Pharmacotherapy 1
MPAS 650

Introduction to Applied Pharmacokinetics

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IOWA PHARMACY

Objectives

- Know the basic terminology for pharmacokinetics.
  - Pharmacokinetics/pharmacodynamics
  - Bioavailability
  - Volume of distribution, clearance, rate of elimination, half-life
  - Steady state, kinetic space.

Objectives

- List the criteria for when monitoring of drug concentrations is appropriate.
- Explain the appropriate timing to measure drug levels when they are clinically indicated.
- Describe the concept of how drug dosing can be individualized prospectively and retrospectively.

Objectives

- Work through an example of knowing when to order drug levels that will allow individualization of dosing.
- Examine two medications and understand how the pharmacokinetic terminology learned can be used to optimize those medications.

Reading

- **Herman RA: General Approaches to Clinical Pharmacokinetic Monitoring. In *Pharmacokinetics in Drug Discovery and Development*, by Ronald Schoenwald, pp 115-126, Boca Raton, FL: CRC Press LLC, 2002.**

Available in pdf format:

http://rherman.pharmacy.uiowa.edu/

Choose the Teaching tab, then the Pharmacokinetics button under Readings select "General Approaches to Clinical Pharmacokinetic Monitoring"

Definition of Terms

- **Pharmacokinetics**
  - The study of the processes of drug absorption, distribution and elimination.
  - The word itself comes from two root words
    - *pharmacon* which is the Greek word for drugs and poisons and
    - *kineticos* which pertains to the rate into and out of.
  - Hence literally pharmacokinetics is the rate of drugs into and out of the body.

Basic Pharmacokinetics

- **L** iberation
- **A** bsorption
- **D** istribution
- **M** etabolism
- **E** limination
- **T** herapeutic Drug Monitoring

Definition of Terms

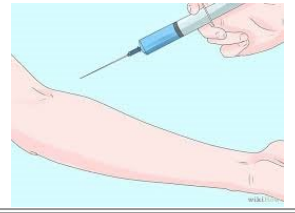
- **Pharmacodynamics**
  - **It is the study of the time course of pharmacological effects.**
    - **It is a pharmacologic effect of the drug that is measured and evaluated over time.**
    - **The *dynamos* is measured in the body.**
  - **Often drug concentrations are correlated to the biological response measurement.**

Definition of Terms

- Comparison of Pharmacokinetics and Pharmacodynamics
  - In pharmacokinetics drug concentrations are measured and evaluated as a function of time.
    - In essence we are examining how the body effects the drug.
  - In pharmacodynamics it is a pharmacologic effect of the drug that is measured and evaluated over time.
    - In essence we are examining how the drug effects the body.

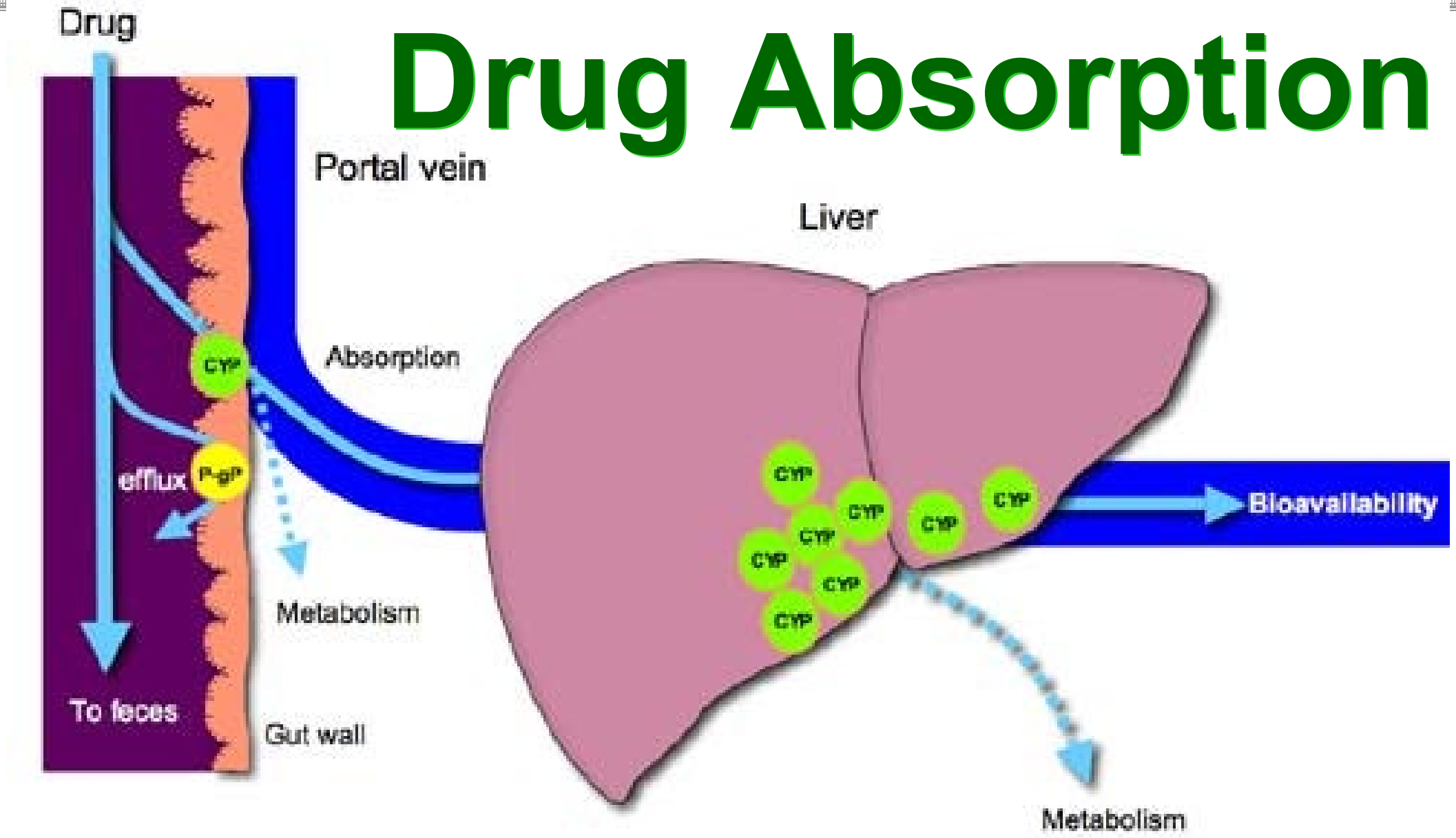
Definition of Terms

- **Bioavailability**
  - **It is fraction of the drug absorbed (F) and is influenced by the rate (T_{max}) and extent of absorption (C_{max}) of a particular dosage form.**
    - **It is not just a measure of how fast**
    - **or how much of the drug is absorbed**
    - **but is a function of both.**



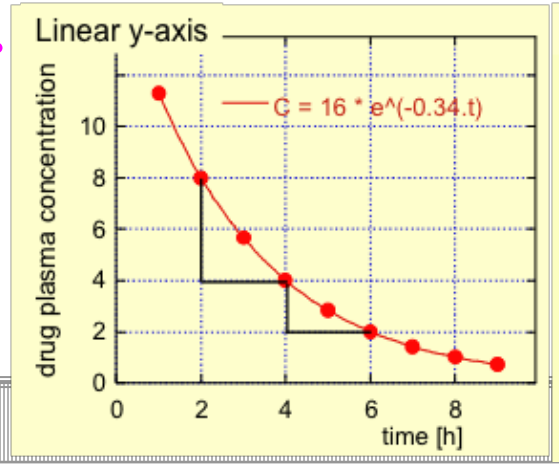


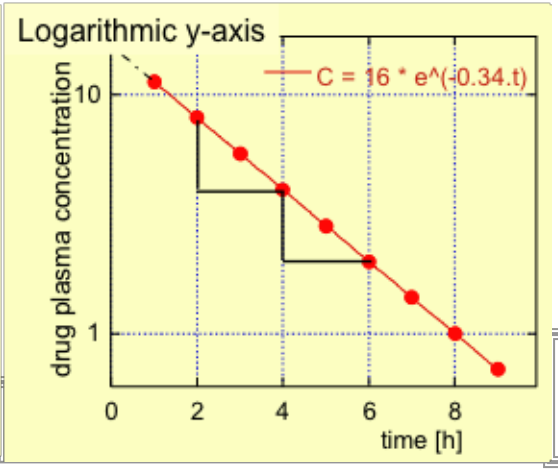
Drug Absorption



Definition of Terms

- **Rate of Elimination (K_e)**
  - **The rate at which drugs are eliminated from the body will determine how frequently they may be dosed again.**
    - **Most small molecule drugs are absorbed and eliminated from the body by diffusion through fluids, membranes and tissues.**
    - **This movement occurs not at a constant rate (zero order), but as a first order exponential process.**

