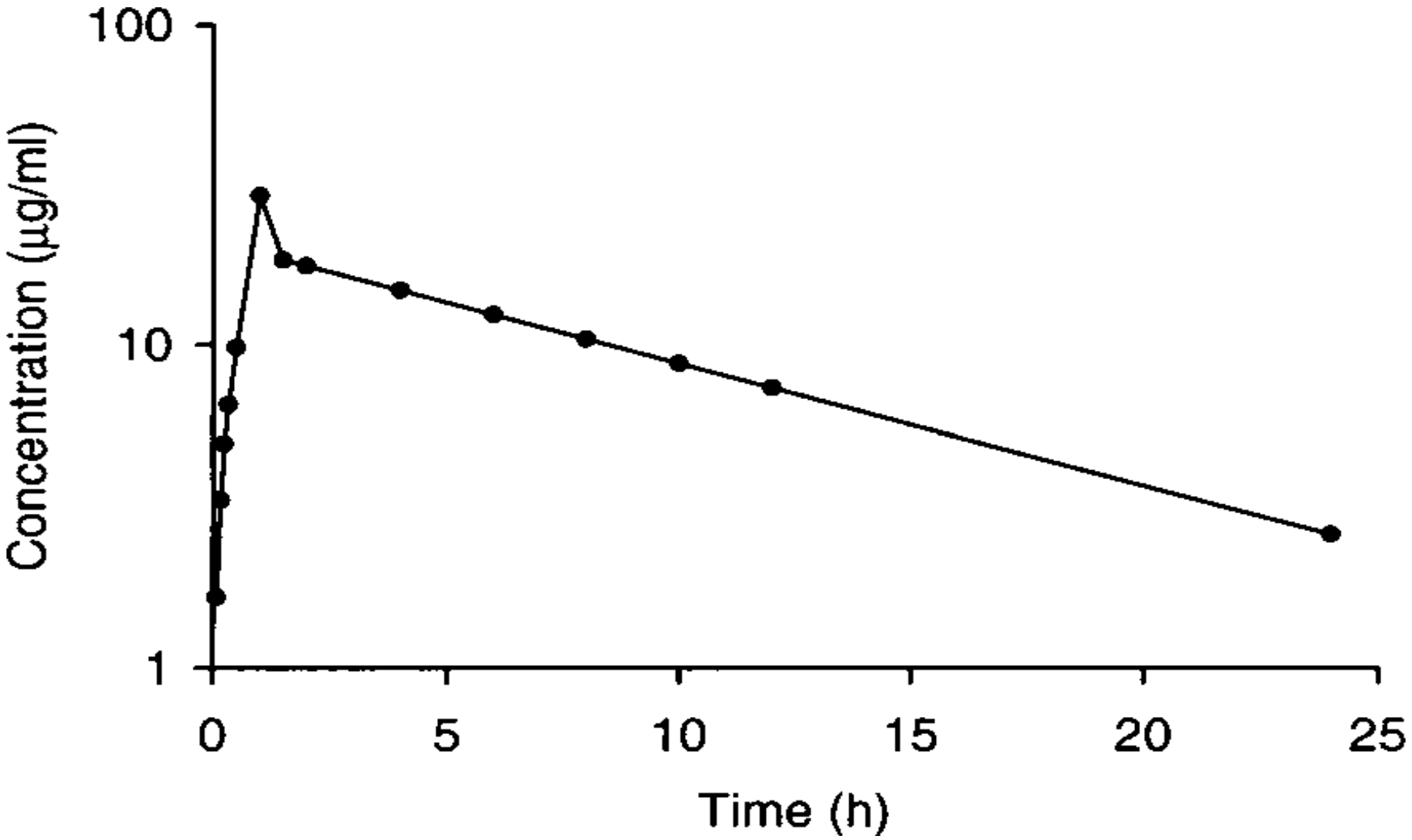
Introduction…

- Bactericidal with time-dependent killing or concentration-independent killing.
- Inhibit cell-wall synthesis.
- Poor oral bioavailability.

