Practical Pharmacokinetics for the Bedside Clinician

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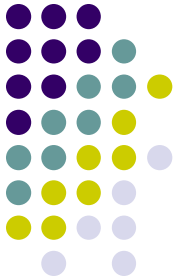
Pop Quiz

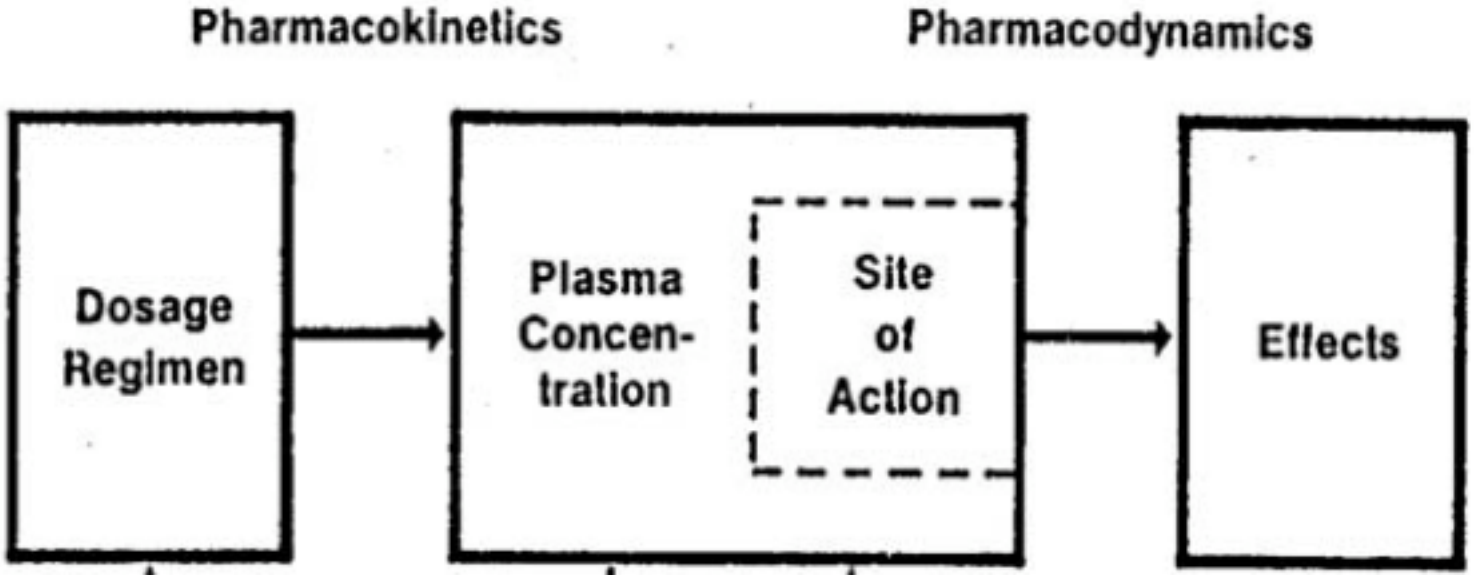
- What brings you here today?
  1. Free lunch
  2. I want to enhance my comfort with pharmacokinetic principles
  3. I need the 3 CEUs
  4. I was voluntold

Objectives



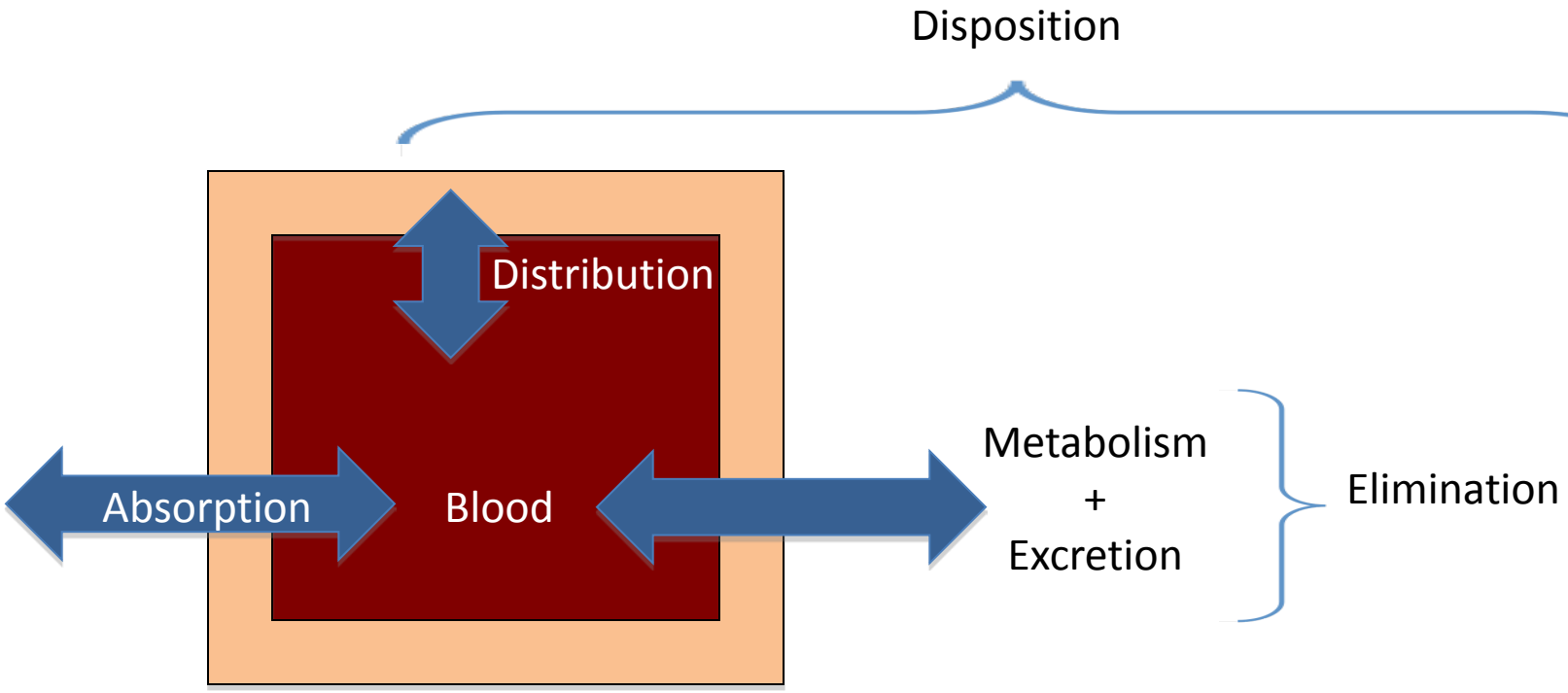
- At the end of this presentation you will be able to:
  - Define pharmacokinetic parameters
    - ADME
    - Vd, Cl, Ke, T ½, Css
  - Perform therapeutic drug monitoring
    - Phenytoin
    - Vancomycin
  - Appreciate the difference between time and concentration dependent-antibiotics