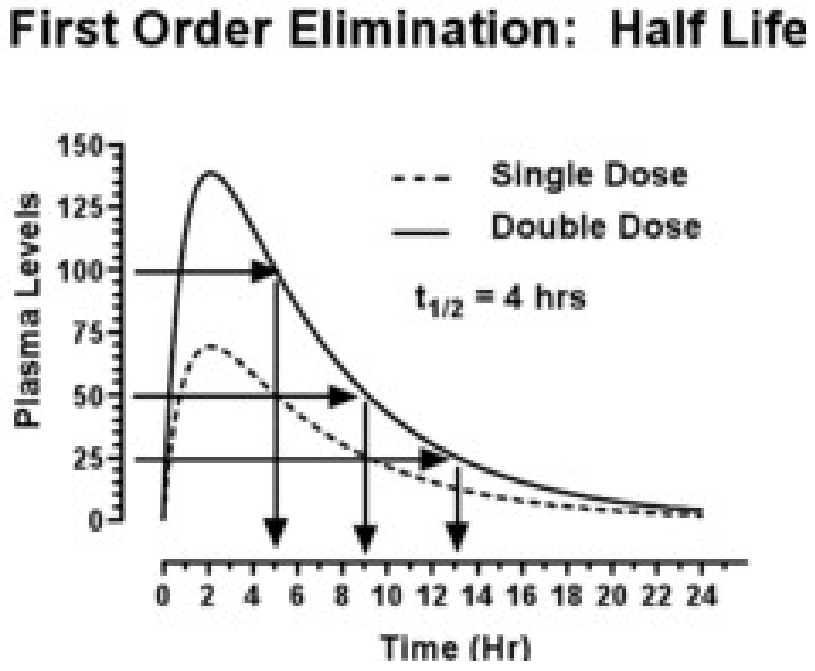




Definition of Terms

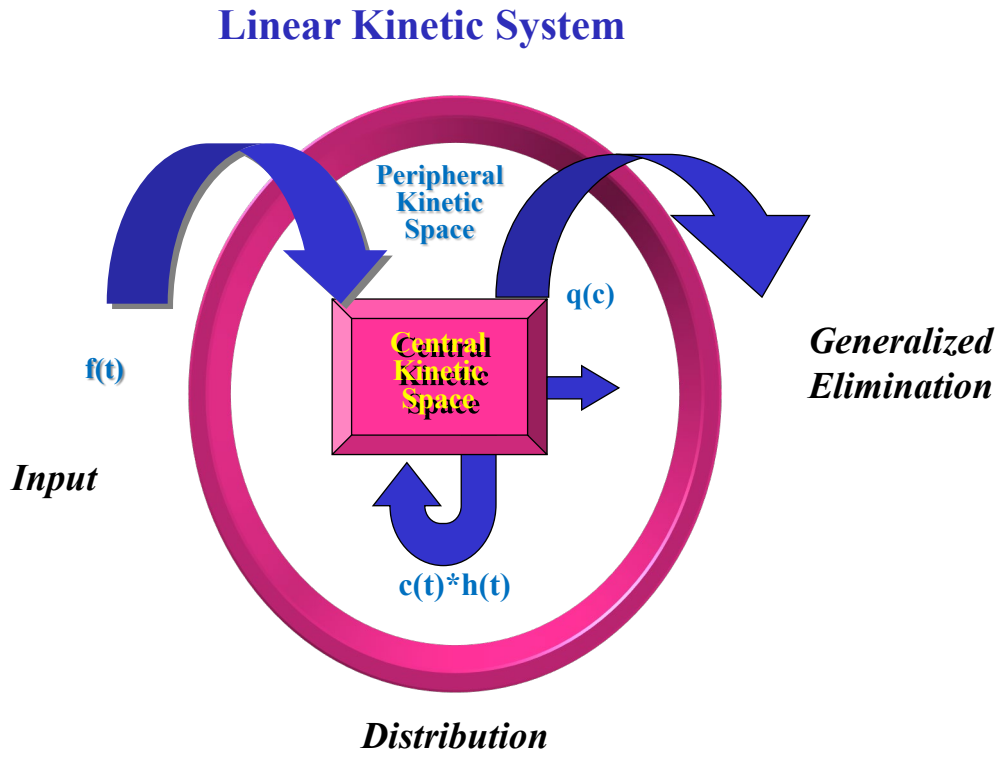
- **Half-life**
  - A half-life is the time it takes for the concentration of the drug to decrease by half of its initial value.

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



Definition of Terms

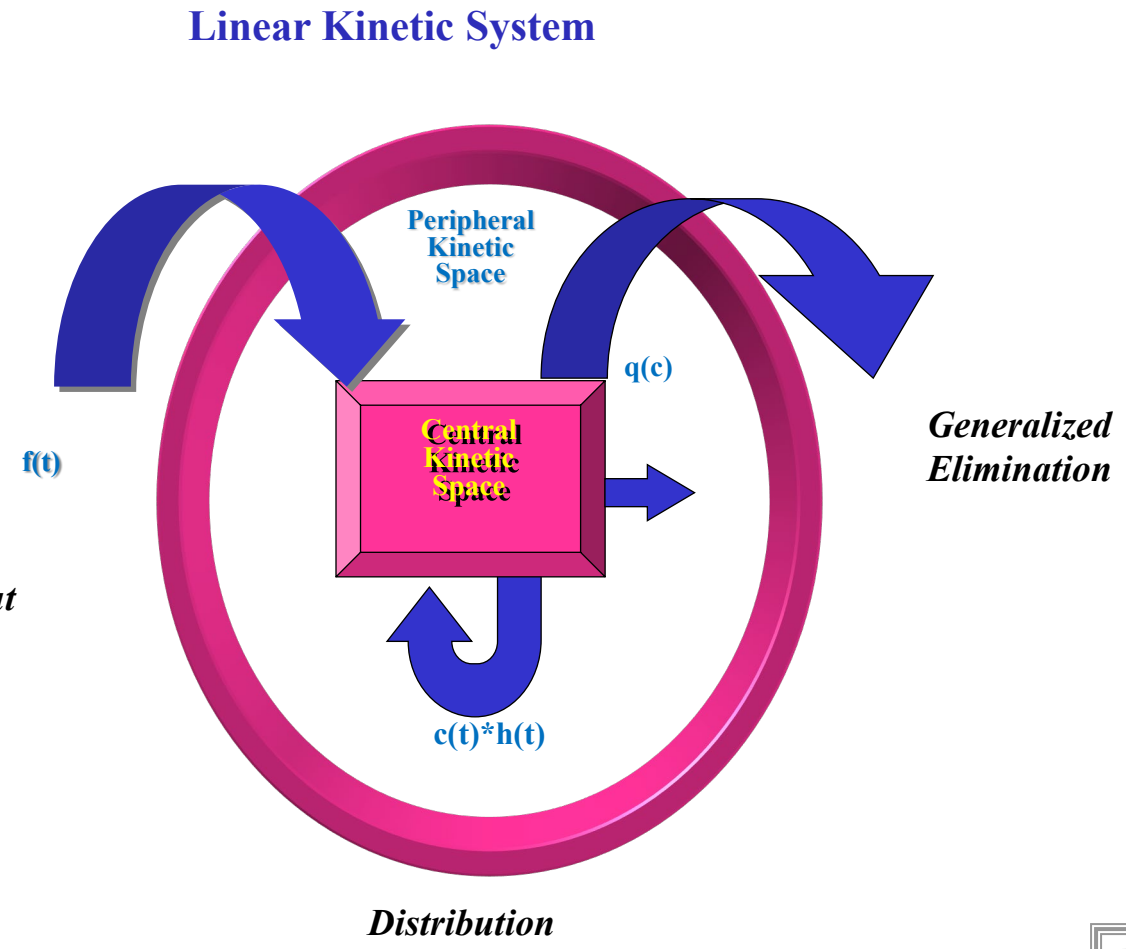
- Kinetic Space
  - It is reference area where the kinetics are being considered.



Definition of Terms

Kinetic Space

- A kinetic space might be a physical space like the entire body.
- It might be the so called central compartment that consists of the blood and all highly perfused tissues and organs.
  - In such a case it is hard to say this kinetic space has clearly defined physical boundaries.

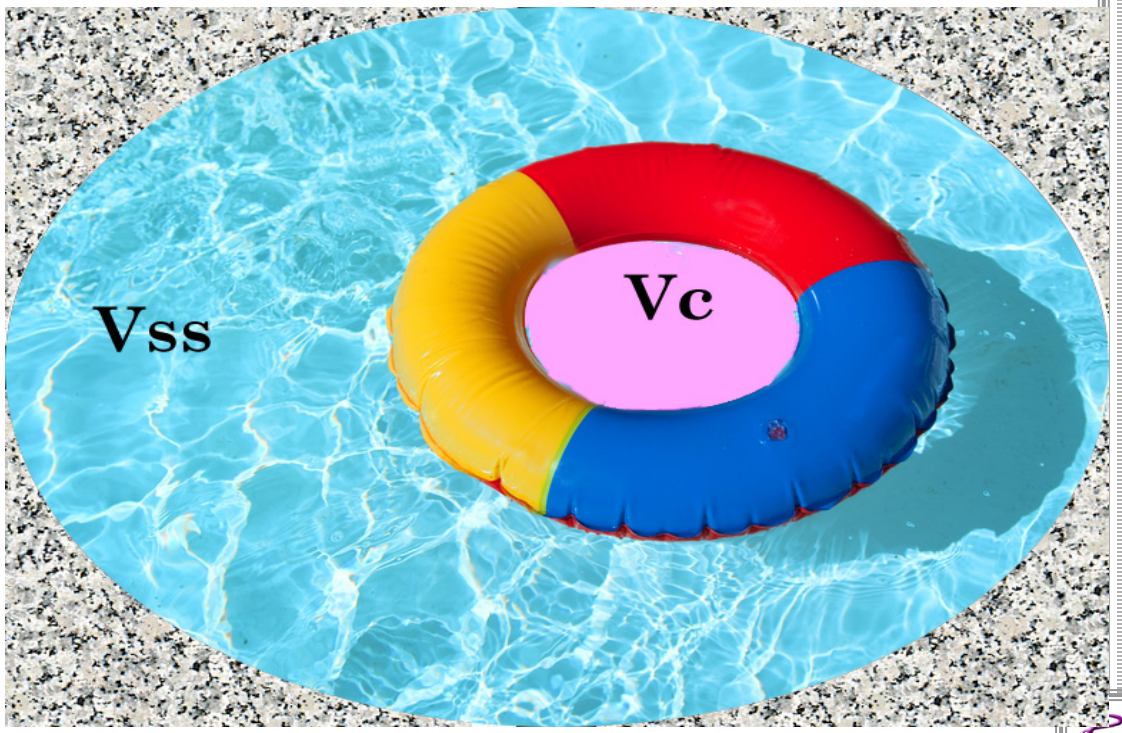


Definition of Terms

- **Volume of Distribution**
  - It is a factor that relates an amount of drug in a certain kinetic space to the concentration in that kinetic space.
  - Volume of distribution is important because it gives an idea of the extent to which a drug is distributed to tissue, but does not have a physical meaning.
    - This is why it is sometimes referred to as the apparent volume of distribution.