Therapeutic Plasma Concentrations

- Administered as a short-term (1-hour) IV infusion.
- Shorter infusions (~30min) ⇨ urticaria, intense flushing, ↑HR, ↓BP.
- $C_{peak} \rightarrow$ 0.5 – 1 hour after infusion completed. (Figure 1)

FIGURE1 Concentration/time plot for vancomycin 1000 mg given as a 1-hour infusion. *When given as a 1-hour infusion, end of infusion concentrations are higher* because the serum and tissues are not in equilibrium. A 1/2- to 1-hour waiting time for vancomycin distribution to tissues is allowed before peak concentrations are measured.



Therapeutic Plasma Concentrations

- C_{peak} = 20-50μg/ml
- C_{trough} = 5-15μg/ml
- Clinical outcomes rates NOT related to C_{peak}.
- C_{trough} are usually related to therapeutic outcomes for vancomycin ⇨ time-dependent bacterial killing.

Therapeutic/Toxic Plasma Concentrations

- C_{peak}
  - TR for steady state C_{peak} 20 – 40 μg/mL.
  - Steady state C_{peak} of 40 – 60 μg/mL or direct admin into the CSF may be considered.
  - Ototoxicity when conc. exceeds 80 μg/mL.

Therapeutic/Toxic Plasma Concentrations

- C_{trough}
  - Optimal bactericidal effects are found at 3 – 5 times the organism's Minimum Inhibitory Conc. (MIC).
  - MIC for *S. aureus* and *S. epidermidis* is 1 to 2 μg/mL.
  - Steady state C_{trough} above 15μg/mL increase incidence of nephrotoxicity.

Vancomycin side effect and Interaction

- Less potential for nephrotoxicity compared to aminoglycosides.
- Vancomycin-related nephrotoxicity is usually reversible.
- When an aminoglycoside and vancomycin are administered concurrently, serum creatinine concentrations should be monitored on a daily basis.
- When vancomycin is administered to patients stabilized on warfarin therapy, the hypoprothrombinemic effect of the anticoagulant may be augmented. For this reason a baseline prothrombin time ratio (INR) must be measured before the antibiotic is administered.

Monitoring Parameters

- Cultures and sensitivities.
- WBC with differentials
- Temperature
- Vancomycin steady-state serum conc. (after 3rd dose as a general rule)
- Advocates of measuring C_{trough} conc.
- Serum creatinine (baseline, 3times weekly)

Clinical Pharmacokinetic Parameters

- Oral bioavailability (F) is poor (< 10%) → systemic infections cannot be treated.
- IM route avoided because of tissue necrosis.
- Recommended dose 30mg/kg/day BD-QID.
- Adults with normal wt: 1000mg q 12hrs.
- Plasma protein binding is ~ 55%.
- > 90% eliminated unchanged in the urine.

Key Pharmacokinetic Parameters

PARAMETER	*VALUE*
Therapeutic Range	•Peak = 20-50µg/ml •Trough = 5-15µg/ml
F (Oral)	< 5%
Half-life ($t_{1/2}$)	6 – 7 hours
V_d	0.7 L/kg
Cl_{vanco}	$0.695(Cl_{cr}) + 0.05$

Disease States & Pharmacokinetics

- Renal dysfunction is the most important disease that influence PK.
- Major burns (30 – 40%) causes ↑ GFR. Average $t_{1/2}$ is burn patients is 4 hrs.
- Obesity (normal Sr_{cr}) have ↑ Cl_{vanco} due to ↑ GFR. $t_{1/2}$ ↓ to 3.3 hrs. Obese individuals best dosed using TBW.

