

# PK / PD Concepts in Clinical Research

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-Dhanashri Gudi, Ph.D.

Founder, *EduCater*

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PhUSE SDE 2014

PKPD Concepts and Programming

06 Dec 2014

Bangalore, INDIA

# Mission- *Building Knowledge-Inspiring Minds*

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- *EduCater* provides highly specialized, practical and theoretical knowledge driven training programs.
- **USP**-Focus on key areas for pharmaceutical R&D where limited training is available in India..
- Training to build solid scientific foundation to create scientists and leaders in the field.
- Experienced and renowned trainers and speakers are hand-picked to bring authentic information and knowledge.
- Limited class-size to enable participants to interact with speakers.

# Training Events at EduCater

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- Workshop on PK/PD modeling (Dec 2011) Jonathan Wagg
- 3 day Course on “Unlocking the Mystery of Pharmacokinetics” (July 2012) Dr. Shashank Rohatagi
- Software based Training: Collaboration with Certara (Pharsight) (since May 2012)
  - Introduction to Phoenix WinNonlin at Mumbai, Hyderabad, Bangalore (7 workshops of 2.5days)
  - IVIVC toolkit for Phoenix WinNonlin, Mumbai
  - Population PKPD analysis using Phoenix NLME
  - Intermediate PK/PD Modeling using PHX WNL
- “Statistics in Pharmaceutical Development” (May 2013)
- “R in Clinical Trial Data Analysis” (June 2014)

AMAZING NEW DISCOVERY is made by doctors who looked  
inside a living person's stomach to determine why

# BAYER BRINGS FASTEST RELIEF

the fastest, most gentle to the stomach relief  
you can get from pain!



Doctors found Bayer Aspirin has  
astonishing action even before known

**Instant Flaking Action**  
so you get relief without delay

The medically designed glass  
beaker above represents the area  
from your mouth to your stomach.  
It illustrates what doctors saw  
in the stomach of a living person:  
that Bayer has an astonishing  
instant flaking action. Therefore,  
a Bayer tablet enters the stomach  
—not whole—but in soft, tiny  
flakes. As a result, there's no  
waiting for relief until the tablet  
disintegrates. Bayer Aspirin is  
ready to go to work instantly—  
without delay—to make you  
feel better fast.



**Men who know medicine  
recommend Aspirin!**

In medical journals, eminent doctors consistently acclaim aspirin for its great and ever-growing values.

In newspapers, public health officials have repeatedly recommended aspirin as the one thing for headaches, muscular pains, fever of a cold.

In personal interviews, hundreds and hundreds of doctors said they recommend aspirin. So buy the best aspirin the world has ever known—Bayer Aspirin!

"I use it for  
**HEADACHE!**"



"I use it for  
**ACHING  
MUSCLES!**"



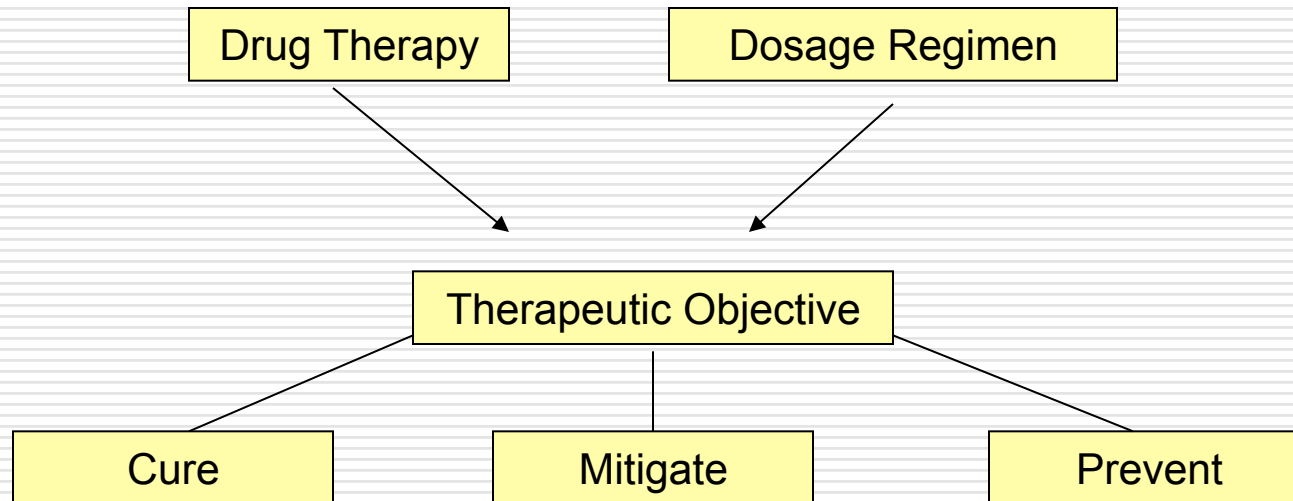
"I use it for  
pain and fever  
of **COLDS!**"



# Outline and Agenda

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- ☐ What is Pharmacokinetics
  - ☐ Why Pharmacokinetics
  - ☐ Processes that govern the Pharmacokinetics
  - ☐ Pharmacokinetic Parameters
  - ☐ Types of Kinetics
  - ☐ Noncompartmental Modeling (Plasma and Urine NCA)
  - ☐ Compartmental Modeling
  - ☐ Examples
  - ☐ What is Pharmacodynamics
  - ☐ Types of PD Models
  - ☐ PK/PD link Models
  - ☐ Demonstration of Phoenix<sup>®</sup> WinNonlin<sup>®</sup>
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**How much?** Recognizes magnitude of therapeutic and toxic responses : Functions of dose

**How often?** Recognizes the importance of time

**How long?** Recognizes that a cost in terms of side effects, toxicity and economics

Earlier lot of trial and error way: obtain the perfect balance between the desired effect and toxicity as achieved.