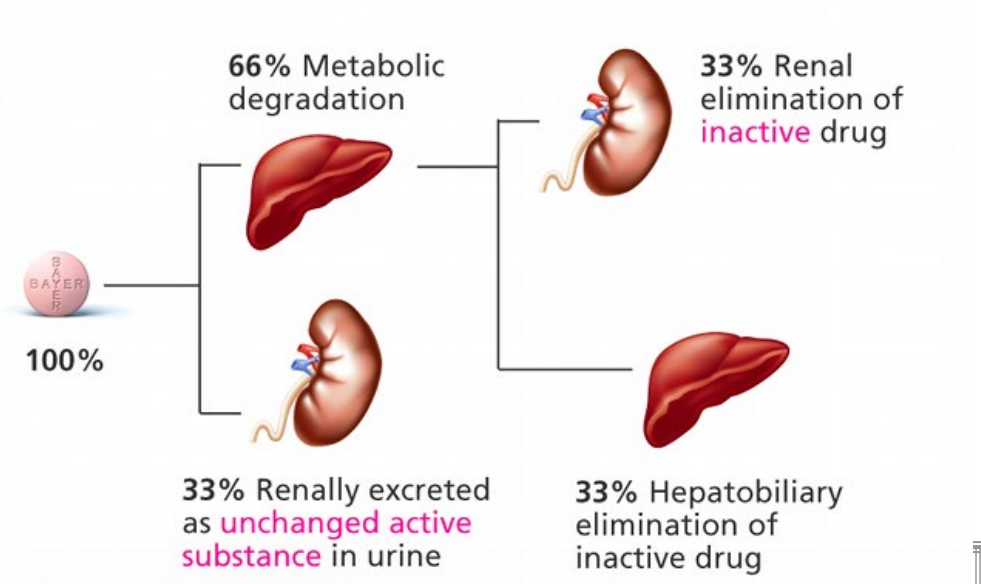
Definition of Terms

- **Volume of Distribution**
  - **There are several types of volumes of distribution that are commonly utilized.**
    - **Volume of the central compartment.**
    - **Volume of distribution at steady state.**



Definition of Terms

- Clearance
  - It is defined as the rate of removal of the drug normalized by the concentration.
    - amt./time / amt./vol. = vol./time
  - Total clearance is composed of renal and metabolic clearance.

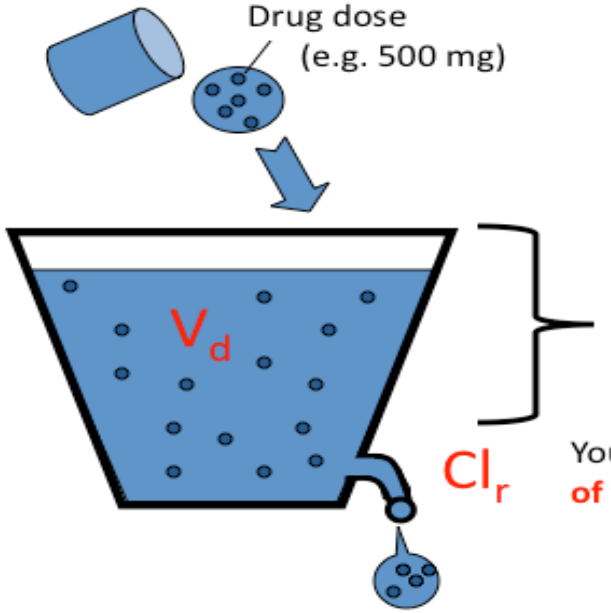


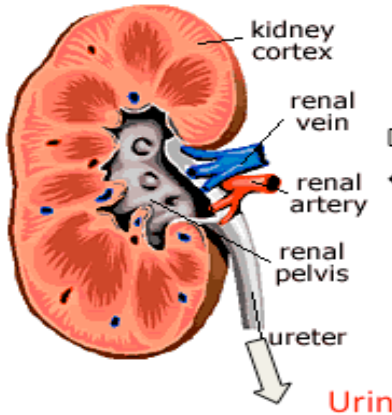
Definition of Terms

❁ Clearance

Example:

Drug Clearance by the Kidney





Blood Out

Blood In

~1 L/min

Normal GFR ≈125 ml/min

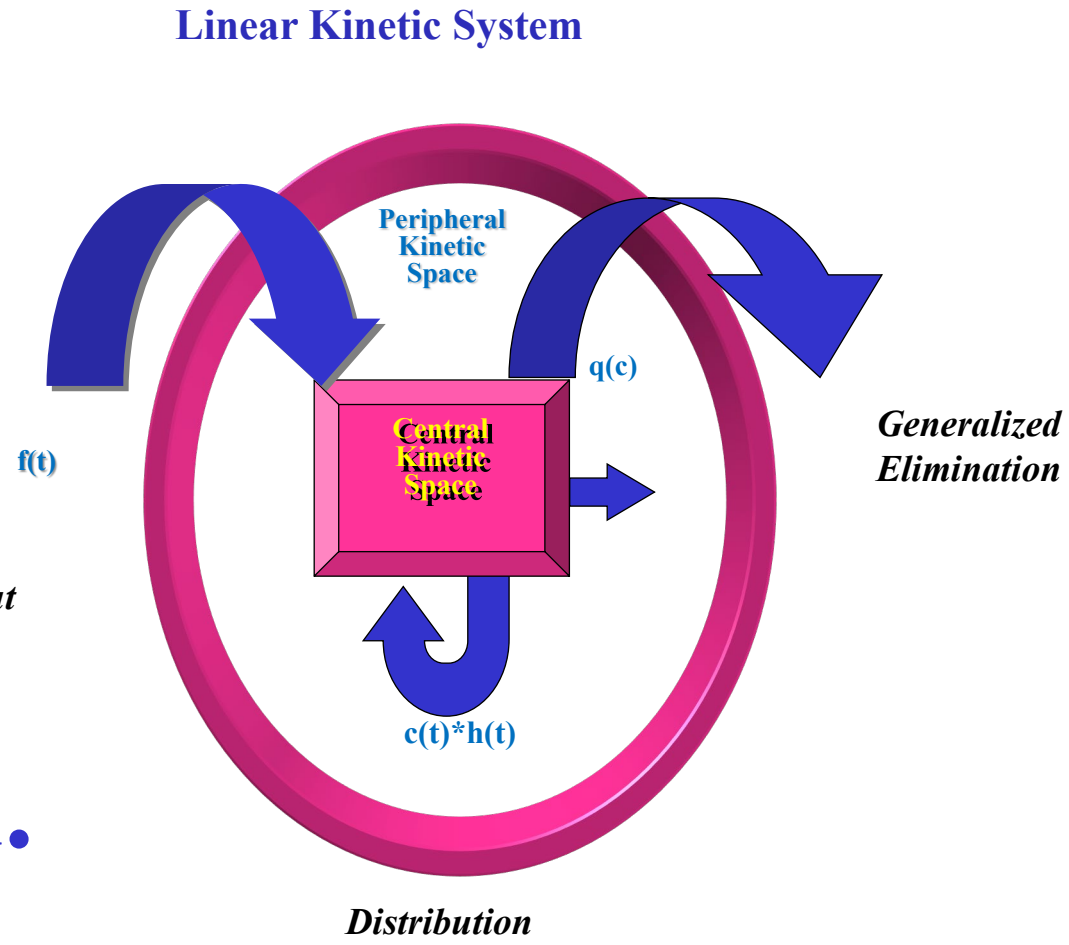
V_d (e.g. 10 L)

Your kidney (filter) will **clear a given volume of fluid per unit time "free of drug".**

L/hr/kg, ml/min etc.

Definition of Terms

- Clearance
  - There is also an elimination and distribution clearance that can be calculated.



Definition of Terms

- **Steady State**
  - Any exponential process reaches steady state in five half-lives.
  - For example, drug elimination:
    - Goes from 100% - 50% in 1 half-life,
    - goes from 50% - 25% by the 2nd half-life,
    - goes from 25%-12.5% by the 3rd half-life,
    - goes from 12.5% to 6.25% by the 4th half-life, and
    - goes from 6.25% to 3.125% by the 5th half-life.

Review

- After we examined the difference between pharmacokinetics and pharmacodynamics;
- We looked at 7 terms that will help us understand the pharmacokinetics of various drugs.

Bioavailability	Volume of Distribution
Rate of Elimination	Clearance
Half-life	Steady State
Kinetic Space	