Initial Dose Determination: PK

- Estimate the creatinine clearance (Cockcroft-Gault equation)

  1- Male: $CLcr = [(140 - age)BW] / (72 \cdot S_{Cr})$

  2- Female: $CLcr = [0.85\ (140 - age)BW] / (72 \cdot S_{Cr})$

- Estimate Cl: $Cl_{vanco} = 0.695(Cl_{cr}) + 0.05.$ (ml/min/kg)
- Estimate V_d: $V_d = 0.7$ L/kg. BW
- Calculate K_e and $t_{1/2}$.
- Calculate required dosage interval (τ) and Dose:

$$\tau = (\ln C_{ssmax} - \ln C_{ssmin}) / ke$$

$$D = C_{ssmax}\ V(1 - e^{-ke\tau})$$

Exercise

- JM is a 50-year-old, 70-kg (5 ft 10 in) male with a methicillin-resistant S. aureus (MRSA) wound infection. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute a vancomycin dose for this patient.

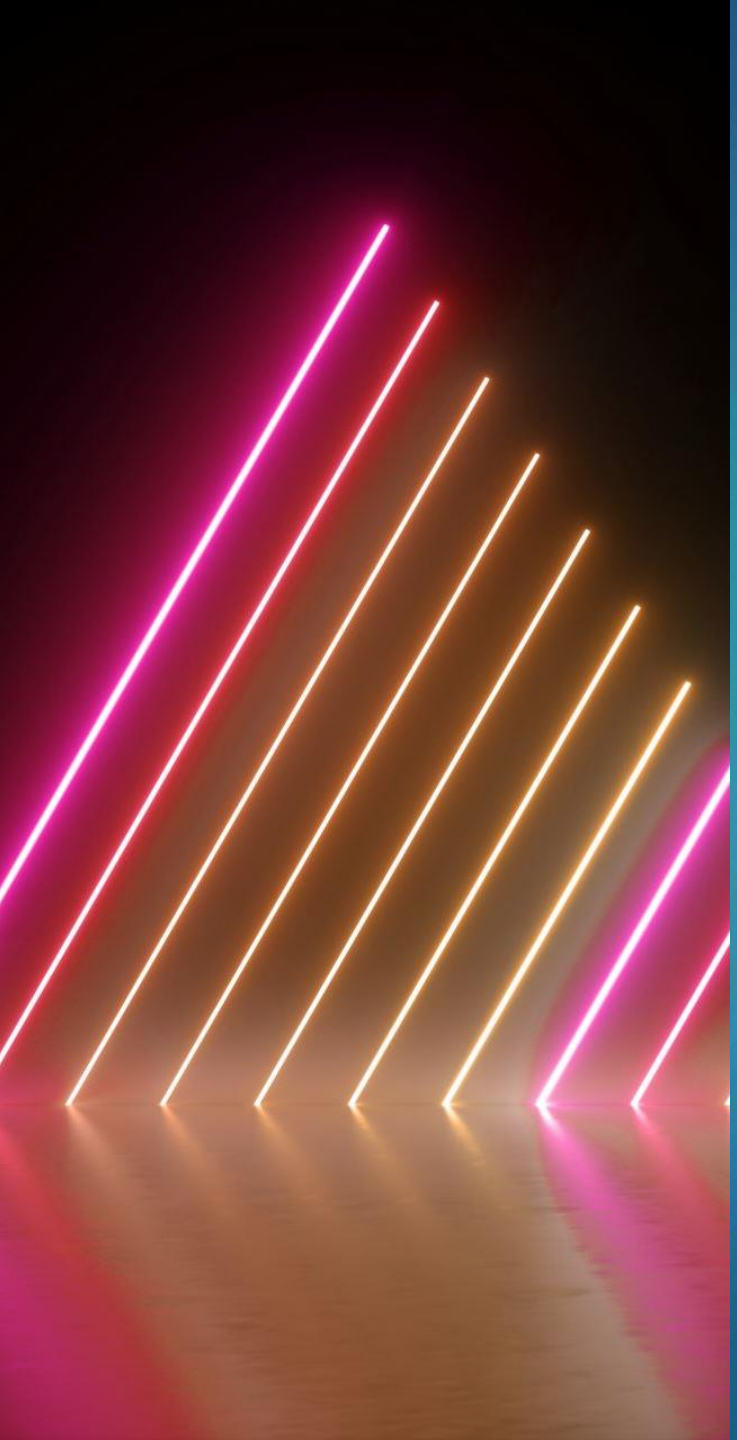
Solutions

- CrClest = [(140 − age)BW] / (72 · SCr) = [(140 − 50 y)70 kg] / (72 · 0.9 mg/dL)=