# What is Pharmacokinetics ?

*pharmakon* -drug

*kinetikos* - to do with motion

A branch of pharmacology concerned with the movement of drugs/metabolites within the body

**Pharmacokinetics-** what the body does to the drug

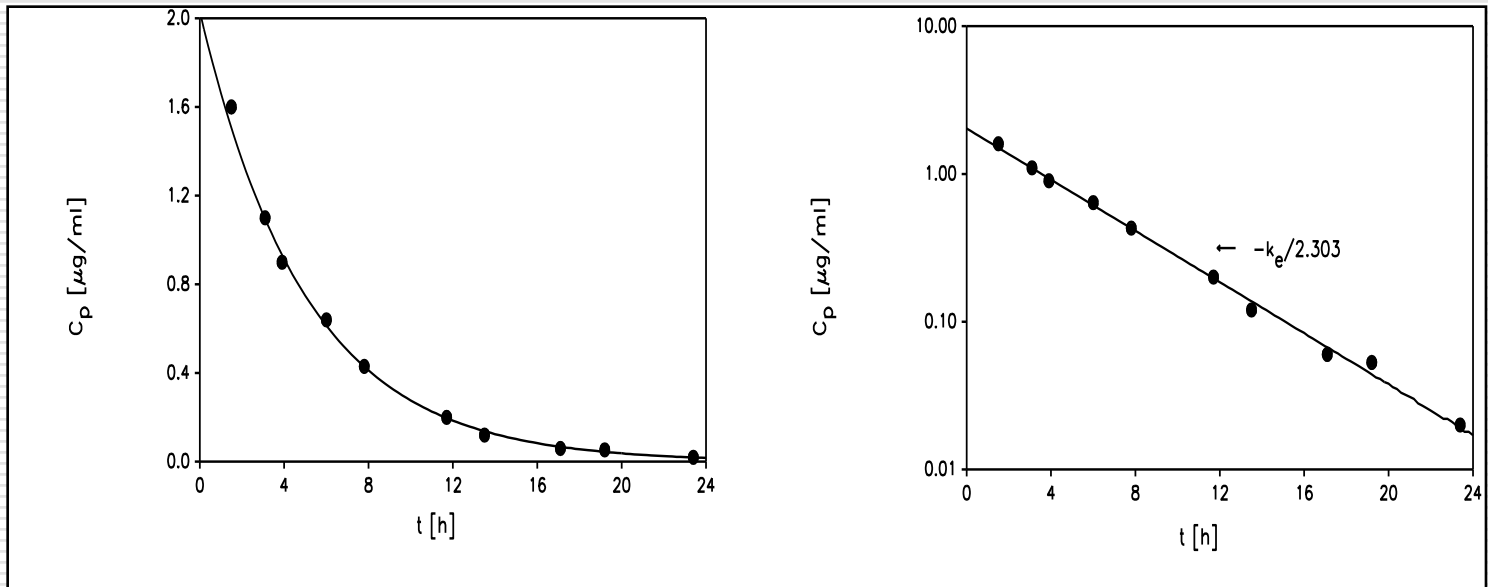
**Pharmacology-** what the drug does to the body

Clinical Pharmacokinetics

Application of pharmacokinetic principles  
to the therapeutic management of patients

# Pharmacokinetics

- the time course of drug concentrations in the body



# Why Pharmacokinetics ?

## Daliresp (Roflumilast) label

### 12.3 Pharmacokinetics

#### Absorption

The absolute bioavailability of roflumilast following a 500 mcg oral dose is approximately 80%. Maximum plasma concentrations ( $C_{max}$ ) of roflumilast typically occur approximately one hour after dosing (ranging from 0.5 to 2 hours) in the fasted state while plateau-like maximum concentrations of the N-oxide metabolite are reached in approximately eight hours (ranging from 4 to 13 hours). Food has no effect on total drug absorption, but delays time to maximum concentration ( $T_{max}$ ) of roflumilast by one hour and reduces  $C_{max}$  by approximately 40%, however,  $C_{max}$  and  $T_{max}$  of roflumilast N-oxide are unaffected. An *in vitro* study showed that roflumilast and roflumilast N-oxide did not inhibit P-gp transporter.

#### Distribution

Plasma protein binding of roflumilast and its N-oxide metabolite is approximately 99% and 97%, respectively. Volume of distribution for single dose 500 mcg roflumilast is about 2.9 L/kg. Studies in rats with radiolabeled roflumilast indicate low penetration across the blood-brain barrier.

#### Metabolism

Roflumilast is extensively metabolized via Phase I (cytochrome P450) and Phase II (conjugation) reactions. The N-oxide metabolite is the only major metabolite observed in the plasma of humans. Together, roflumilast and roflumilast N-oxide account for the majority (87.5%) of total dose administered in plasma. In urine, roflumilast was not detectable while roflumilast N-oxide was only a trace metabolite (less than 1%). Other conjugated metabolites such as roflumilast N-oxide glucuronide and 4-amino-3,5-dichloropyridine N-oxide were detected in urine.

While roflumilast is three times more potent than roflumilast N-oxide at inhibition of the PDE4 enzyme *in vitro*, the plasma AUC of roflumilast N-oxide on average is approximately three times that of roflumilast.

*In vitro* studies and clinical studies have shown that roflumilast is not a substrate for CYP 1A2 and CYP 2D6. A low probability of relevant drug-drug interactions is demonstrated no induction of CYP 1A2 and CYP 2D6.

#### Elimination

The plasma clearance after intravenous administration of roflumilast is approximately 1.5 L/h. The median plasma effective half-life of roflumilast and its N-oxide metabolite are approximately 17 and 30 hours, respectively. Steady state plasma concentrations of roflumilast and its N-oxide metabolite are reached after approximately 4 days for roflumilast and 6 days for roflumilast N-oxide following once daily dosing. Following intravenous or oral administration of radiolabeled roflumilast, about 70% of the radioactivity was recovered in the urine.

-----DOSAGE AND ADMINISTRATION-----  
The recommended dosage for patients with COPD is one 500 mcg tablet per day, with or without food. (2)

# Why Pharmacokinetics ?

## Daliresp (Roflumilast) label

### Special Populations

#### Hepatic Impairment

Roflumilast 250 mcg once daily in subjects with Child-Pugh A and B (8 subjects in each group) compared to healthy subjects and by 26% in subjects with mild liver impairment (Child-Pugh A).

#### Renal Impairment

In twelve subjects with mild renal impairment, AUCs were decreased by 33%. No dosage adjustment is necessary for patients with mild renal impairment.

#### Age

Roflumilast 500 mcg once daily in subjects (> 65 years of age) were compared to roflumilast-N-oxide than in healthy subjects.

#### Gender

In a Phase I study evaluating the pharmacokinetics of roflumilast and roflumilast-N-oxide in healthy female subjects as compared to healthy male subjects. No dosage adjustment is necessary for patients with mild renal impairment.

#### Smoking

The pharmacokinetics of roflumilast and roflumilast-N-oxide in 12 non-smokers and 12 smokers were compared. No dosage adjustment is necessary for patients with mild renal impairment.

#### Race

As compared to Caucasians, roflumilast and 43%, 27% in Caucasians, Hispanics, and Japanese, respectively, for roflumilast and roflumilast-N-oxide.