Applied Pharmacokinetics

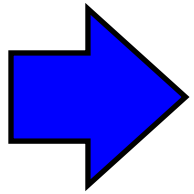
aka Clinical Pharmacokinetics

aka Therapeutic Drug Monitoring

Drug Concentration

Pharmacokinetic Principles

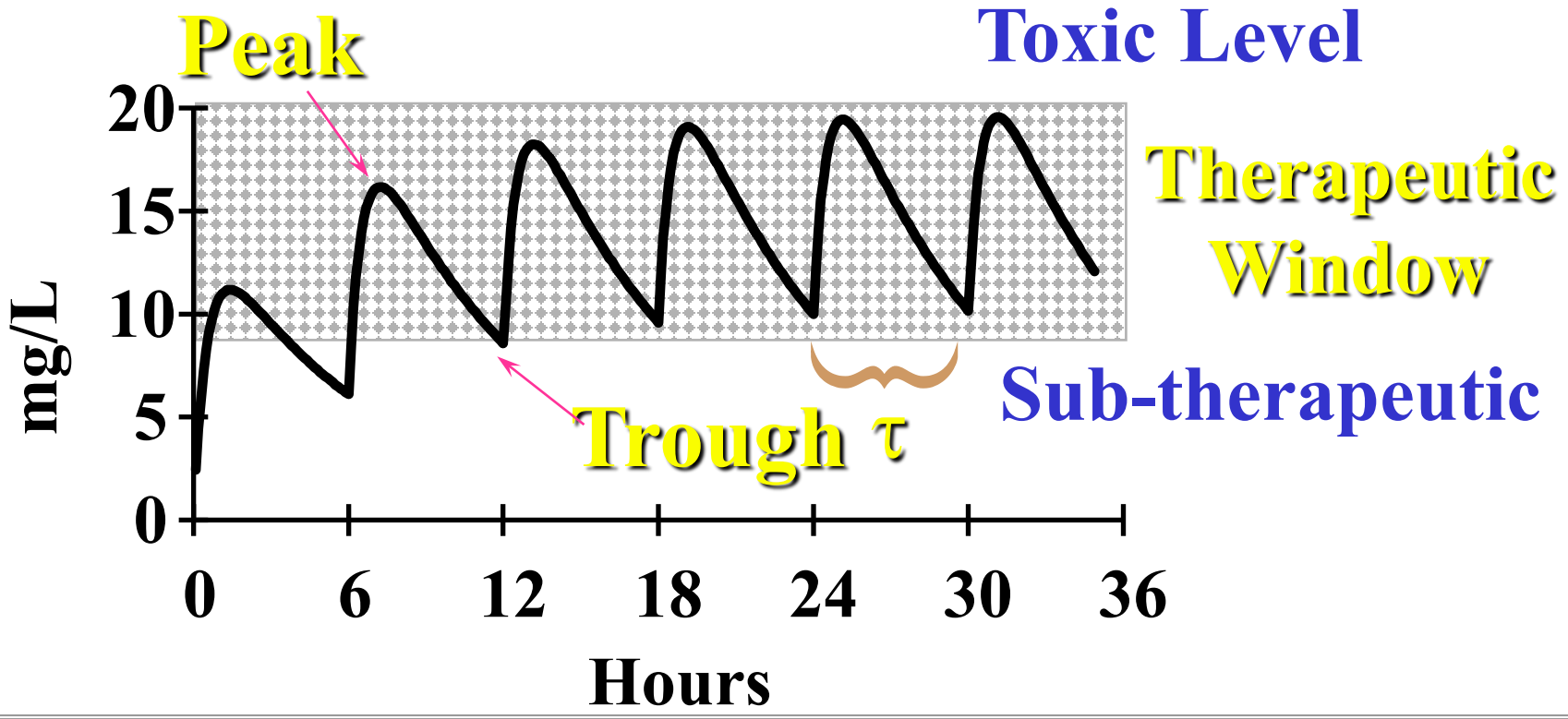
Clinical or Pharma-cological Response



To optimize drug therapy for the patient.

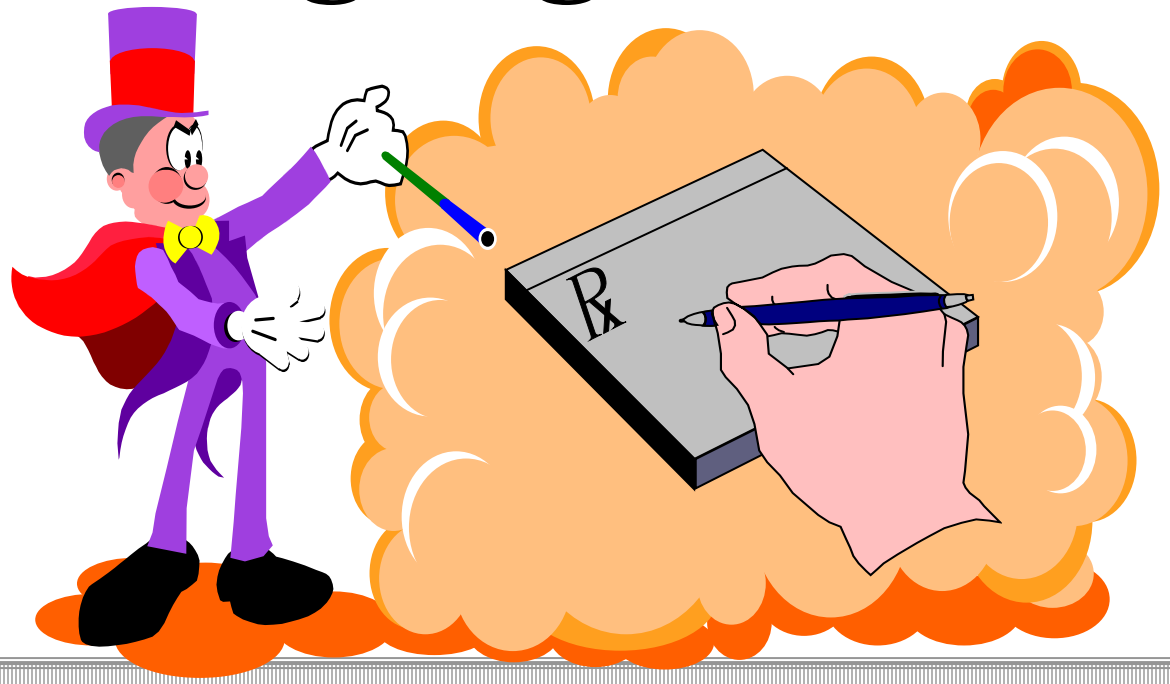
Blood Level Determinations

Steady State Concentration



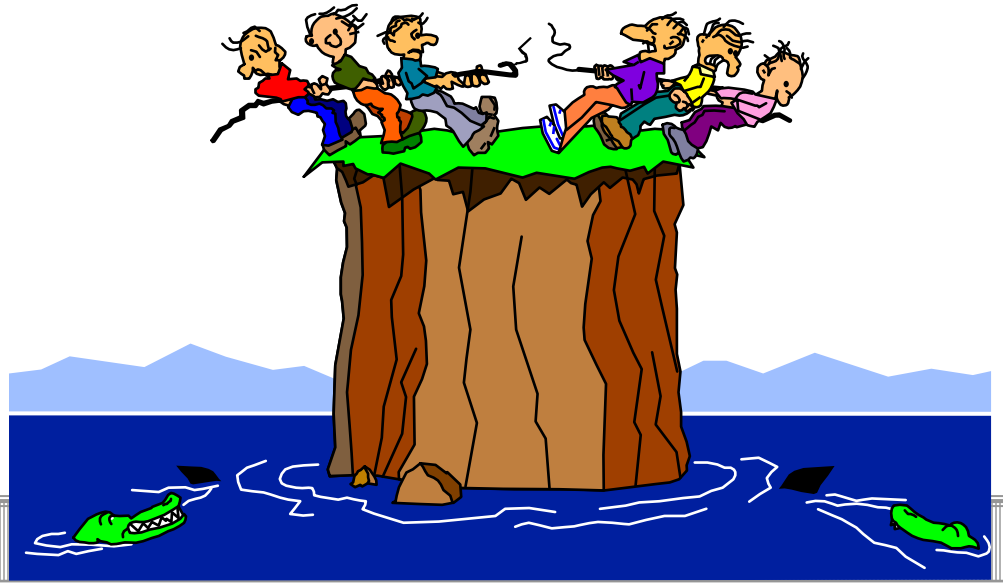
Blood Level Determinations

- Determine the best possible safe dosing regimen.



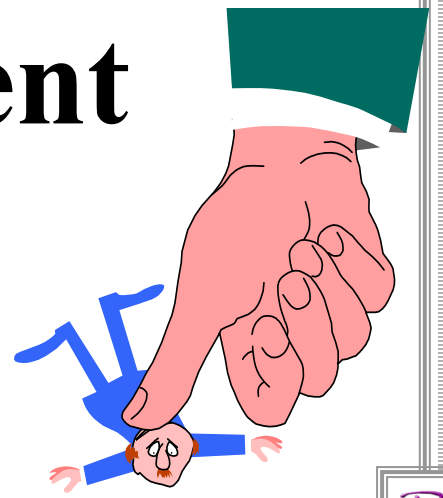
Blood Level Determinations

- Determine the best possible safe dosing regimen.
- **Maintain optimal therapy.**

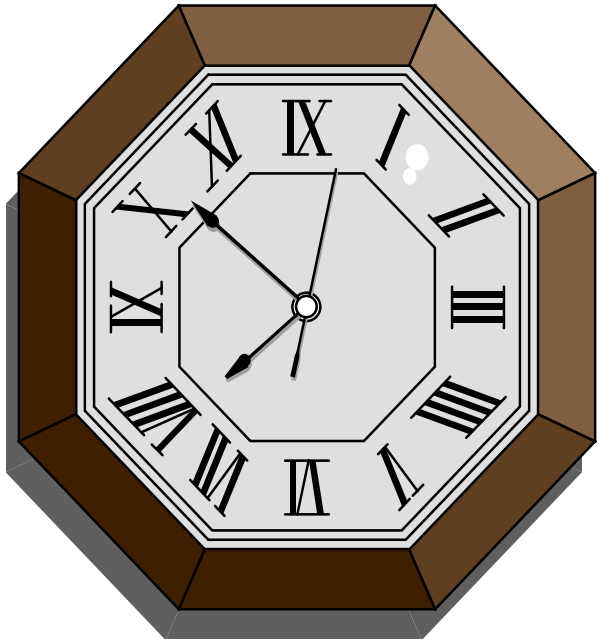


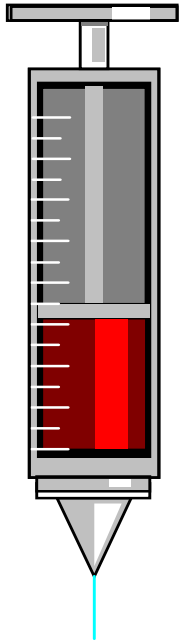
Blood Level Determinations

- Determine the best possible safe dosing regimen.
- Maintain optimal therapy.
- **Aid in the identification of patient non-compliance.**