  CrClest = 97 mL/min

- Cl = 0.695(CrCl) + 0.05 = 0.695[(97 mL/min)/70kg] + 0.05 = 1.015 mL/min/kg
- V = 0.7 L/kg · 70 kg = 49 L
- ke = Cl/V = (1.015 mL/min/kg · 60 min/h) / (0.7 L/kg · 1000 mL/L) = 0.087 h–1
- t1/2 = 0.693 / ke = 0.693 / 0.087 h–1 = 8 h
- τ = (ln Cssmax − ln Cssmin) / ke = (ln 20 μg/mL − ln 7 μg/mL) / 0.087 h–1 = 12.1 h
- D = Cssmax V(1− e −keτ) = 20 mg/L · 49 L [1 − e−(0.087 h–1)(12 h)] = 635 mg

Thank you



Volume of Distribution (Vd)
Loading Dose (LD)
Half-life (T1/2)

DR. SAIF KHALID ALKHAFAF

PHD IN PHARMACOLOGY

Volume of Distribution

- The volume of fluid to which a drug is distributed.
- Drugs with large volume of distribution will have a longer half-life and duration of action

Cont,

- Volume of distribution (Vd) is an important pharmacokinetic parameter because it determines the loading dose (LD) that is required to achieve a particular steady-state drug concentration immediately after the dose is administered.

- The volume of distribution is a hypothetical volume that relates drug serum concentrations to the amount of drug in the body.

- volume of distribution is in volume units, such as L, mL, dL.

- At any given time after drug has been absorbed from extravascular sites and the serum and tissue drug concentrations are in equilibrium, the serum concentration for a drug (Conc.) is equal to the quotient of the amount of drug in the body (AB) and the volume of distribution:

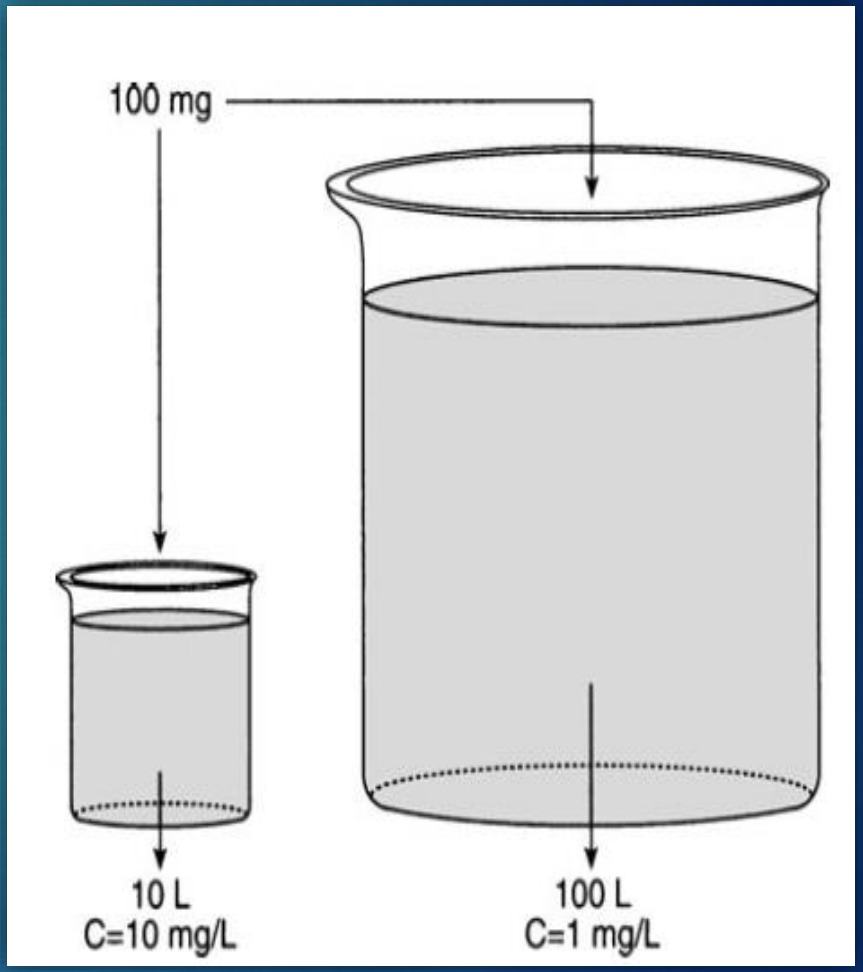
$$Conc. = AB/Vd$$

- The volume of distribution can be very small if the drug is primarily contained in the blood (Warfarin V = 5–7 L).

- The volume of distribution can be very large if the drug distributes widely in the body and is mostly bound to bodily tissues(Digoxin V = 500 L).

- e.g. if two drugs A & B, are given as 100mg intravenous bolus doses and the measured plasma concentration are 10mg/L and 1mg/L.

- The corresponding volumes of distribution would be 10L and 100L,respectivily.



Factors that alter Vd

1) Obesity (Total Body Weight vs. Ideal Body Weight)
2) Changes in Binding Affinity to Plasma protein or Tissue Sites
3) Disease States (renal failure, Ascites, dehydration, surgery)
4) Drug interactions (e.g. beta-lactam antibiotics can bind and inactivate aminoglycosides.)

Cont,

- **Factors that tend to keep the drug in the plasma or increase Conc. (such as low lipid solubility ,increase plasma protein binding, or decrease tissue binding) *reduce the apparent Vd.***

- **Factors which decrease Conc. (such as decrease plasma protein binding, increase tissue binding , and increase lipid solubility) *increase the apparent Vd.***

Loading dose

- The loading dose is administered in order to achieve a therapeutic amount in the body more rapidly than would occur only by accumulation of the *repeated smaller or maintenance doses*.

- A loading dose is most useful for drugs that are eliminated from the body relatively slowly. Such drugs need only a low maintenance dose in order to keep the amount of the drug in the body at the appropriate level, but this also means that, *without an initial higher dose, it would take a long time for the amount of the drug in the body to reach that level*.

Loading dose calculation

$$\text{Loading dose} = \frac{(V)(C)}{(S)(F)}$$

Where V is the volume of distribution , C is the desired plasma level, and (S)(F) represents the fraction of the dose administered that will reach the systemic circulation

$$\text{Incremental loading dose} = \frac{(V)(C_{desired} - C_{initial})}{(S)(F)}$$

It is a loading dose used to estimate the loading dose required to achieve a higher conc.

Question

- What is the total LD (drug A) required for Patient (Male, 60 y.o., 75 kg) if;
  - Target concentration is 10 mg/L
  - VD is 0.75 L/kg

Compartment concept in pharmacokinetics

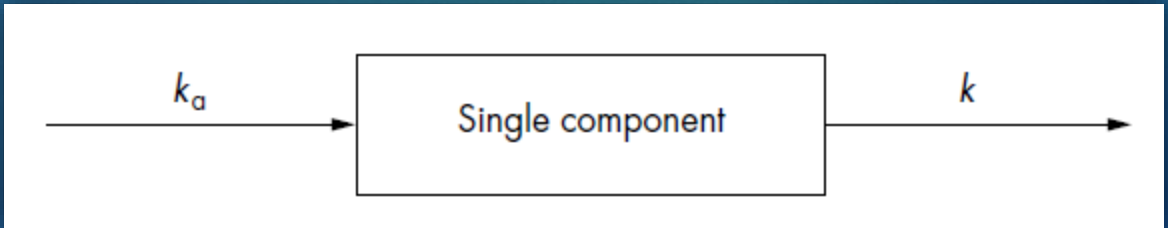
- Pharmacokinetic models are hypothetical structures that are used to describe the fate of a drug in a biological system following its administration.