### Nursing Mothers

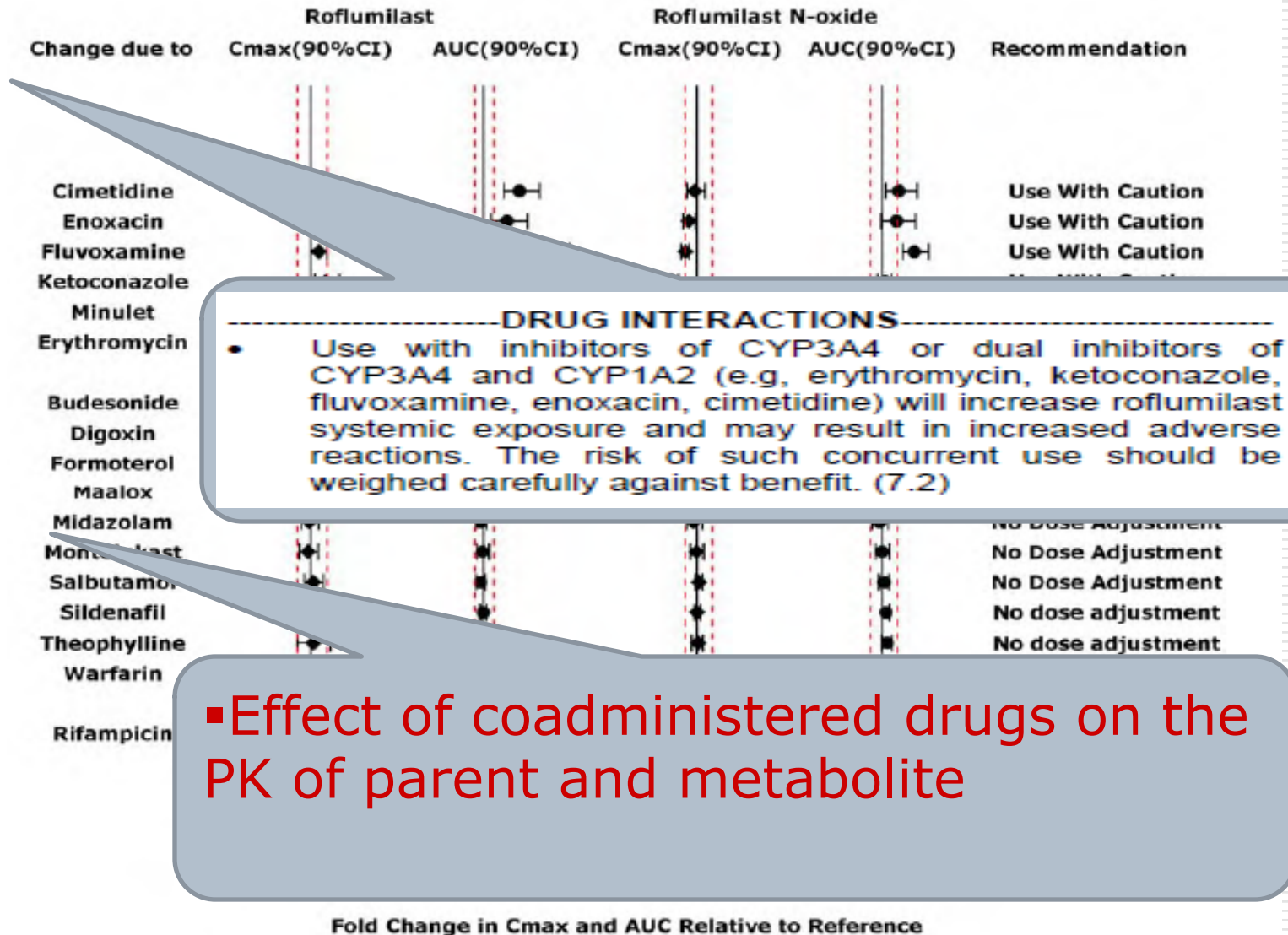
Women who are nursing infants should not take DALIRESP. Excretion of roflumilast and/or its metabolites into human milk is probable and there are no human studies that have investigated effects of DALIRESP on breast-fed infants. (8.3)

- Daliresp not recommended for patients with moderate to severe hepatic impairment
- No dose adjustment needed in renal impairment
- No dose adjustment needed for elderly/ gender/ race

### 8.3 Nursing Mothers

Roflumilast and/or its metabolites are excreted into the milk of lactating rats. Excretion of roflumilast and/or its metabolites into human milk is probable. There are no human studies that have investigated effects of DALIRESP on breast-fed infants. DALIRESP should not be used by women who are nursing.

# Why Pharmacokinetics ?

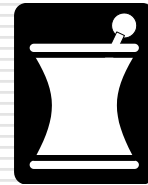


# Why clinical pharmacokinetics?

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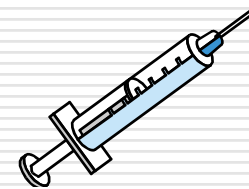
## Drug therapy optimization:

Dose: How much?