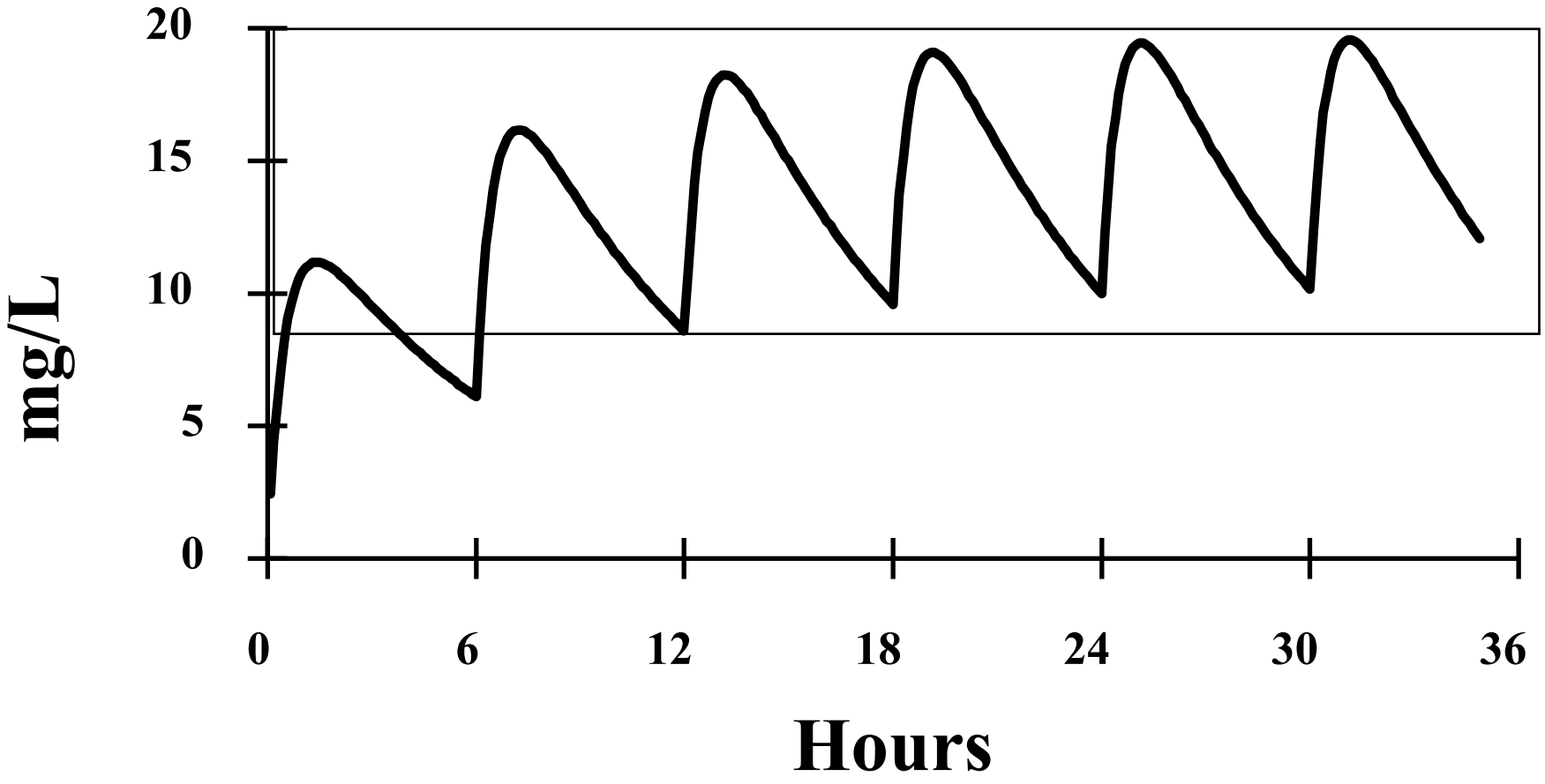
Drug Level Determinations



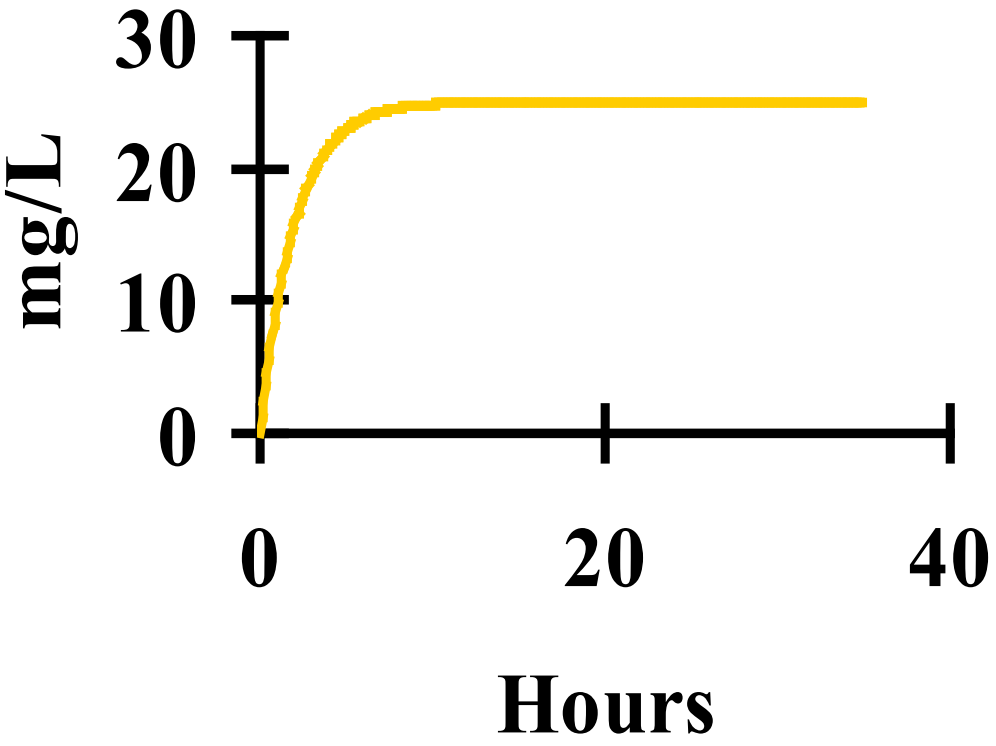


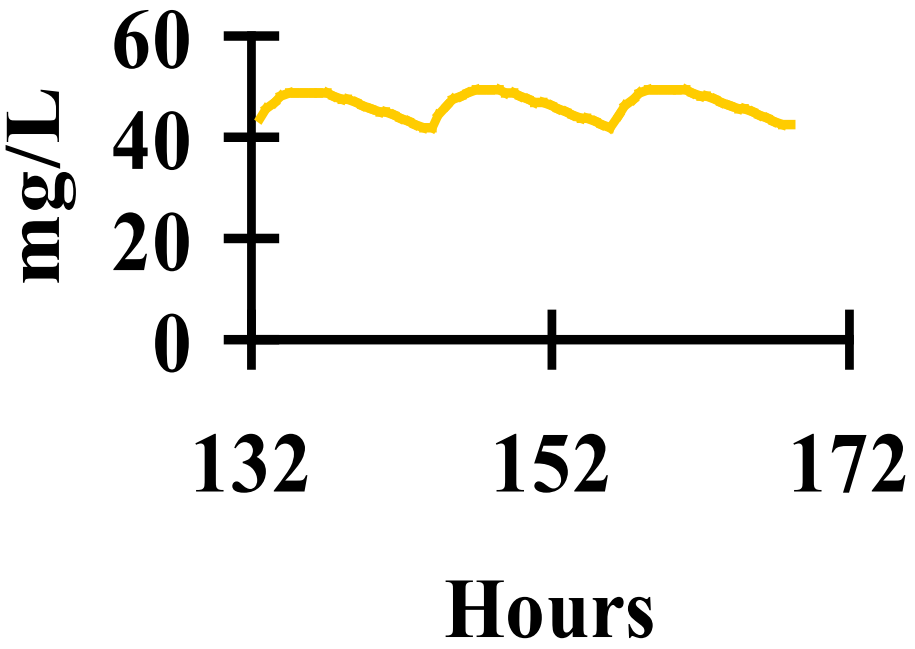
When do we draw levels?

Most often at steady state.