One compartment model

- The one compartment model is the simplest model and considers body as a single homogeneous unit.
- Describes the pharmacokinetics of drugs which rapidly equilibrate or distribute evenly between blood and various tissues.
- Rather It assumed that changes in drug concentration in blood (plasma conc.) reflect proportional (quantitative)changes in drug conc. throughout the body.

Cont,

- It is important to note that this **does not** imply that the drug concentration in plasma (*Cp*) *is equal to the drug concentration in the* tissues. However, **changes in the plasma concentration quantitatively reflect changes in the tissues.**



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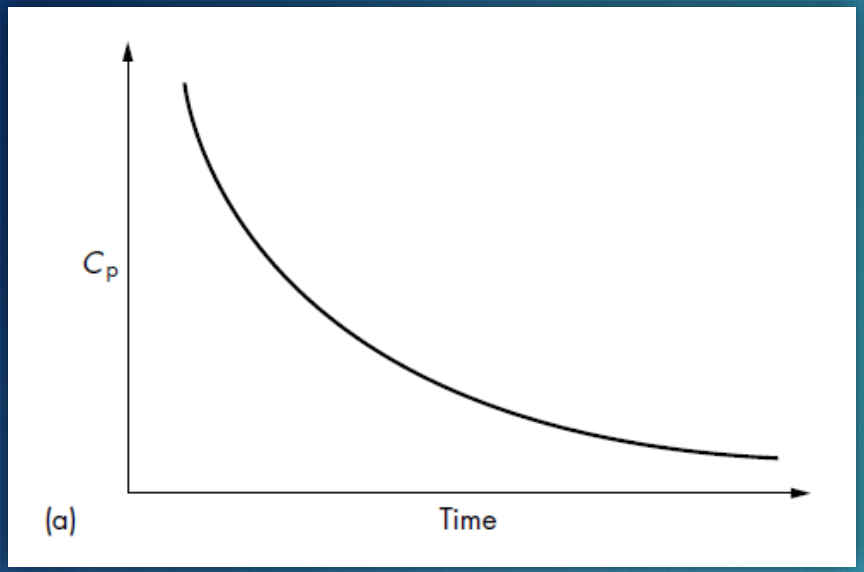
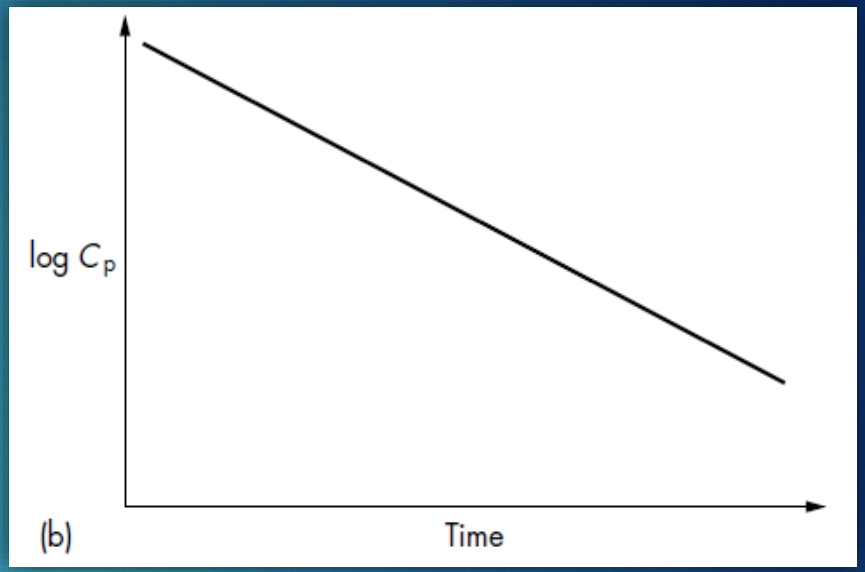