Back to the Basics



- Pharmacokinetics
  - describes the action of the body on the drug
- Pharmacodynamics
  - describes the action of the drug on the body

Principles of Pharmacokinetics

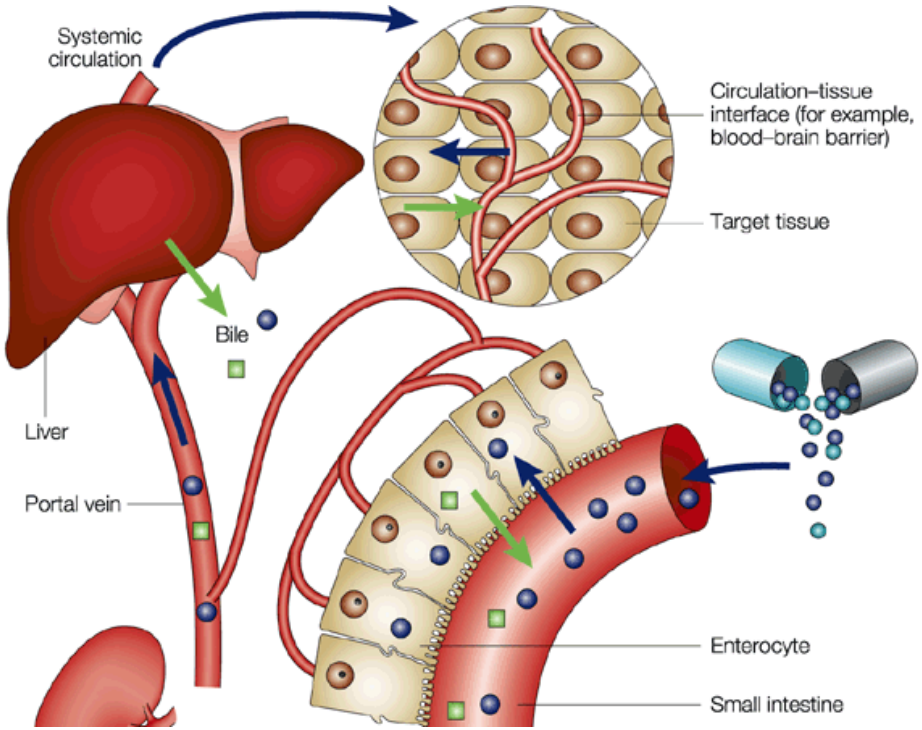


Principles of Pharmacokinetics

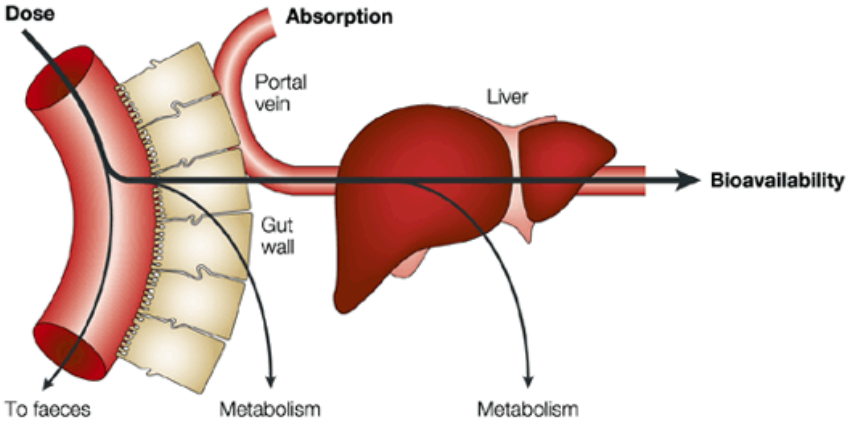
- Absorption
  - Administration
    - PO, SL, PR, PV
    - SC, IM, IV
    - Transdermal, INH, ocular, intranasal
  - Dosage Form
    - XR, SR, CR, EC, ODT
  - Properties
    - Lipophilicity, solubility, particle size
  - Gut
    - pH, metabolism, gastric emptying, intestinal transit, active transport

Principles of Pharmacokinetics

- Distribution
  - Binding to plasma proteins, red blood cells, tissue
  - Permeability of membranes
  - Physiological volumes
  - Perfusion of tissues
  - Drug lipophilicity

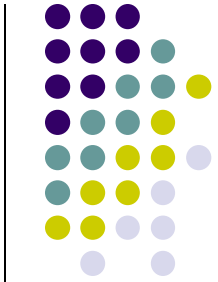


Principles of Pharmacokinetics



- Metabolism
  - Activate pro-drugs
  - Occurs in:
    - Liver
      - Phase I
        - CYP 450
        - Introduce/unmask polar groups
      - Phase II
        - Conjugation
        - Increases polarity for excretion
    - Skin, lung, kidneys, GI tract
  - Dependent on:
    - blood flow, genetics, diseases, other drugs

Principles of Pharmacokinetics



- Excretion
  - Urinary
    - Filtration, secretion, reabsorption by kidney
    - Affected by pH
  - Biliary
    - Enterohepatic recycling
  - Fecal
  - Other
    - Sweat, tears, saliva, breast milk

Pop Quiz

- MA is a 64 y.o. female of SE Asian. ER C/O epigastric pain with radiation to the left arm. Troponin peaks at 0.1 ➔ NSTEMI ➔ drug eluding stent. You have been requested to provide discharge counseling. What considerations might you take into account?