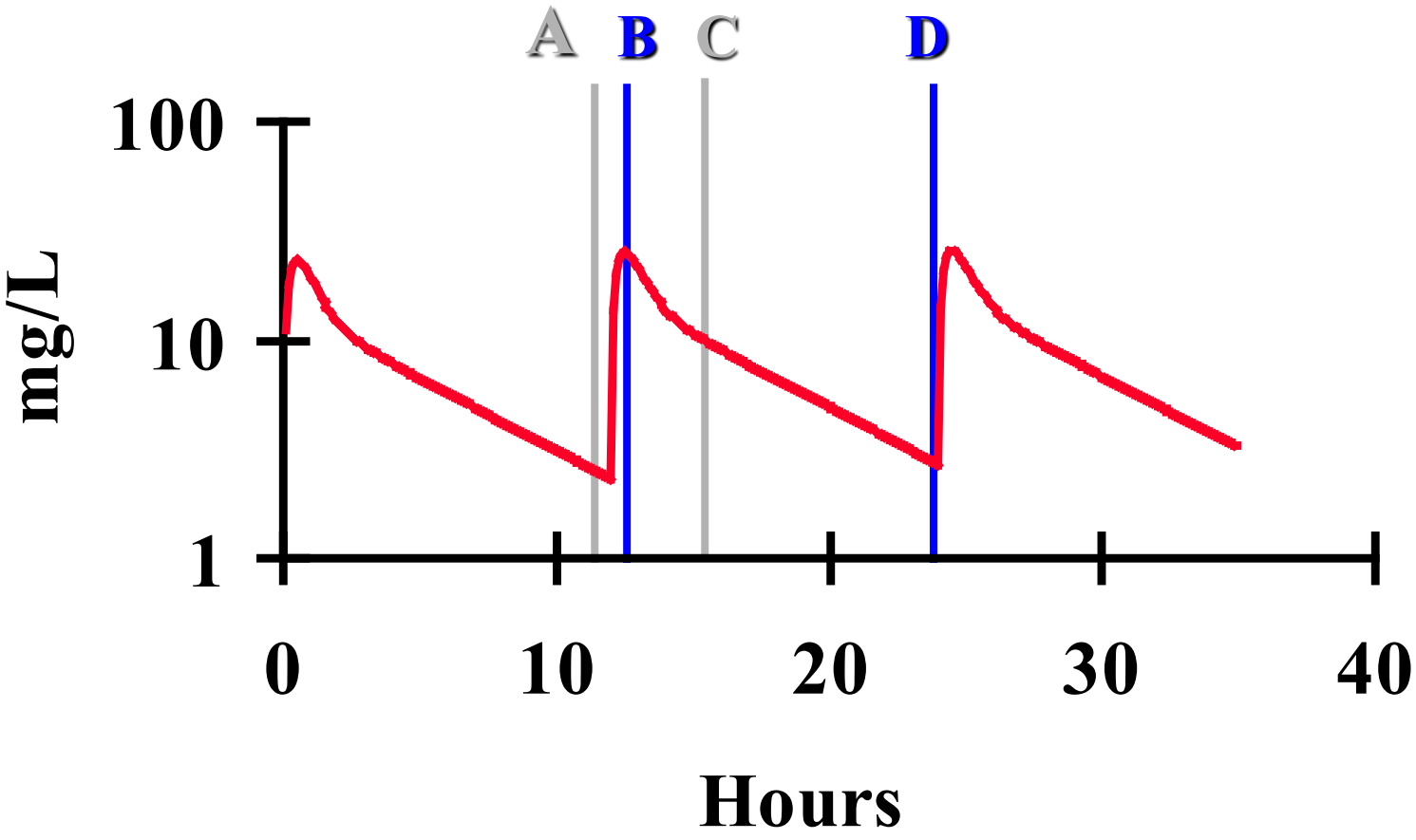


Sometimes a single level.

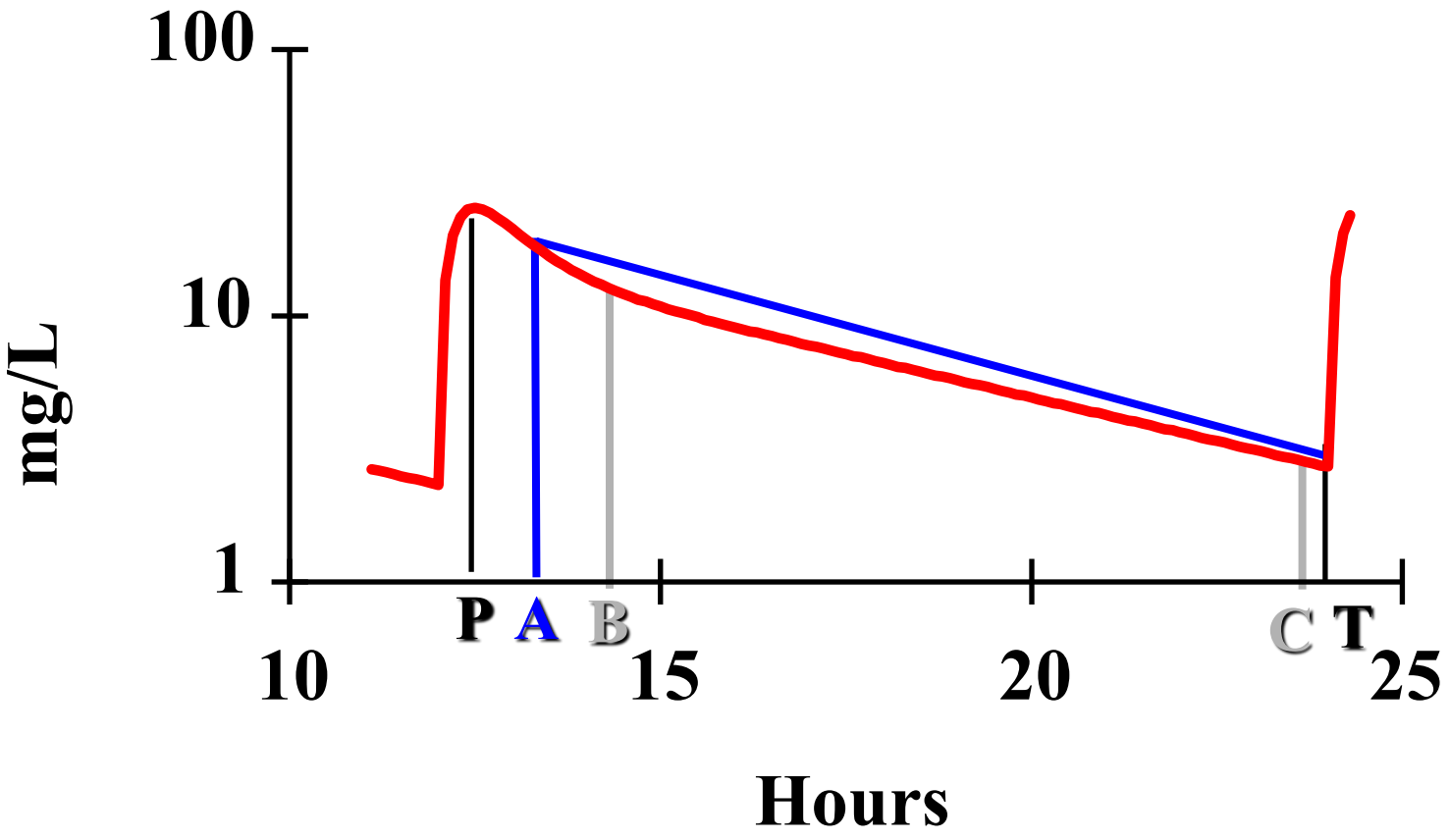




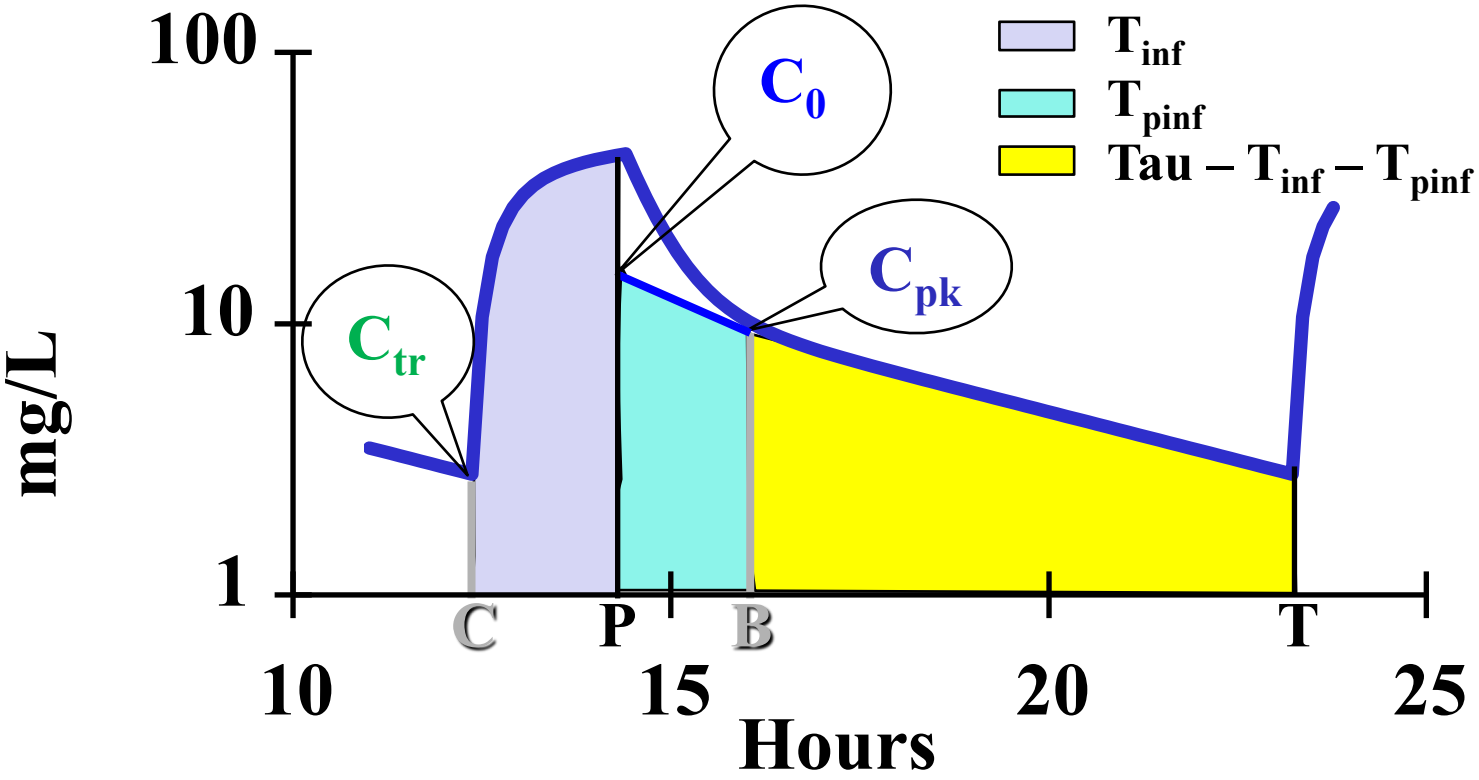
Often a peak and a trough.



When is the peak drawn?