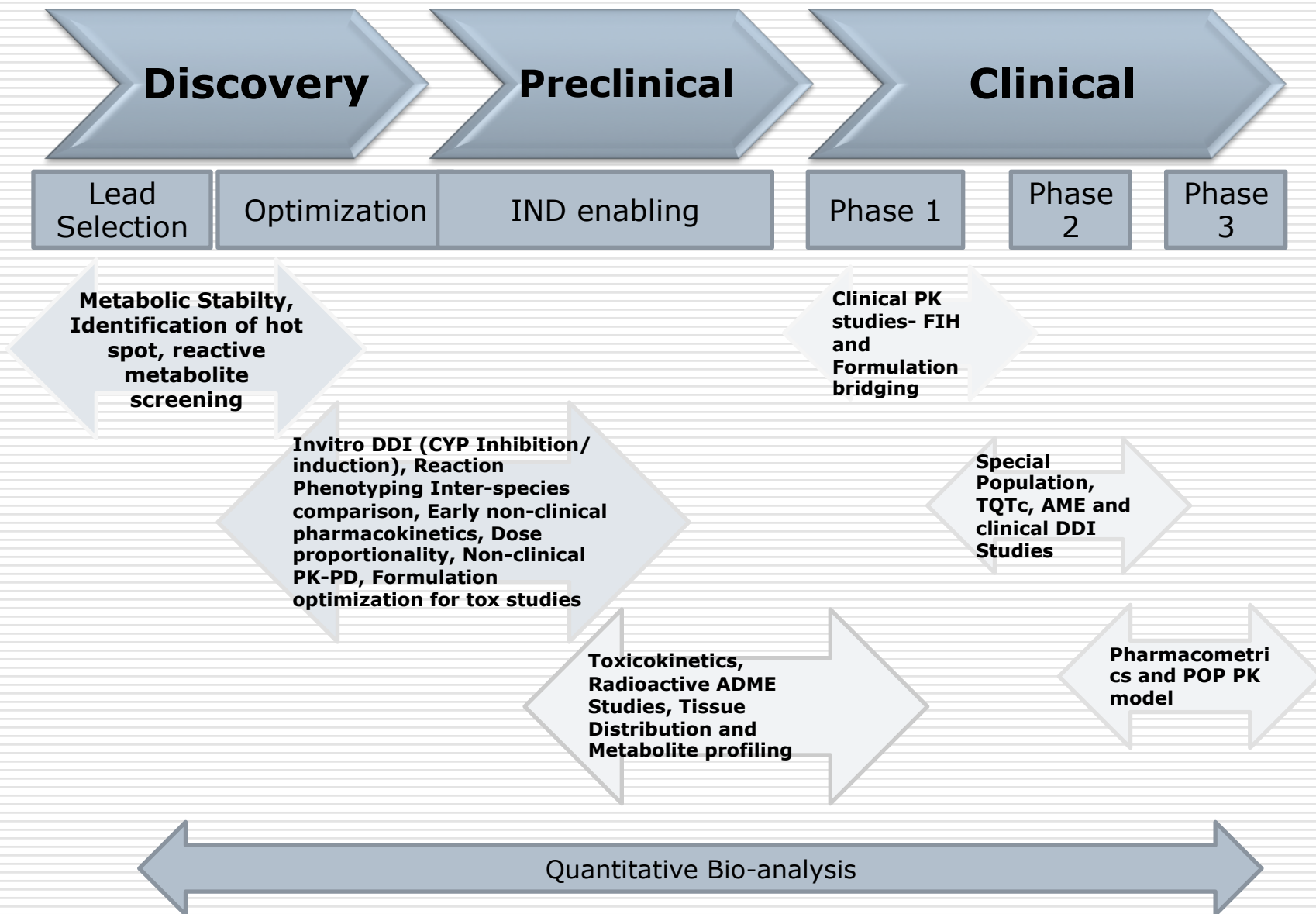


Dosing regimen: How often? How long?

Dosage form: what formulation?



# Role of Pharmacokinetics



# Introduction to Pharmacokinetics

Pharmacokinetics is a mathematical description of the time course of drug and/its metabolite in the body . ADME determines the drug concentration in the body

**Absorption**

**Distribution**

**Elimination**

**Metabolism**

**Excretion**

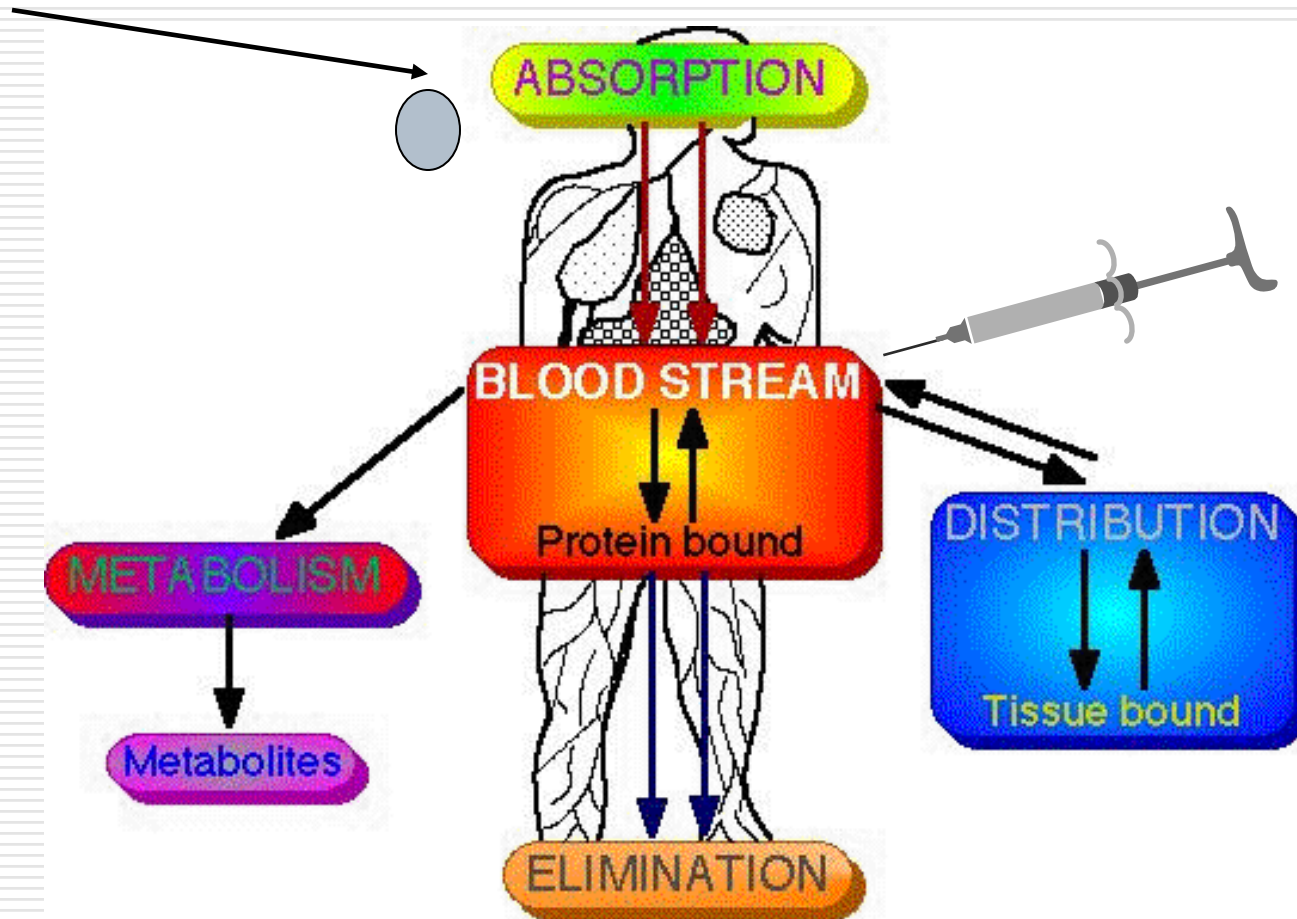


# Pharmacokinetics

What happens to a drug after its administration ?