  A. MA is giving up smoking and therefore will be more sensitive to the effects of caffeine

  B. MA may be at risk of stent thrombosis secondary to suboptimal therapy from the antiplatelets she has been prescribed

  C. Both of the above

  D. I don't work in cardiology

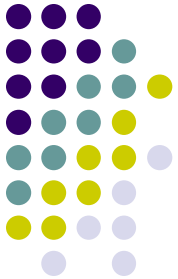
Independent Parameters

- Clearance
  - Volume of serum or blood completely cleared of drug per unit time (L/h or ml/min)
  - $CL_{tb} = Cl_{hepatic} + Cl_{renal}$
  - Used for calculating maintenance doses
- Volume of Distribution (Vd)
  - Not a real volume
  - Different for different patients, different drugs
  - A large Vd has extensive tissue distribution
  - Used for calculating loading doses

$$Cl = K \times Vd$$

$$Vd = \frac{Dose}{Cp_0}$$

Dependent Parameters



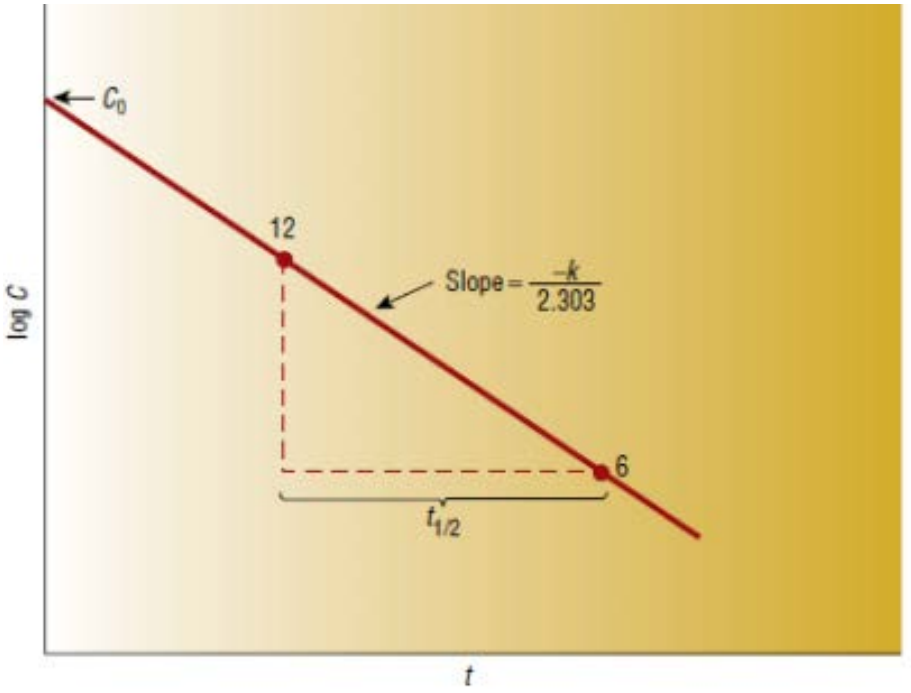
- Elimination rate constant (Ke)
  - Fraction of drug eliminated from body per unit time.
  - The higher concentration of drug, the more drug eliminated per unit time but the same fraction will be eliminated regardless of the concentration.

Time	Amount	Amt Eliminated	Fraction Eliminated
0	24 litres	-	-
1 minute	18 litres	6 litres	0.25
2 minutes	13.5 litres	4.5 litres	0.25
3 minutes	9.625 litres	3.375 litres	0.25

Dependent Parameters

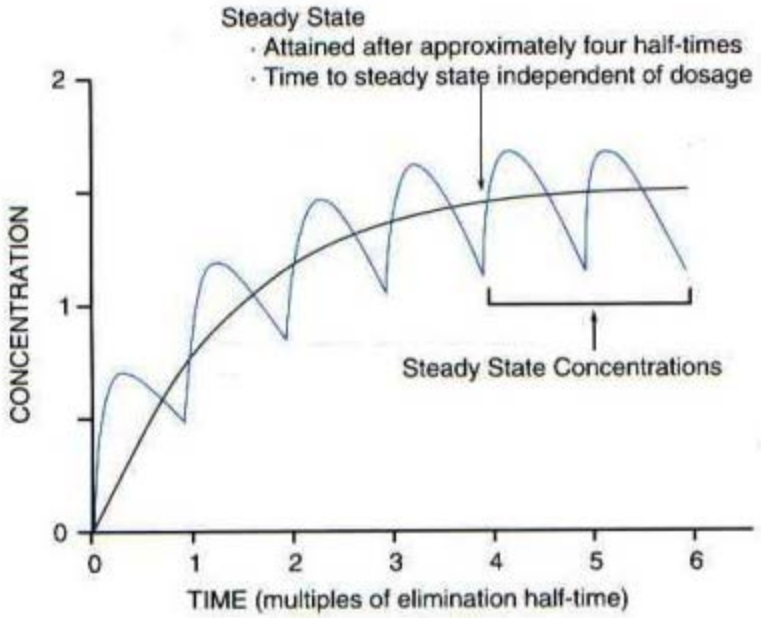
- Half Life (t1/2)
  - Time for serum concentrations to decrease by one half
  - Time (sec,min,hr)
  - Only useful in FIRST ORDER kinetics

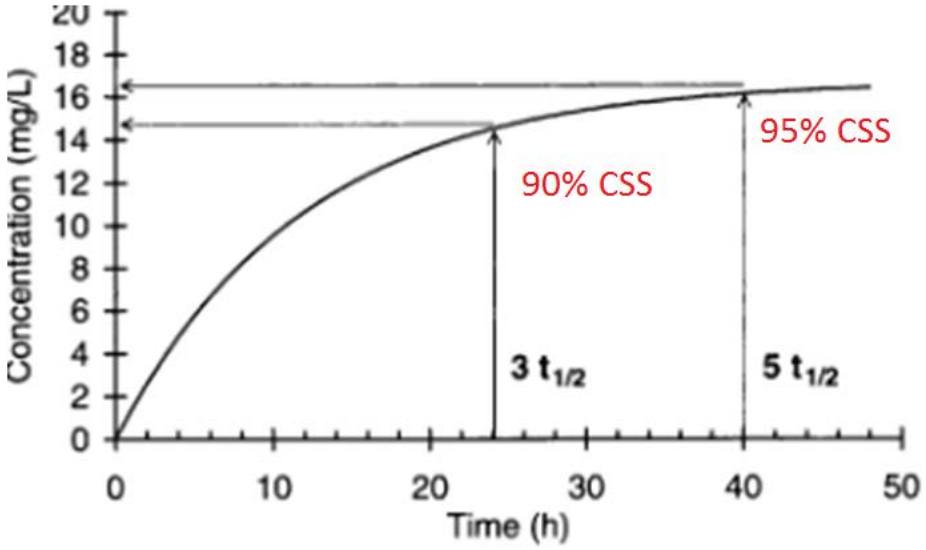
$$t_{1/2} = 0.693/k_e$$



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy A Pathophysiologic Approach, 8th Edition*: www.accesspharmacy.com

Css





Source: Bauer LA: *Applied Clinical Pharmacokinetics, 2nd Edition*: http://www.accesspharmacology.com

Pop Quiz

- Drug A (Vd = 10, $T_{1/2}$= 4) is administered with Drug B which displaces Drug A from plasma protein. As a result, drug A's Vd is increased by a factor of 2. What will happen to Drug A's other parameters?