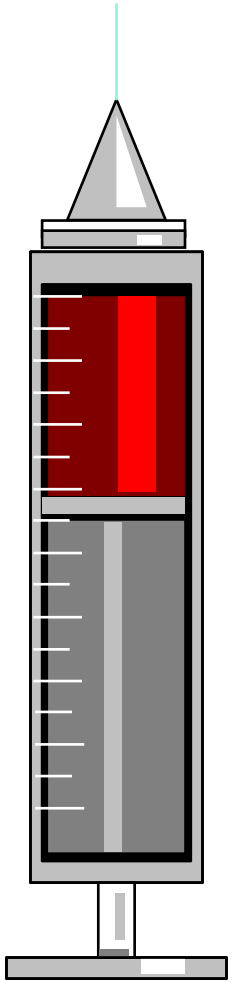
Times & Concentrations



- C_0 is where the blue line intersects P
- C_{pk} is where the blue line intersects B
- T_{inf} is the time from C to P
- T_{pinf} is the time from P to B
- The peak (C_{pk}) is measured when distribution is complete (B)
- The trough (C_{tr}) is measured within 30 minutes of the administration (C)

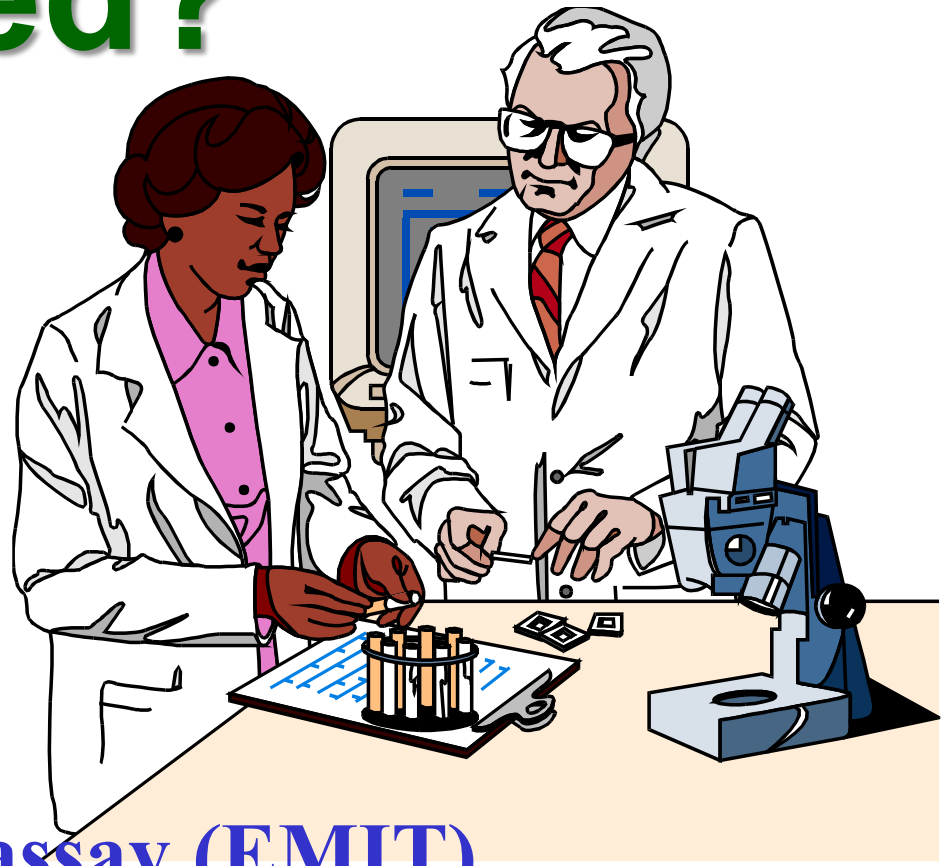
Optimum Peak Sampling Times

- Gentamicin and Tobramycin
  - Infuse over 30 minutes
  - Draw the peak 30 minutes after the infusion stops.
- Vancomycin
  - Dose ≤ 1.25 g infuse over 90 minutes
  - Dose 1.5 - 2 g infuse over 120 minutes
  - Draw the peak 60 minutes after the infusion stops.



How are drug concentrations measured?

- Sample Collection
  - Venous vs Arterial
  - Plasma vs Serum
- Assay Method
  - Microbiological
  - HPLC
  - GLC
  - Radio-immunoassay
  - Enzyme Meditated Immunoassay (EMIT)
- Units



Review

- Drug concentrations can be valuable to individualize drug therapy.
- Each drug you study in the weeks to come you will need to discover for that drug:
  - Is concentration monitoring necessary?
  - Do I need to measure a peak & trough, or only a single level?
  - When should the levels be obtained?
  - Plasma or serum?
  - What is the assay method?

Therapeutic Drug Monitoring

Individualizing Drug Therapy

- Need to know:
  - Target Concentrations
  - Volume of distribution
  - Elimination rate
- Prospectively
  - Population Estimates
- Retrospectively
  - Blood Level Data

Individualizing Drug Therapy

- Steady state - single sample
  - Constant rate infusions
  - Extravascular Administration

$$D_{new} = \frac{D_{current} \cdot C_{desired}}{C_{ss,measured}}$$

Sawchuk - Zaske Approach to Dosage Adjustment

1. **Calculate the elimination rate constant.**

$$k_e = \frac{\ln C_1 - \ln C_2}{t_2 - t_1} = \frac{\ln\left(C_1 / C_2\right)}{\tau - t_{pk}} = \frac{\ln\left(C_{pk} / C_{tr}\right)}{\tau - t_{\inf} - t_{pi}}$$

2. **Calculate C_o (t_{pk} = elapsed time from start of infusion)**

$$C_0 = \frac{C_{pk}}{e^{-k_e\,(t_{pk} - t_{\inf})}}$$

Sawchuk - Zaske Approach to Dosage Adjustment

3. **Calculate the half-life.**

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

4. **Calculate the volume of distribution.**

$$V_{ss} = \frac{R_0}{k_e} \cdot \frac{1 - e^{-k_e t_{\inf}}}{(C_0 - C_{tr} \cdot e^{-k_e t_{\inf}})}$$

Sawchuk - Zaske Approach to Dosage Adjustment

5. **Calculate the dosing interval.**

$$\tau = \frac{\ln\left(C_{Max,desired} / C_{Min,desired}\right)}{k_e} + t_{\inf}$$

6. **Calculate the new infusion rate.**

$$R_0 = C_{Max,desired} \cdot k_e \cdot V_{ss} \cdot \frac{\left(1 - e^{-k_e \tau}\right)}{\left(1 - e^{-k_e t_{\inf}}\right)}$$

Sawchuk - Zaske Approach to Dosage Adjustment

7. **Calculate the new peak.**

$$C_{ss,pk} = \frac{R_0}{V_{ss} \cdot k_e} \cdot \frac{\left(1 - e^{-k_e t_{\inf}}\right)}{\left(1 - e^{-k_e \tau}\right)}$$

8. **Calculate the new trough.**

$$C_{ss,tr} = C_{ss,pk} \cdot e^{-k_e\left(\tau - t_{\inf}\right)}$$

Vancomycin Example

- **BJ is a 65 YO 5'4" man with cellulitis from *Staph aureus*.**
  - **His weight is 70 Kg (IBW = 57 Kg)**
  - **His serum creatinine is 1.4 mg/dl.**
  - **Her measured CrCl was 52.0 ml/min.**
- **To give you a target peak of about 36 mg/L and trough of 15 mg/L:**
  - **What dose (mg) of vancomycin would you recommend for initiation of therapy?**
  - **And what dosing interval?**

Vancomycin Example

- Target Concentration
  - Peak 30-40 mg/L
  - Trough = 15 mg/L

- Volume of Distribution
  - 0.7 L/Kg
- Elimination Rate Constant
  - $K_e = (8.3*CrCl + 44)/10^4$

Target Concentrations

- Vancomycin
  - Peak 30-40 mg/L
  - Trough 10-20 mg/L

Prospectively

- Population Pharmacokinetic Estimates

$$CrCl = \frac{(140 - Age) \cdot CrClWt}{72 \cdot SrCr}(0.85 + Sex \cdot 0.15)$$

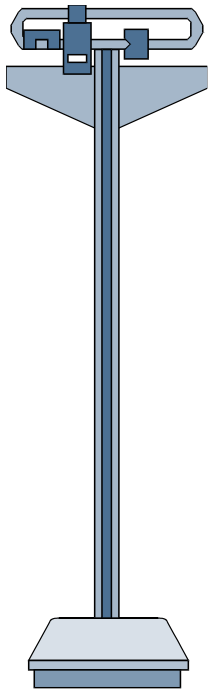
Cockcroft & Gault:
Nephron 1976;6:31-41.

$$Est.\ k_e = \frac{8.3 \cdot CrCl + 44}{10000}$$

Matzke and coworkers:
Antimicrob Agents Chemother 1984; 25:433-437.

$$Est.\ V_{ss} = 0.7L/Kg \cdot \text{ActWT}$$

Dosing Weight



IBW (males) =

50 Kg + 2.3 Kg/inch over 5 feet

IBW (females) =

45.5 Kg + 2.3 Kg/inch over 5 feet

If ActBW is > 30% over IBW, then

AdjWT = (ActBW - IBW)(0.4) + IBW

Sawchuk-Zaske Approach

- Equation 1
  - Prospectively estimate K_e.
  - Normally you would need to first estimate CrCl from Cockcroft & Gault, but note that the measured CrCl was given to you, so use that.
- Equation 2
  - Determine the half-life (from K_e).

Sawchuk-Zaske Approach

- Equation 3
  - Prospectively C_0 is your target peak concentration (here 36 mg/dl) so no calculation is necessary.
- Equation 4
  - Prospectively estimate V_{ss} from the V_d, factor for vancomycin (here 0.7 L/Kg).

Sawchuk-Zaske Approach

- Equation 5
  - Now you can estimate the dosing interval from the target peak and trough and the calculated K_e.
  - You must select a practical Tau.
- Equation 6
  - Now use the practical Tau to determine the dose.
  - Equation 6 gives you R_0, the rate of infusion, so to get the dose you have to take the length of the infusion times R_0.
  - Remember to select a practical dose.

Sawchuk-Zaske Approach

- Equations 7 & 8
  - Verify that this practical dose and practical interval that you have chosen give you a steady state peak and trough near your targets.

Review

- These two examples were given to show what takes place when these calculations are done.
- Your major responsibility will not be to do these calculations, but will be to order drug concentrations and make dosage adjustments based on these measurements.
- The remainder of our time will focus on that.