ADME "Fate of the Drug"

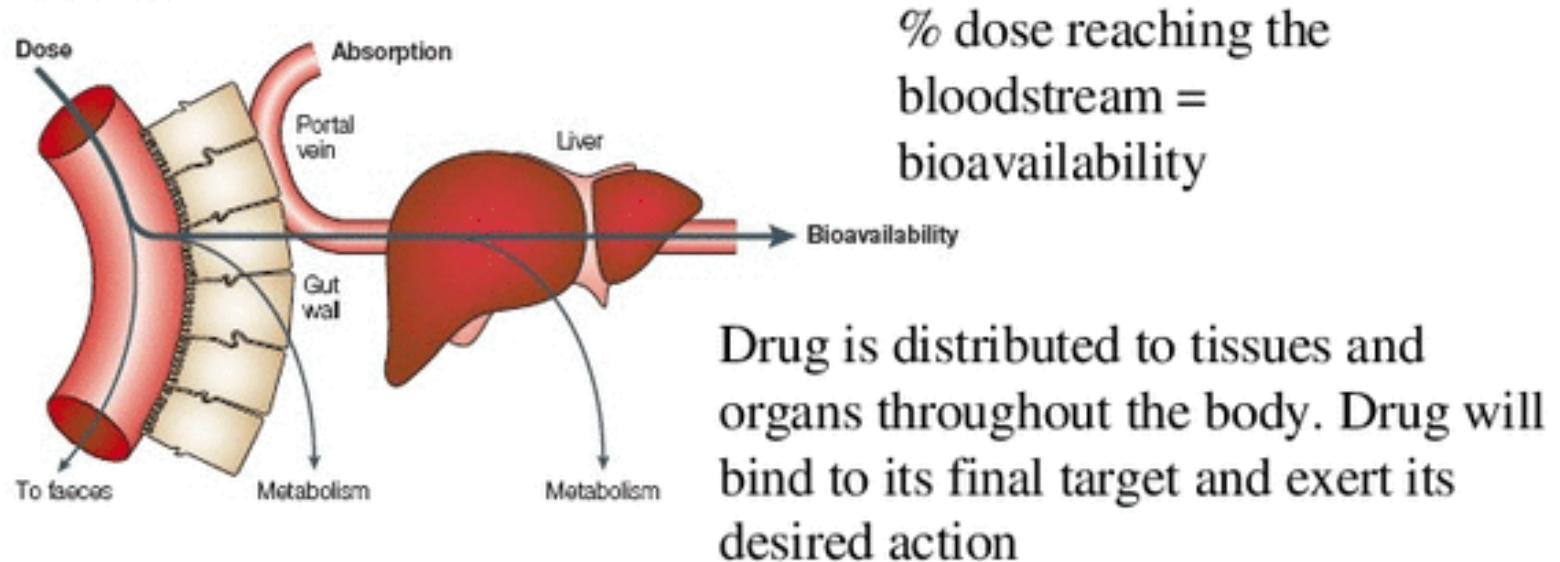
Liberation



## Pharmacokinetics in drug design

Pharmacokinetics is how a drug is **A**bsorbed, **M**etabolized, **D**istributed, and **E**liminated. (ADME)...

Most drugs are given orally: dissolves in the GI tract and is absorbed through the gut; passes through the liver and into the blood stream.



How is pharmacokinetics monitored? Measurement of drug concentrations in the blood or plasma

# Absorption

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## **Defination**

Movement of drug molecules across physiological barriers from the site of administration to the blood stream

Or

The process by which unchanged drug proceeds from site of administration to site of measurement within the body.

## **Intravascular administration (No Absorption):**

- intravenously or intra-arterially.

## **Extravascular administration:**

- Oral , sublingual, buccal, intramuscular, subcutaneous, dermal, pulmonary, and rectal routes
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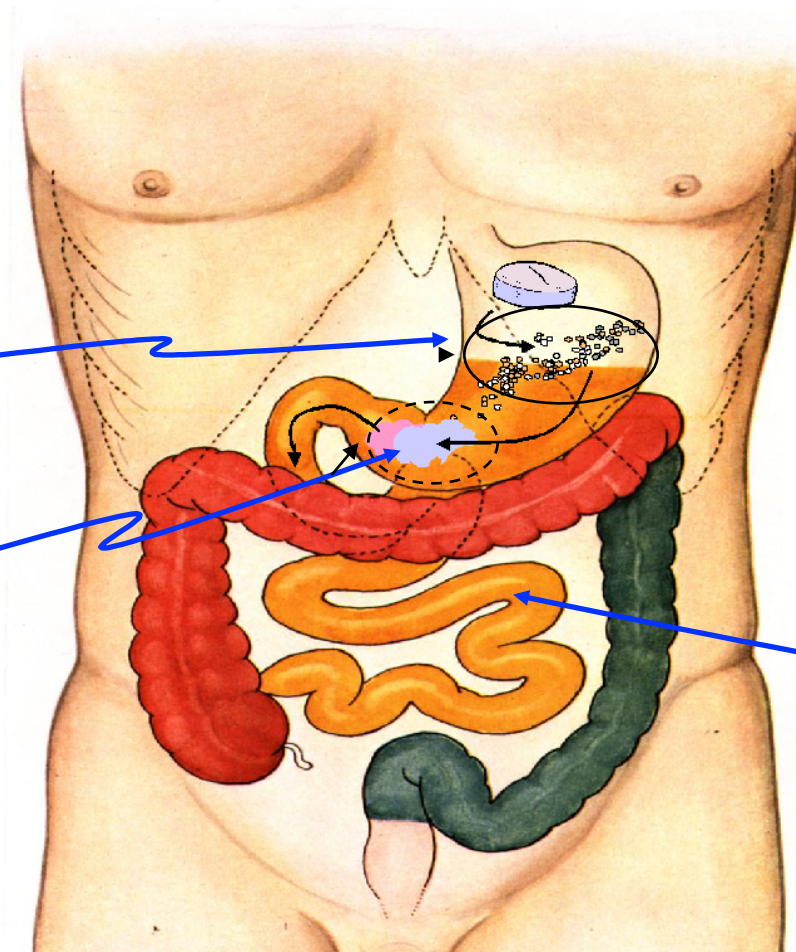
# Oral Absorption



**Disintegration**

**Dissolution**

**Gastric emptying**



Orally administered drugs predominantly absorbed in the small intestine

# First Pass Effect

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- The loss as drug passes, for the first time,
    - through sites of elimination, such as
      - the gastrointestinal membranes and
      - the liver,during absorption is known as the first-pass effect.
  - The term may also apply to other extravascular sites of administration, e.g.,
    - intramuscular and
    - subcutaneous.
-