A) If ↑ Vd then ↑ Cl and ↑ $t_{1/2}$

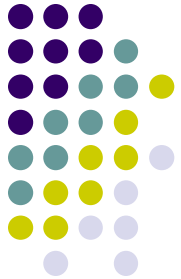
B) If ↑ Vd then ↓ Cl and ↓ $t_{1/2}$

$$t_{1/2} = \frac{0.693}{Ke} = \frac{0.693Vd}{Cl}$$

C) If ↑ Vd then no change Cl and ↑ $t_{1/2}$

D) If ↑ Vd then no change Cl and ↓ $t_{1/2}$

Answer - C



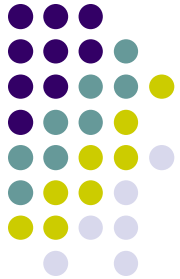
- If ↑ Vd then no change Cl and $t_{1/2}$ ↓
- Clearance is an independent variable that will not change if Vd is changed.
- But you still need to know what the clearance is in order to determine the new half life of the drug.

$$Cl = \frac{0.693Vd}{t_{1/2}} = \frac{0.693\ (10\ L)}{4\ h} = 1.7\ L/h$$

- Half life is a dependent variable, so changes in Vd cause it to change

$$t_{1/2} = \frac{0.693Vd}{Cl} = \frac{0.693(20\ L)}{1.7\ L/h} = 8.15\ h$$

Application of Pharmacokinetics



- LL is a 71 y.o. Caucasian male 150cm 59kg
- Admitted to the Moncton hospital July 10/12 with a left hip fracture.
- PMH
  - BPH
  - Atrial fibrillation
  - Lung cancer in 2001 for which a pneumonectomy was preformed as well as a metastatic brain resection
  - Grand mal seizure in 2009
- Medications on admission included:
  - Carbamazepine CR 200mg BID
  - Finasteride 5mg daily
  - Furosemide 20mg daily
  - Tamsulosin CR 0.4mg daily
  - Ramipril 20mg daily
  - Multivitamin daily

Course in Hospital

Date	Patient Care Notes
July 11	Carbamazepine D/C Started on phenytoin 100mg TID
July 21	Phenytoin dose increased to 100mg BID and 200mg QHS
Aug 17	PT states patient lacks appetite
Aug 20	Weight has dropped 4 kg since admission Only able to eat 50% of meals with +++ encouragement
Aug 23	OT noticed a decrease in cognition Unable to remain awake more than 5-10 min during assessment
Aug 24	PT reports patient weak and tired Difficulty initiating and following through with tasks Decline in mobility compared to last week

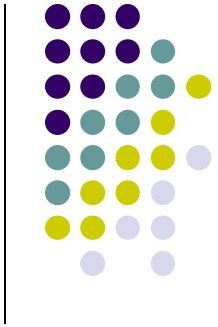
What is Going On?

Phenytoin trough levels (umol/L)	
July 20	22.2
July 24	27.2
Aug 25	**85.9**

Phenytoin Pharmacokinetics

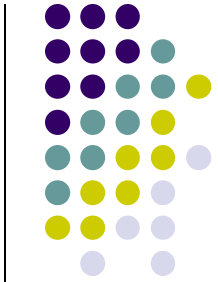
- Absorption
  - F = 0.2 to 0.9
  - Food ↑ absorption
- Distribution
  - Vd = 0.7L/kg
  - 90% protein bound
- Metabolism
  - CYP 2C9, 2C19
- Elimination
  - Concentration dependent T½
- Therapeutic range
  - 40-80 umol/L

Phenytoin: Protein Binding



- Not only was LL's phenytoin level elevated; his albumin was 27 g/L
- Causes of hypoalbuminemia
  - Hepatic cirrhosis
    - ↓ synthesis
  - Nephrotic syndrome & end-stage renal disease
    - Shifts from plasma to urine
  - Burns
    - Shifts into the extracellular fluid
  - Pregnancy
  - Inflammation
  - Cancer
  - Cystic fibrosis
  - Malnutrition

Phenytoin: Albumin Displacement



- Uremia
  - Renal failure
- Hyperbiliruinemia
- Medications
  - ASA
  - Indomethacin
  - Naproxen
  - Valproate
  - Sulfamethoxazole
  - Furosemide

Pop Quiz

Which of the following statements are true regarding hypoalbuminemia and its effect on the total phenytoin level?

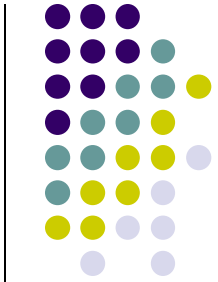
A. ↓ [albumin] = ↓ f_u = ↓ clearance = ↑ total

B. ↓ [albumin] = ↓ f_u = ↑ clearance = ↓ total

C. ↓ [albumin] = ↑ f_u = ↑ clearance = ↓ total

D. ↓ [albumin] = ↑ f_u = ↓ clearance = ↑ total

Phenytoin: Interpretation of Total Phenytoin Concentration

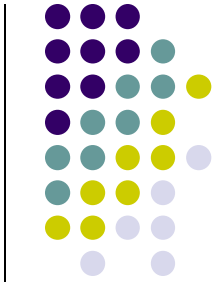


- Aug 24
  - Total serum phenytoin 85.9 umol/L
  - Serum albumin 27 g/L

- ↓ serum albumin = ↑ fraction unbound of PHT
- ↑ fraction unbound of PHT = ↑ clearance of PHT
- ↑ clearance of PHT = ↓ total PHT concentration

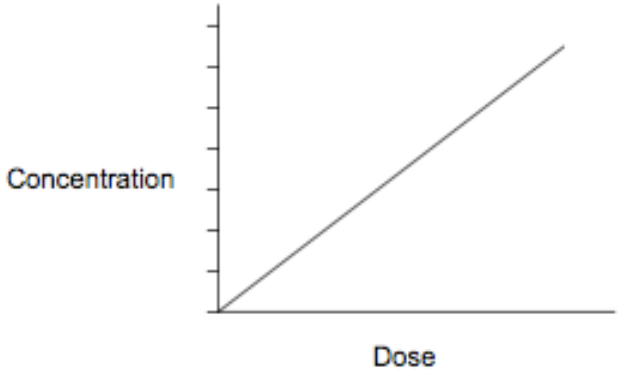
- Can measure level of free phenytoin
  - Therapeutic range (4-8umol/L) less well established
  - Temperature variability
  - Additional cost and time
  - Not available everywhere

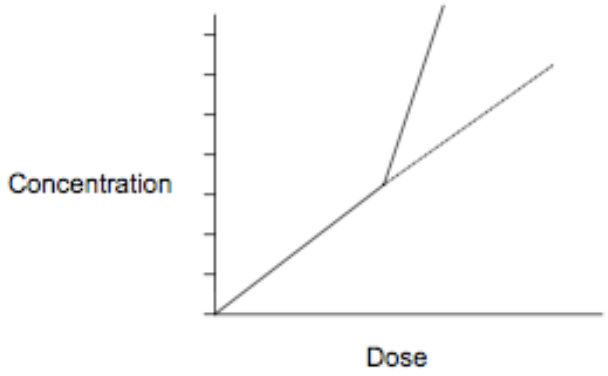
Phenytoin: Correction for Hypoalbuminemia