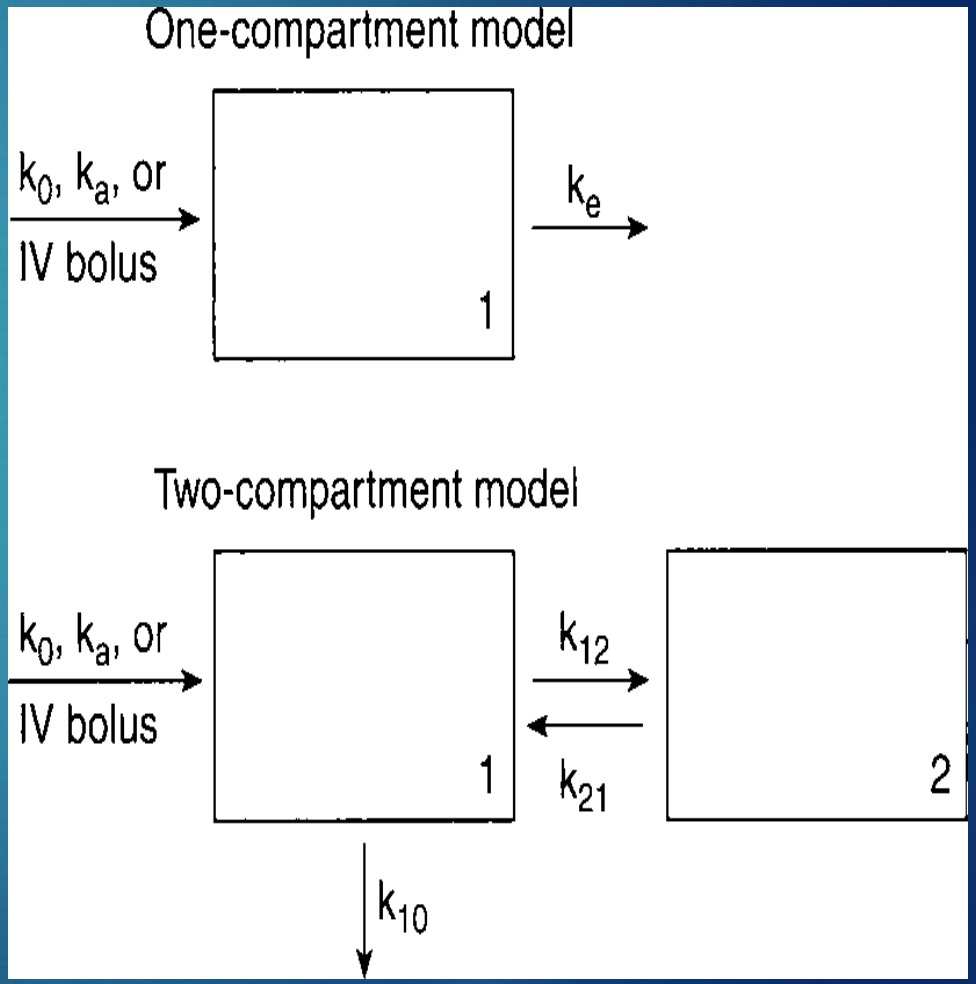
(a) :Plasma concentration (Cp) versus time profile of a drug showing a one-compartment model. (b) Time profile of a one-compartment model showing log Cp versus time.

Two compartment model

- The two-compartment model resolves the body into a central compartment and a peripheral compartment.
- Although these compartments have no physiological or anatomical meaning, it is assumed that the central compartment comprises tissues that are highly perfused such as heart, lungs, kidneys, liver and brain.
- The peripheral compartment comprises less well-perfused tissues such as muscle, fat and skin.

Two-compartment model

- **Two-compartment model. k12, k21 and k are first-order rate constants:**
- **k12 rate of transfer from central to peripheral compartment; k21 rate of transfer from peripheral to central compartment; k rate of elimination from central compartment.**