# Distribution

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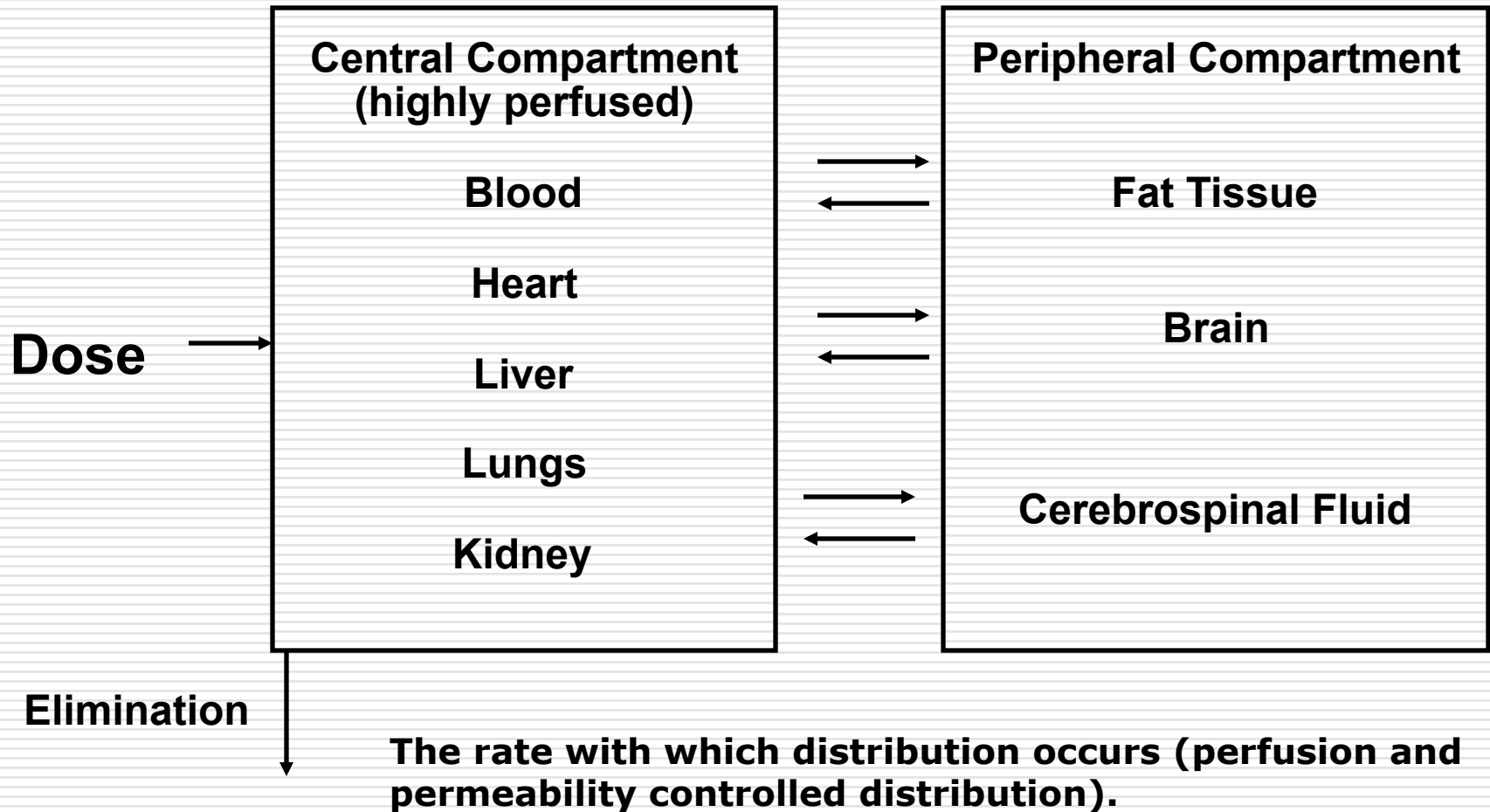
Reversible transfer of drug from one place to another place within the body

- Blood flow through tissues

Heart, lungs, kidneys, spleen, liver etc. equilibrates rapidly

- Permeability of drug to the tissues
  - Protein binding
-

**Drug molecules will distribute throughout the body (assuming drug is able to leave the central compartment)**



# Factors that influence distribution

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- **Perfusion**
- **Permeability**
- **Binding within blood and tissue**
- **Partitioning into fat**

**Tissue uptake, commonly called extravasation, continues toward equilibrium of the diffusible form between tissue and blood perfusing it.**

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# Introduction to Pharmacokinetics

## Elimination

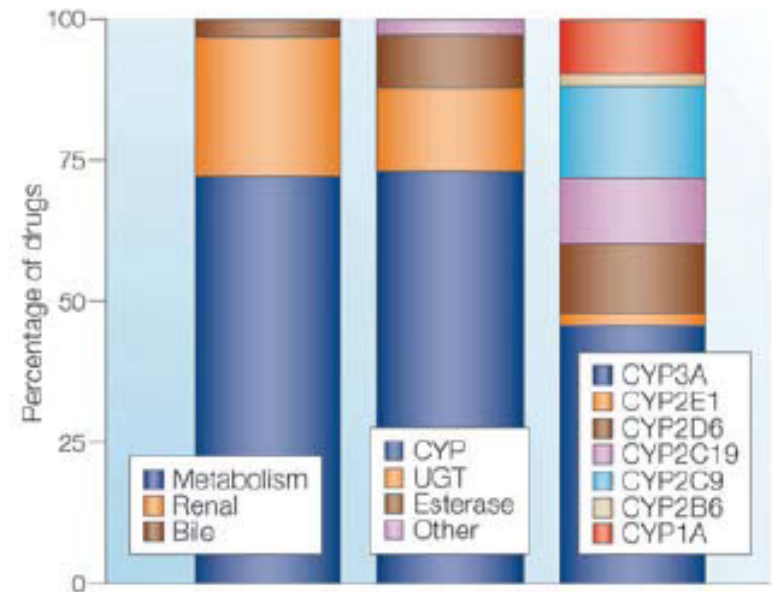
Irreversible loss of drug from the site of measurement