- Sheiner-Tozer Equation
  - Predicted total phenytoin = $\frac{\text{observed total phenytoin}}{(0.02 \times \text{albumin}) + 0.1}$
- LL's Case
  - Predicted total phenytoin = $\frac{85.9 \text{ umol/L}}{(0.02 \times \text{albumin}) + 0.1}$
  - Predicted total phenytoin = 134 umol/L

- Also remember to correct Ca^{++} for hypoalbuminemia
  - Corrected Ca^{++} = total Ca^{++} + 0.02 (40g/L – albumin)



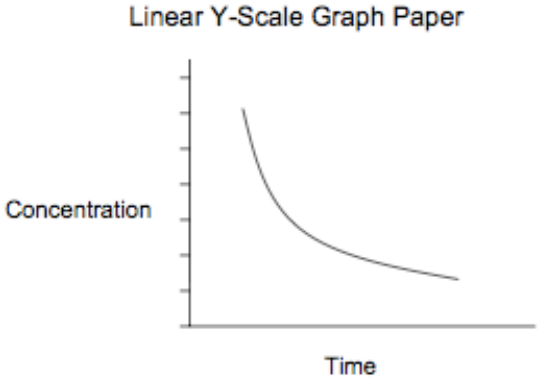


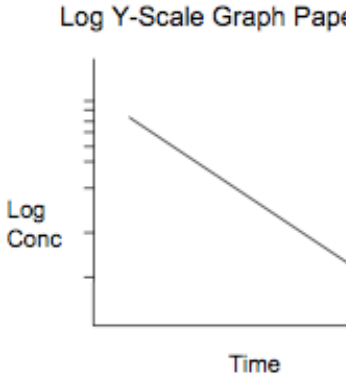
Linear or 1st order

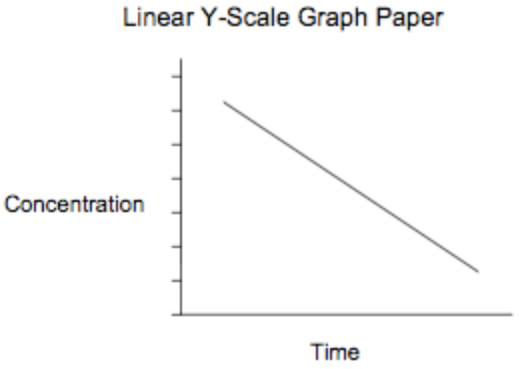
- Serum concentrations increase proportional to an increase in dose

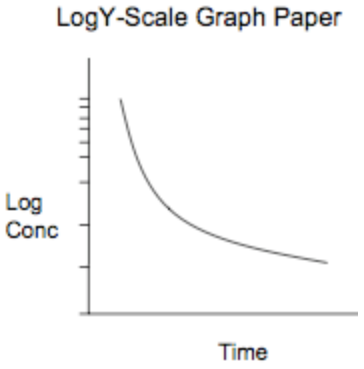
Non-linear or zero order

- As dose increases there is a disproportionate increase in serum concentration

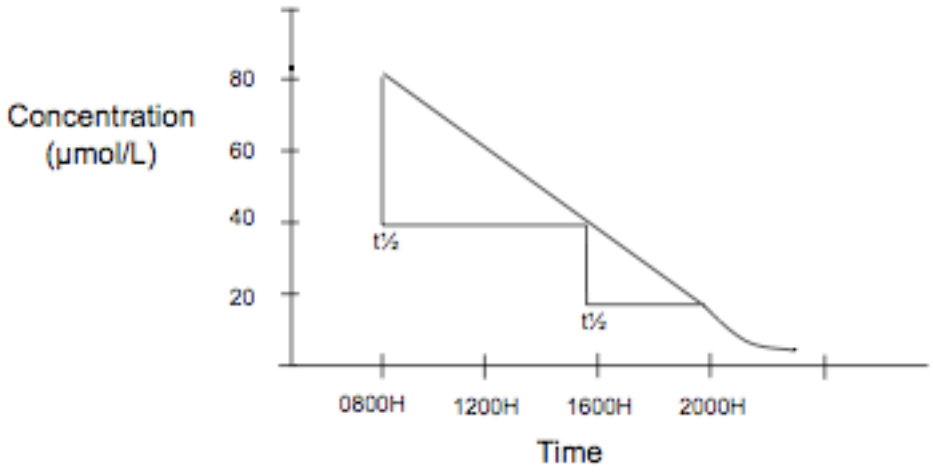






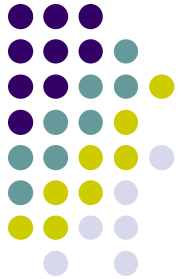


Phenytoin: Non-linear PK



- Low concentrations = 1st order
- High concentrations = zero order
- T½ depends on the serum concentration
- Clearance is not constant

Phenytoin: Therapeutic Drug Monitoring



- Unstable patients
  - 1 hr after IV loading dose
  - 6-8 hr after PO loading dose
  - Monitor weekly
- Stable patients
  - One steady-state trough concentration prior to next dose
    - Five T½ usually equates to 7-10 days
  - Repeat steady-state trough concentration
    - post dose changes
    - at first signs of toxicity (confusion, delirium, ataxia, drowsiness)
    - when another drug is added or removed that could affect serum concentration

Phenytoin: Integrated Michaelis-Menten Equation

- Used when drug concentration is too high, to determine how long until patient achieves a concentration within the therapeutic range

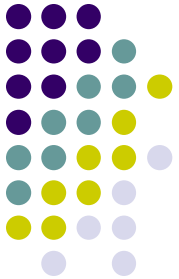
$$T\ (\text{days}) = \frac{[(Km) \times (\text{Ln}\ C_0/C)] + (C_0 - C)}{Vmax/Vd}$$

Where:

- C_0 = measured concentration (mg/L)
- C = desired concentration (mg/L)
- Km = assumed Michaelis constant
- Vmax = maximum rate of elimination
- Vd = volume of distribution
- Note: umol/L ÷ 4 = mg/L

Age (yrs)	Vmax (mg/kg/day)	Km (mg/L)	Vd (L/Kg)
0.5-3	14	6.6	1.6
4-6	10.9	6.8	0.6
7-9	10.1	6.5	0.6
10-19	8.3	5.7	0.6
20-39	7.5	5.7	0.7
40-59	6.6	5.4	0.7
60-79	6	5.8	0.7