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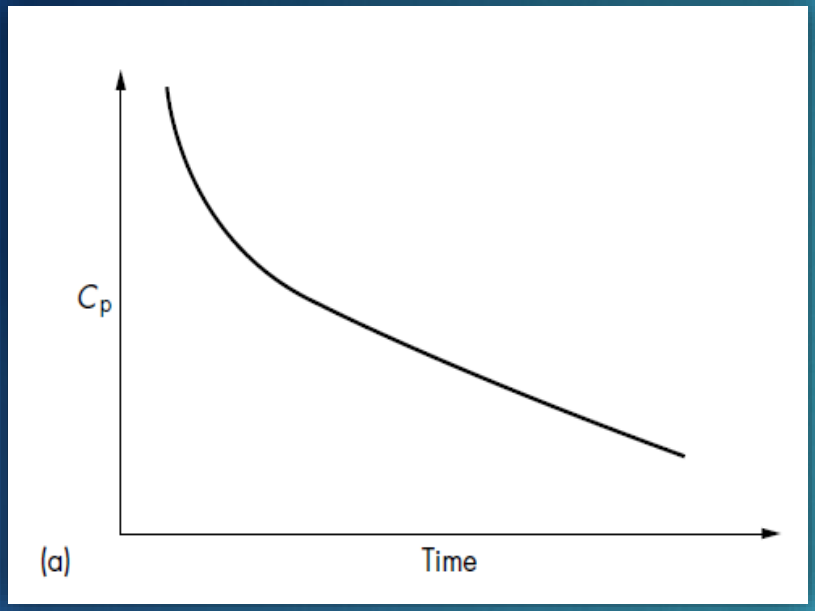

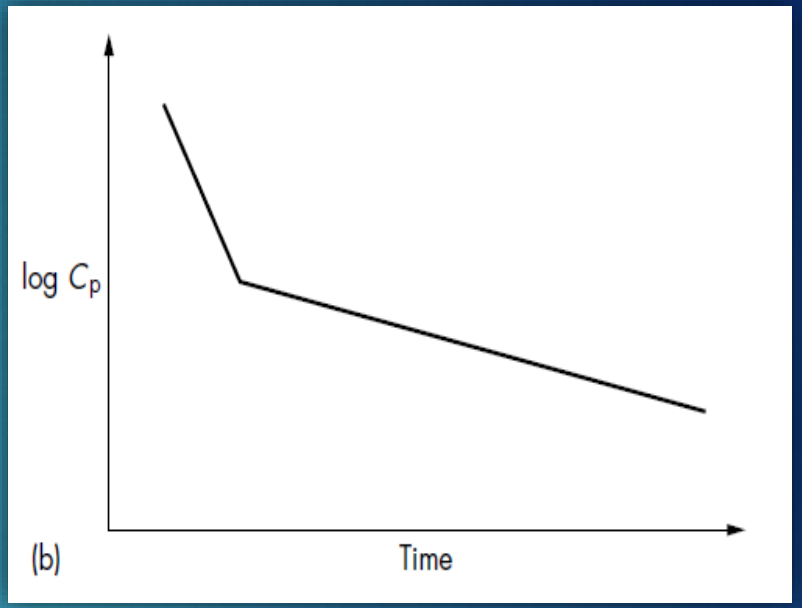

(a) Plasma concentration versus time profile of a drug showing a two compartment model.
(b) Time profile of a two-compartment model showing log Cp versus time.

Half- life ($T_{1/2}$)

- Time required to decrease the concentration of the drug in the plasma by 50%.
- Often used to determine frequency of administration.
- Determines the time to attain steady-state concentration.

Half-Life and k

- Half-life is the time taken for the drug concentration to fall to half its original value.
- The elimination rate constant (ke) is the fraction of drug in the body which is removed per unit time.

$$T_{1/2} = 0.693/K_e$$

Half- life ($T_{1/2}$)

- Drug needs about **4-5 half lives** to be completely eliminated from the body.
- E.g. Paracetamol (ACET) 500 mg half-life 4 hrs
  - after 1st 4 hrs = 250 mg.
  - after 2nd 4 hrs = 125 mg.
  - after 3rd 4 hrs = 62.5 mg.
  - after 4th 4 hrs = 31.25 mg.
  - after 5th 4 hrs = 15. 63 mg.

Half- life (T½)

$$T_{1/2} = \frac{0.693 \times VD}{CL}$$

- Where:
  - Vd = volume of distribution
  - Cl = clearance

To be continued !!!!!