### 1. Metabolism:

Conversion of one chemical to another

### 2. Excretion

Irreversible loss of chemically unchanged drug



# Introduction to Pharmacokinetics

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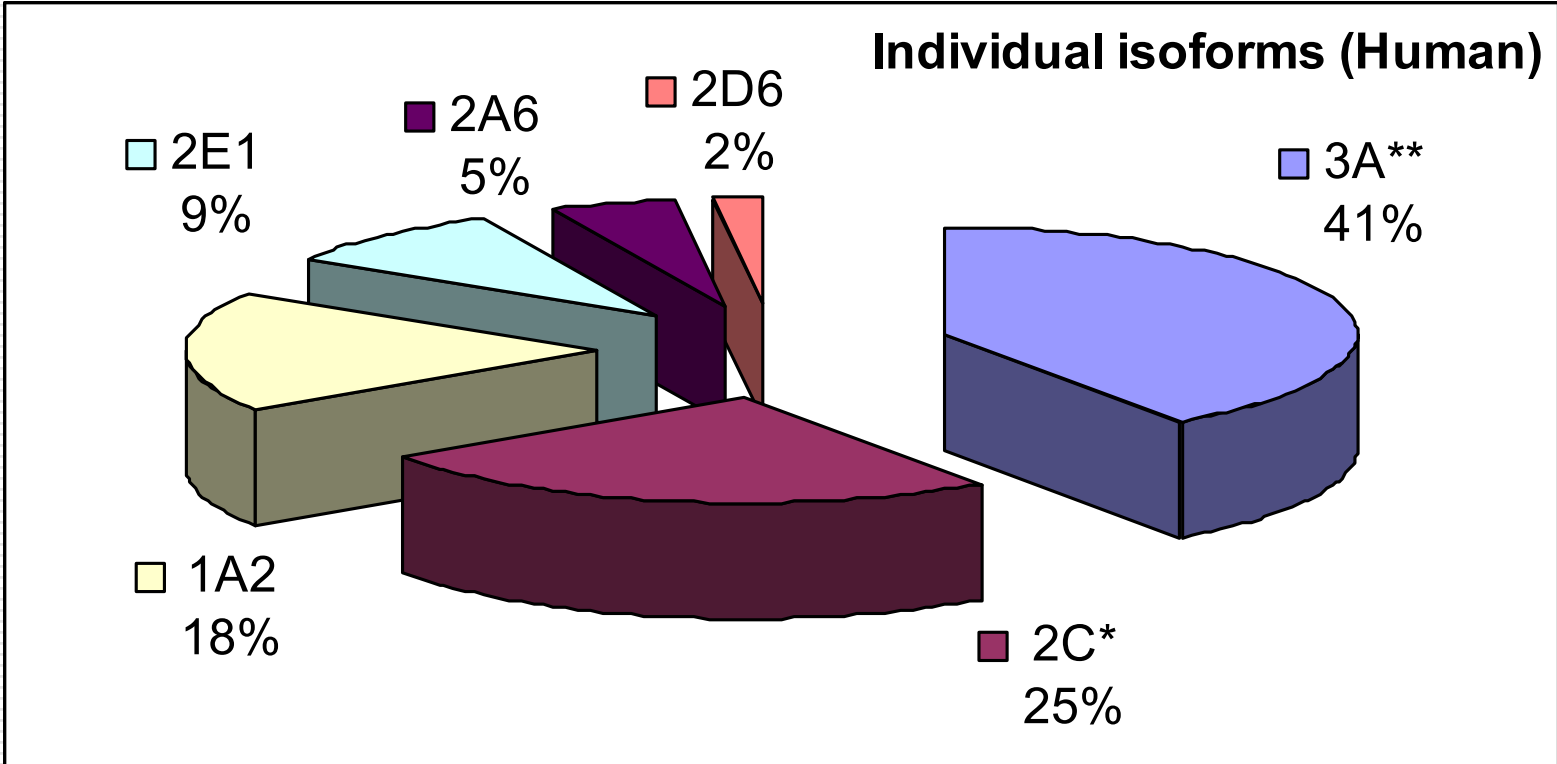
## Metabolism

- ❑ Overall goal to produce more polar compound
  - ❑ **Phase 1** (Oxidation, reduction, hydrolysis)
  - ❑ Major enzyme system involved is Cytochrome P 450
  - ❑ The enzymes can be induced or inhibited by many drugs
  - ❑ **Phase 2** (Conjugation reactions)
- Glucuronidation, Sulfation, Acetylation leads to more water soluble compounds
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Phase I Reactions of Biotransformation