Application of Pharmacokinetics



For LL:

- C_0 = 134umol/L ÷ 4 = 33.5 mg/L
- C = 40 umol/L ÷ 4 = 10 mg/L
- Km = 5.8 mg/L (assumed)
- Vmax = 6 mg/kg/d
- Vd = 0.7 L/kg

$$T\ (\text{days}) = \frac{[(Km) \times (\text{Ln}\ C_0/C)] + (C_0 - C)}{Vmax/Vd}$$

$$T\ (\text{days}) = \frac{[(5.8) \times (\text{Ln}\ 33.5/10)] + (33.5-10)}{6/0.7} = 3.5 \text{ days}$$

- LL's phenytoin should be held for approximately 3.5 days

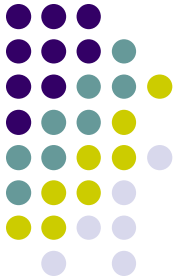
Application of Pharmacokinetics

- Aug 25th
  - LL's phenytoin was held
- Aug 29th
  - Phenytoin reinitiated at 100mg TID
- Sept 4th
  - More alert and able to participate in activities
  - Corrected phenytoin level is 32.5 umol/L
- Remember
  - Older patients are more sensitive to the side effects of phenytoin and may exhibit toxicity at lower doses (need ~21% less)
  - 50% of patients achieve seizure control at a concentration below therapeutic range

Phenytoin Level

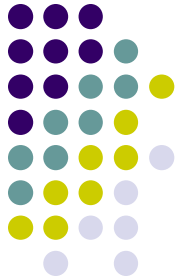
- Aug 27 – 96.1 umol/L
- Aug 28 – 66.2 umol/L
- Aug 29 – 44.8 umol/L
- Sept 4 – 24.0 umol/L

Carbamazepine: Enzyme Induction



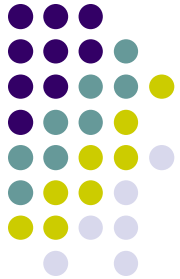
- Induces CYP 3A4, 2D6 and 2C
- Also metabolized by CYP 3A4
  - T ½ is often 2-3x shorter after auto-induction
- Complete induction of enzymes may take 3-4 wks
  - Dosage adjustments and monitoring required
- De-induction
  - Assumed to be linear therefore expect return to baseline after 19.2 days or 3 weeks

Carbamazepine: Therapeutic Drug Monitoring



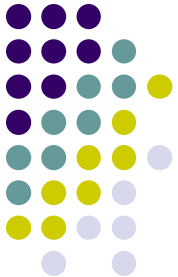
- Usual adult therapeutic level is 4-12 mcg/mL (20-50 umol/L)
- Draw 1 hr prior to next dose once steady state is reached
  - Anywhere from 2-10 days but usually say 5
  - Only true steady state after auto-induction
- Indicated:
  - dramatic increase in seizure frequency
  - verification of patient compliance
  - during pregnancy
  - when treating children or adolescents
  - in suspected absorption disorders
  - in suspected toxicity
    - especially where more than one drug is being used
    - dizziness, drowsiness, ataxia, diplopia

Application of Pharmacokinetics



- AL is a 67 yo Caucasian male 172 cm 95.45 kg
- Admitted to the Moncton Hospital on Oct 12/12 with Staph. Epidermis bacteremia
- HPI
  - Presented to emerg on Oct 11th with malaise, low grade fever
  - Blood cultures and discharged on Ceftriaxone
  - Readmitted once Staph Epi identified.
- Labs
  - Scr 68
- Medications on admission
  - Cyclophosphamide
  - Gliclazide 80mg AM/PM po
  - Metformin 1g BID po
  - Pantoprazole 40mg QHSpo
  - Rosuvastatin 40mg QHS po
- PMH
  - Multiple meloma (dx 2006)
  - GERD
  - DM
- Plan
  - 14 day course of Vancomycin

Course in Hospital



Levels

- October 12th
  - Vancomycin 1000mg Q12H IV (15:30pm)
- October 14th
  - Trough (9:01am) **8.5**
  - Vancomycin 1500mg Q12H IV (10:00am)
- October 16th
  - Trough (9:31am) **22**

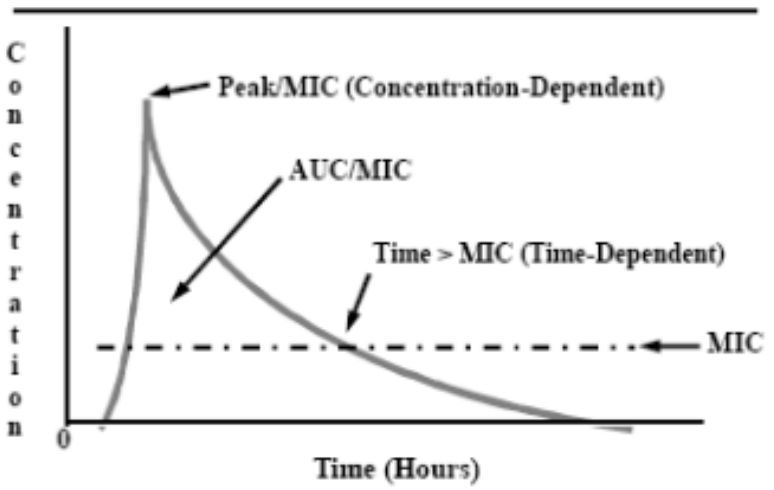
Vancomycin PK

- Absorption
  - Given IV (poor oral F)
- Distribution
  - Vd = 0.4 – 1 L/kg (av 0.7 L/kg)
  - Protein binding ~55%
- Elimination
  - Renal, unchanged drug
  - $T_{1/2}$ = 6 – 8 hours
- Therapeutic Range
  - 10 – 20 (15 – 20 in more serious infections)