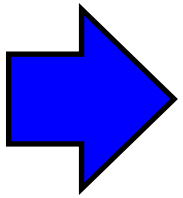
Our Goal

- **Optimize therapy:**

Drug Concentration

Pharmacokinetic Principles

Clinical or Pharma-cological Response.



To optimize drug therapy for the patient.

Ordering Drug Levels

- Remember not every drug requires therapeutic monitoring.
- Those that do, know whether you need a Pk/Tr pair, or is a single level sufficient.
- Remember levels need to be done at steady state.

Drugs Commonly Monitored in Clinical Practice

Drug	Therapeutic range	Drug	Therapeutic range
Digoxin	0.5 – 2.1 ng/ml	Theophylline	10 – 20 mg/L
Amiodarone	1.0 – 2.5 mg/L	Lithium	0.6 – 1.2mg/L
Lidocaine	1.5 – 6.0 mg/L	Phenytoin	10 – 20 mg/L
Quinidine	2.0 – 8.0 mg/L	Carbamazepine	4 – 12 mg/L
Flecainide	0.2 – 0.9 mg/L	Sodium valproate	50 – 100 mg/L
Mexilitine	0.5 – 2.5 mg/L	Phenobarbital	10 – 40 mg/L
Salicylate	150 – 300 mg/L	Lamotrigine	2.5 – 15 mg/L
Cyclosporine	50–125 microgram/L (serum or plasma)	Gentamicin, tobramycin, netilmicin	trough <2 mg/L; peak >5 mg/L
Sirolimus	150–400 microgram/L (whole blood)	Amikacin	trough <5 mg/L; peak >15 mg/L
Tacrolimus	5–20 microgram/L (whole blood)	Vancomycin	trough 15 mg/L; peak 20 – 40 mg/L

Case 1 – Ordering Levels

- You have a new drug
  - It has a narrow therapeutic index
  - It has a significant Pk/Tr fluctuation
  - The main elimination half-life is 8 hours.
  - The distribution phase is observable with a half-life of 0.4 hours.
  - The drug is given by intermittent infusion 100 mg Q8H with a 0.5 hour infusion.
- When do you order the Pk/Tr?
  - Tr at steady state (5x8 hours=40 hours) so measure right before the 6^{th} dose.
  - Pk after distribution is complete, (5x0.4 hr = 2 hours) so measure 2 hours after the infusion is complete.

Kinetic Data is Available

- That will help optimize drug therapy.
  - Goodman & Gilman, Pharmacologic Basis of Therapeutics – Appendix II Table 1
  - Handbook of Clinical Drug Data
  - MicroMedex, Lexi-Comp, Clincal Pharmacology Online.

Case 2 - Example from

Goodman & Gilman

BioAVAIL-ABILITY (ORAL) (%)	URINARY EXCRETION (%)	BOUND IN PLASMA (%)	CLEARANCE (mL/min/kg)	VOL. DIST. (L/kg)	HALF-LIFE (hours)	PEAK TIME (hours)	PEAK CONC.
Acetaminophen[a]							
88 ± 15	3 ± 1	<20	5.0 ± 1.4[b]	0.95 ± 0.12[b]	2.0 ± 0.4	0.33–1.4[d]	20 µg/mL[e]

[a] Values reported are for doses <2 g; drug exhibits concentration-dependent kinetics above this dose.
[b] Assuming a 70-kg body weight; reported range, 65-72 kg.
[c] Acetaminophen-induced hepatic damage or AVH.
[d] Absorption rate, but not extent, depends on gastric emptying; hence, it is slowed after food as well as in some disease states and co-treatment with drugs that cause gastroparesis.
[e] Mean concentration following a 20-mg/kg oral dose. Hepatic toxicity associated with levels >300 µg/mL at 4 hours after an overdose.

Reference: Forrest JA, et al. Clinical pharmacokinetics of paracetamol. *Clin Pharmacokinet,* **1982**, *7*:93–107.

Case 2 – Lessons Learned

- **Oral Bioavailability**
  - **Is fairly good, about 88% so this is a reasonable route of administration with a rapid absorption and good peak.**
- **Urinary Excretion**
  - **Is about 2-4%, so it is not necessary to adjust the dose in renal failure, however, since it is mostly hepatically eliminated, you may need to decrease the dose with declining liver function.**

Case 2 – Lessons Learned

- **Protein Binding**
  - It is minimal, 20%.
- **Clearance, volume of distribution and half-life.**
  - Volume of distribution is larger than the blood volume, so there is distribution outside of the central compartment, and the half-life indicates that steady state should be achieved within 12 hours.
  - Note footnote (a). These values are valid only when less than 2 g/day is administered. Larger doses of acetaminophen will exhibit a dose dependent pharmacokinetics.
- **No need to measure concentrations unless there is an overdose.**

Case 3 - Example from

Goodman & Gilman

BioAVAIL-ABILITY (ORAL) (%)	URINARY EXCRETION (%)	BOUND IN PLASMA (%)	CLEARANCE (mL/min/kg)	VOL. DIST. (L/kg)	HALF-LIFE (hours)	PEAK TIME (hours)	PEAK CONC.
Gentamicin [a]							
IM: ~100	>90	<10	$CL = 0.82CL_{cr} + 0.11$	0.31 ± 0.10	2-3[a]	IM: 0.3-0.75[b]	IV: 4.9 ± 0.5 µg/mL[b]
[a] Gentamicin has a very long terminal $t_{1/2}$ of 53 ± 25 hours (slow release from tissues), which accounts for urinary excretion for up to 3 weeks after a dose. [b] Following a single100-mg IV infusion (1 hour) or IM injection given to healthy adults.				*References*: Matzke GR, et al. Pharmacokinetics of cetirizine in the elderly and patients with renal insufficiency. *Ann Allergy,* **1987**, *59*:25–30. Regamey C, et al. Comparative pharmacokinetics of tobramycin and gentamicin. *Clin Pharmacol Ther,* **1973**, *14*:396–403.				

Case 3 – Lessons Learned

- **Bioavailability**
  - Gentamicin is usually given by IV infusion in this country but IM absorption is complete (100%) and rapid (15-45 minutes) so it is an acceptable route of administration.
- **Urinary Excretion**
  - More than 90%, so as renal function changes, the dose will need to change, but no adjustments are required in hepatic failure.

Case 3 – Lessons Learned

- Protein Binding
  - It is minimal, 10%.
- Clearance, volume of distribution and half-life.
  - Volume of distribution is slightly larger than the blood volume, so there is distribution outside of the central compartment, but not large. It does not distribute into adipose tissue, so dosing in obese patients should not be made on actual body weight, but using an adjusted weight.
  - Note footnote (a). This slow elimination is not seen during typical courses of therapy lasting 10 days or less.
- Concentration monitoring is necessary, especially when renal function is changing.

Summary

- Properly collected serum drug concentrations can be very useful to optimize drug therapy for those agents that have a narrow therapeutic window.
- They can be used to calculate patient specific PK parameters and then make dosage adjustments.

Another- Example from

Goodman & Gilman Appendix II, Table 1

BioAVAIL-ABILITY (ORAL) (%)	URINARY EXCRETION (%)	BOUND IN PLASMA (%)	CLEARANCE (mL/min/kg)	VOL. DIST. (L/kg)	HALF-LIFE (hours)	PEAK TIME (hours)	PEAK CONC.
Midazolam							
44 ± 17[b]	<1%	98	6.6 ± 1.8	1.1 ± 0.6	1.9 ± 0.6	PO: 0.67 ± 0.45[d]	IV: 113 ± 16 ng/mL[d] PO: 78 ± 27 ng/mL[d]

[a] Metabolically cleared exclusively by CYP3A.
[b] Undergoes extensive first-pass metabolism by intestinal and hepatic CYP3A. Bioavailability appears to be dose dependent; 35-67% at 15-mg, 28-36% at 7.5-mg, and 12-47% at 2-mg oral dose, possibly due to saturable first-pass intestinal metabolism.
[c] Increased *CL* due to increased plasma free fraction; unbound *CL* is unchanged.
[d] Following a single 5-mg IV bolus or 10-mg oral dose.

References:
Garzone PD, et al. Pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet*, **1989**, *76*:337–364.
Thummel KE, et al. Oral first-pass elimination of midazolam involves both gastrointestinal and hepatic CYP3A-mediated metabolism. *Clin Pharmacol Ther*, **1996**, *59*:491–502.

Another- Example from

Goodman & Gilman Appendix II, Table 1

BioAVAIL-ABILITY (ORAL) (%)	URINARY EXCRETION (%)	BOUND IN PLASMA (%)	CLEARANCE (mL/min/kg)	VOL. DIST. (L/kg)	HALF-LIFE (hours)	PEAK TIME (hours)	PEAK CONC. (ng/ml)
Nifedipine							
50 ± 13	~0	96 ± 1	7.0 ± 1.8	0.78 ± 0.22	1.8 ± 0.4[b]	IR: 0.5 ± 0.2[c] ER: ~6[c]	IR: 79 ± 44[c] ER: 35-49[c]

[a] Metabolically cleared by CYP3A; undergoes significant first-pass metabolism.
[b] Longer apparent $t_{1/2}$ after oral administration because of absorption limitation, particularly for extended-release (ER) formulations.
[c] Mean following a single 10-mg immediate-release (IR) capsule given to healthy male adults or a range of steady-state concentrations following a60-mg ER tablet given daily to healthy male adults. Levels of 47 ± 20 ng/mL were reported to decrease diastolic pressure in hypertensive patients.

References:
Glasser SP, et al. The efficacy and safety of once-daily nifedipine: The coat-core formulation compared with the gastrointestinal therapeutic system formulation in patients with mild-to-moderate diastolic hypertension. Nifedipine Study Group. *Clin Ther,* **1995**, *17*:12–29.
Renwick AG, et al. The pharmacokinetics of oral nifedipine—A population study. *Br J Clin Pharmacol,* **1988**, *25*:701–708.
Soons PA, et al. Intraindividual variability in nifedipine pharmacokinetics and effects in healthy subjects. *J Clin Pharmacol,* **1992**, *32*:324–331.