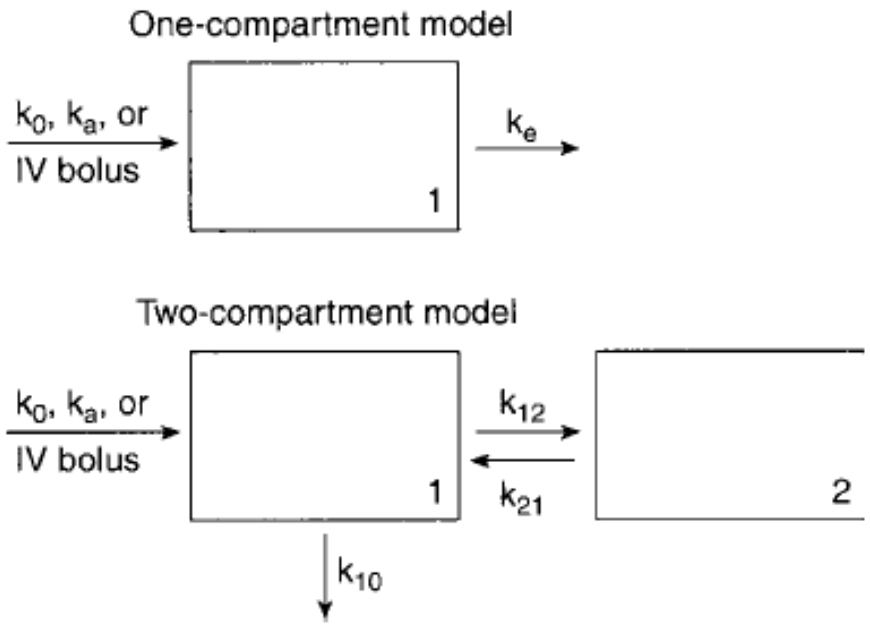
DRP: Our patient's trough is not within therapeutic range. (Target 15 – 20)

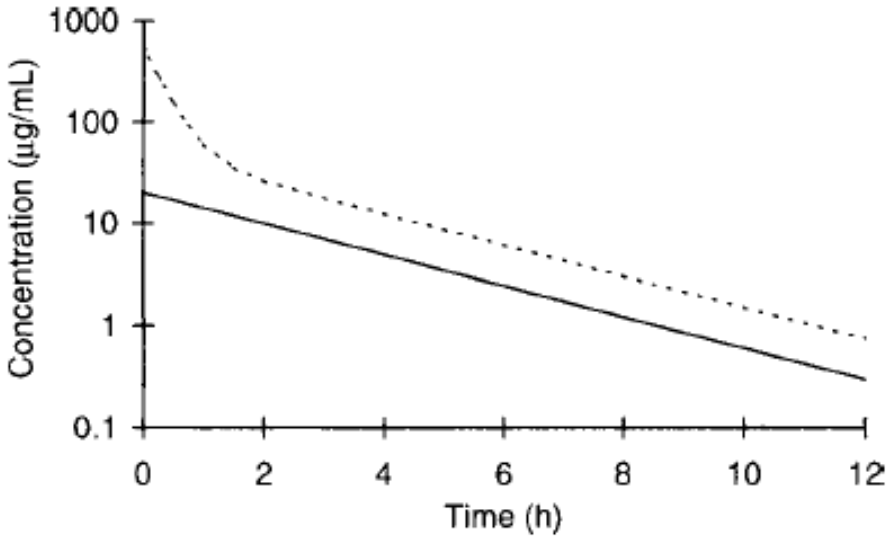
Therapeutic Drug Monitoring

- **Concentration Dependent**
  - Killing depends on achieving high serum concentration
  - Aminoglycosides, FQ
- **Time Dependent**
  - Killing depends on amount of time above MIC
  - Beta lactams, vancomycin
  - Cure rates not associated with peak serum concentrations (typically 20 – 40g/ml)
  - Evidence does not support monitoring peaks
- **Area Under the Curve /MIC**
  - Best predictor of efficacy (in animal PK studies)
  - For Vancomycin target AUC/MIC >400 when MIC is 1g/L



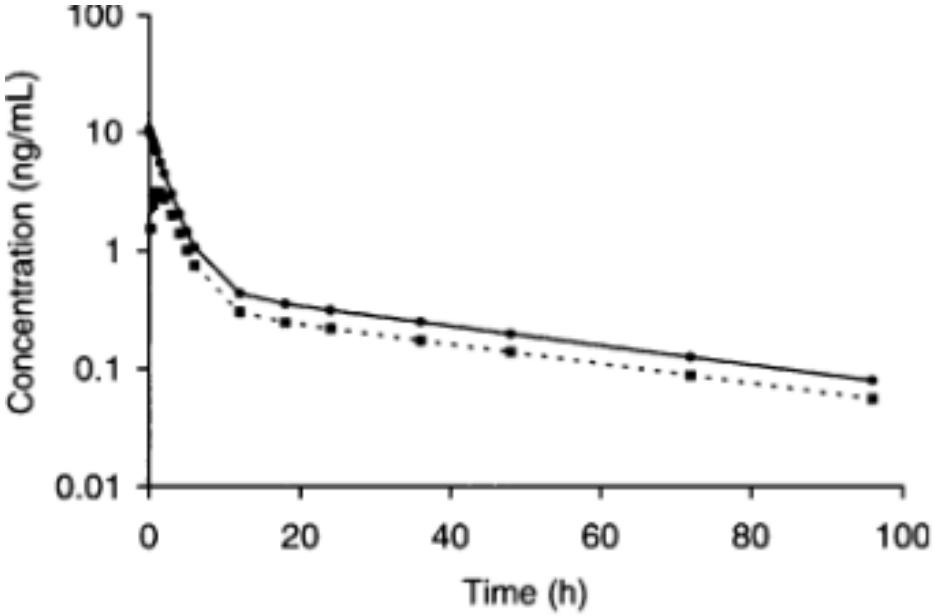
Multicompartment Models





Digoxin Multicompartment Model

- Two-compartment model with a long distribution phase (8 – 12 hours)
- Sampling within the distribution phase (too close to a dose) will result in a serum concentration that appears high
  - Serum concentration not in equilibrium with tissues (doesn't reflect concentration at site of action)
- Once in elimination phase, digoxin serum and tissue in equilibrium
- Ke and $T_{1/2}$ only for elimination phase



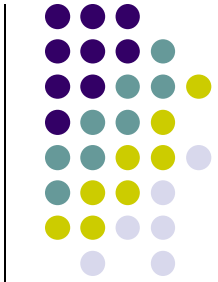
Source: Bauer LA: *Applied Clinical Pharmacokinetics, 2nd Edition*: http://www.accesspharmacology.com

Drawing Vanco Troughs

- Monitoring
  - IDSA recommends trough level should be drawn 30 minutes prior to 4th dose. Why?
  - Who to monitor?
  - Frequency? Once stable, once weekly troughs for hemodynamically stable patients.

Example of Accumulation: ICU patient with empyema. Vanco 1250mg Q12H IV started Oct 3rd	Oct 9th 10.8
	Oct 16th 10.6
	Oct 23 20.7 (no change in CrCL noted)

Evaluate Serum Levels Critically



- Back to AL
- At a trough level of **25**, AL may be at risk of supratherapeutic dosing (nephrotoxicity, ototoxicity)
  - Were his troughs drawn appropriately?
  - His MAR administration times for vanco are 10:00 and 22:00
    - 1.5g BID ordered Oct 14th 10:00am, trough **22** Oct 16th 9:31am

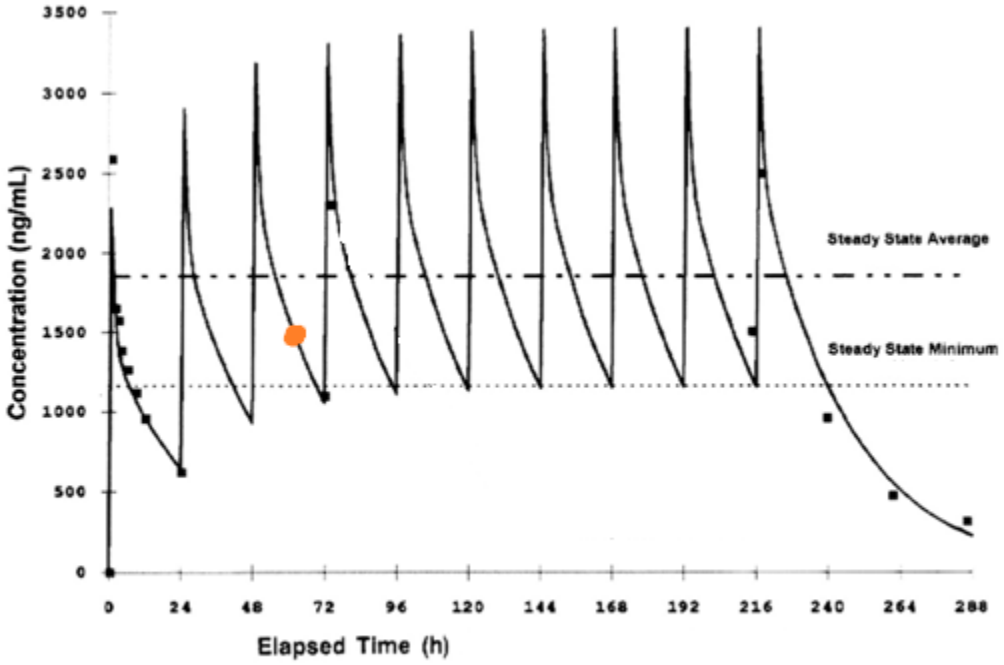
Pop Quiz

If AL's trough had been drawn at 7:00am (3 hours prior to 4th dose it would have…

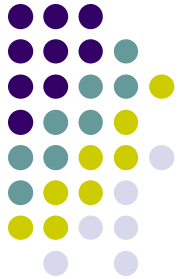
a) Appeared higher than it truly was (overestimate)
b) Appeared lower than it truly was (underestimate)
c) Appeared either higher or lower than it truly was (difficult to predict)

Pop Quiz - A

- If AL's trough had been drawn at 7:00am (3 hours prior to 4th dose it would have appeared higher than it truly was (overestimate)



Dosing



- Dose it right from the start
- Initial dosing is based on weight (actual body weight)
  - 15mg/kg – 20mg/kg Q8 – Q12H
  - Round to nearest 250mg
- Dose Adjustments
  - Proportional changes
  - Avoid large dosage adjustments

Geriatric Considerations

- Decrease in total body water (because decrease in muscle mass)
  - Water soluble drugs (lithium, aminoglycosides, digoxin) – serum levels may increase (decreased Vd).
- Fat soluble (diazepam, trazadone), increased $t_{1/2}$
- Changes in (albumin, alpha acid glycoprotein)

Table 2. PHARMACOKINETIC CHANGES WITH AGING

Absorption	**Metabolism**
↑ Gastric pH	↓ Hepatic mass
↓ (Delayed) gastric emptying	↓ Hepatic blood flow
↓ Splanchnic blood flow	↓ Phase I metabolism
↓ Intestinal motility	= (Unchanged) phase II metabolism
Distribution	**Elimination**
↑ Body fat	↓ Creatinine clearance
↓ Total body water	↓ Glomerular filtration rate
↓ Albumin	↓ Tubular secretion
↑ $Alpha_1$-acid glycoprotein	↓ Creatinine production

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Empiric dosing of vancomycin (for adults)

Initial dose: 20 mg/kg (rounded to nearest 250 mg)

Maintenance dose: based on estimated creatinine clearance, weight and target trough (see below)*

Creatinine clearance (ml/min)	Weight (actual)					
	50-59 kg	60-69 kg	70-79 kg	80-89 kg	90-99 kg	100 kg
Target trough 15-20 mcg/mL						
<10	Repeat dose when spot serum concentration ≤20 mcg/ml)					
10-19	750 mg q 48 h	1000 mg q 48 h	1000 mg q 48 h	1250 mg q 48 h	1250 mg q 48 h	1500 mg q 48 h
20-29	500 mg q 24 h	750 mg q 24 h	1000 mg q 36 h	1250 mg q 36 h	1250 mg q 36 h	1250 mg q 36 h
30-39	750 mg q 24 h	750 mg q 24 h	1000 mg q 24 h	1250 mg q 24 h	1250 mg q 24 h	1250 mg q 24 h
40-49	750 mg q 18 h	750 mg q 18 h	1000 mg q 18 h	1250 mg q 18 h	1250 mg q 18 h	1250 mg q 18 h
50-59	750 mg q 18 h	1000 mg q 18 h	1000 mg q 18 h	1250 mg q 18 h	1250 mg q 18 h	1500 mg q 18 h
60-69	750 mg q 12 h	750 mg q 12 h	1000 mg q 12 h	1000 mg q 12 h	1250 mg q 12 h	1250 mg q 12 h
70-79	750 mg q 12 h	1000 mg q 12 h	1000 mg q 12 h	1250 mg q 12 h	1250 mg q 12 h	1500 mg q 12 h
80-89	750 mg q 12 h	1000 mg q 12 h	1250 mg q 12 h	1250 mg q 12 h	1500 mg q 12 h	1500 mg q 12 h
90-99	1000 mg q 12 h	1000 mg q 12 h	1250 mg q 12 h	1500 mg q 12 h	1500 mg q 12 h	1500 mg q 12 h
> = 100	1000 mg q 12 h	1250 mg q 12 h	1250 mg q 12 h	1500 mg q 12 h	1500 mg q 12 h	1750 mg q 12 h

Bottom line: base empirically as best as possible using weight, crcl and adjust based on the patient's response.

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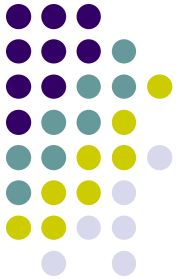
Application of Pharmacokinetics



- October 17th
  - Vancomyin 1250mg Q12H IV (15:30pm)
- October 19th
  - Trough (9:19am) **16.4**

- Overall, good clinical response
- Repeat blood cultures negative
- No anticipated delay in transplantation

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