Cytochrome P450 Enzyme System

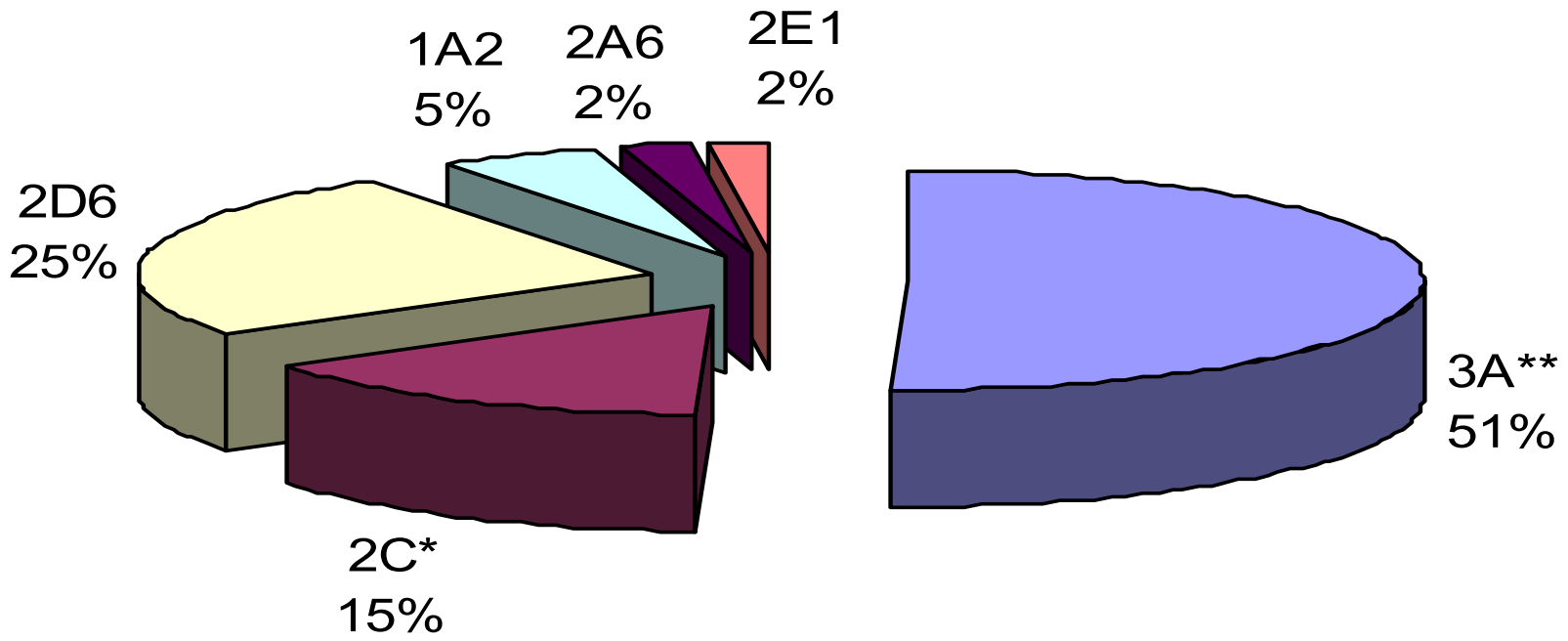
Metabolism



\*\* Sum of 3A3, 3A4, 3A5, and 3A7

\* Sum of 2C8, 2C9, 2C10, 2C18 and 2C19

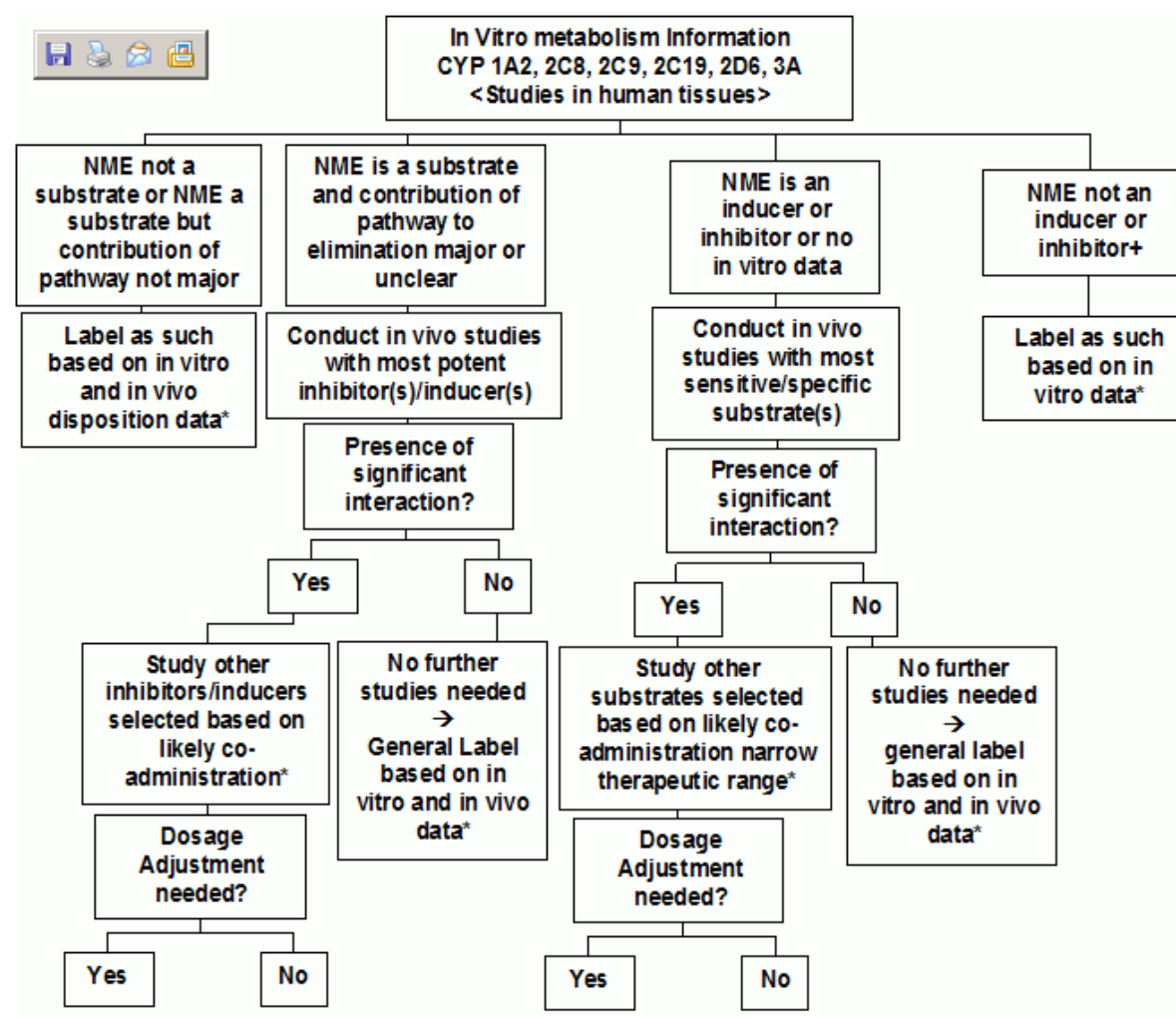
Drugs on the market metabolized by various P450 isoforms



\*\* Sum of 3A4 and 3A5  
\* Sum of 2C8, 2C9, 2C18 and 2C19

**Figure 1. CYP-Based Drug-Drug Interaction Studies**

- Refer to Journal of Clinical Pharmacology, 39:1006-1014, 1999
- See page 21 of the MaPP "[Clinical Pharmacology and Biopharmaceutics NDA Review Template](#)" 



NME: New molecular entity

\* Additional population pharmacokinetic analysis may assist the overall evaluation.

+ negative results from an in vivo cocktail study would preclude further evaluation to determine whether an NME is an inhibitor or particular CYP enzyme

# Introduction to Pharmacokinetics

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## **Excretion**

- ☐ Drugs or metabolites may be excreted by bile, kidneys, lungs, breast milk, saliva, sweat
  - ☐ Water soluble small drugs gets filtered through the glomerulus
  - ☐ Drugs or metabolites excreted through bile can lead to enterohepatic recirculation
-

# Patterns of biotransformation of representative drugs

| Prodrug | Drug                 | Active metabolite          | Inactive metabolite                                                                                               |
|---------|----------------------|----------------------------|-------------------------------------------------------------------------------------------------------------------|
|         | Acetylsalicylic acid | Salicylic acid (H)         | Salicyl (acid) glucuronide (C)<br>Salicyl (phenolic) glucuronide (C)<br>Salicyluric acid (C)<br>Gentisic acid (O) |
|         | Glutethimide         | Hydroxyglutethimide (O)    | Hydroxyglutethimide glucuronide (C)                                                                               |
|         | Morphine             | Morphine-6-glucuronide (C) | Morphine-3-glucuronide (C)                                                                                        |
|         | Phenytoin            |                            | p-Hydroxyphenytoin (O)                                                                                            |
|         | Prednisone           | Prednisolone (R)           |                                                                                                                   |
|         | Succinylcholine      |                            | Succinylmonocholine (H)                                                                                           |
|         | Theophylline         |                            | 1-Methylxanthine (O)<br>1,3-Dimethyluric acid (O)                                                                 |

**(O), oxidation; (R), reduction; (H), hydrolysis; (C), conjugation.**

# Description of clearance by organ, process or site of measurement

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- **Organ**

- Hepatic clearance or non-hepatic clearance
- Renal clearance or non-renal clearance
- Pulmonary clearance

- **Process**

- Metabolic clearance
- Excretory clearance

- **Site of measurement**

- Plasma
  - Blood
-

# Plasma versus blood clearance

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- If clearance is used to estimate extraction ratio, blood clearance is required.
- Plasma clearance is more often reported, but it can be converted to blood clearance if necessary.

$$\frac{\text{Plasma clearance}}{\text{Blood clearance}} = \frac{\text{Blood concentration}(C_B)}{\text{Plasma concentration}(C)}$$

$$\frac{C_B}{C} = 1 + H(\rho \cdot f_u - 1)$$

**H:** hematocrit

**$\rho$ :** affinity of blood cell for the drug

**$f_u$ :** unbound fraction

# Additivity of clearance

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- **The anatomy of the human body dictates the additivity of clearance.**

$$\text{Rate of elimination} = \text{Rate of renal excretion} + \text{Rate of hepatic metabolism}$$

$$\frac{\text{Rate of elimination}}{C} = \frac{\text{Rate of renal excretion}}{C} + \frac{\text{Rate of hepatic metabolism}}{C}$$

$$\text{Total clearance} = \text{Renal clearance} + \text{Hepatic clearance}$$

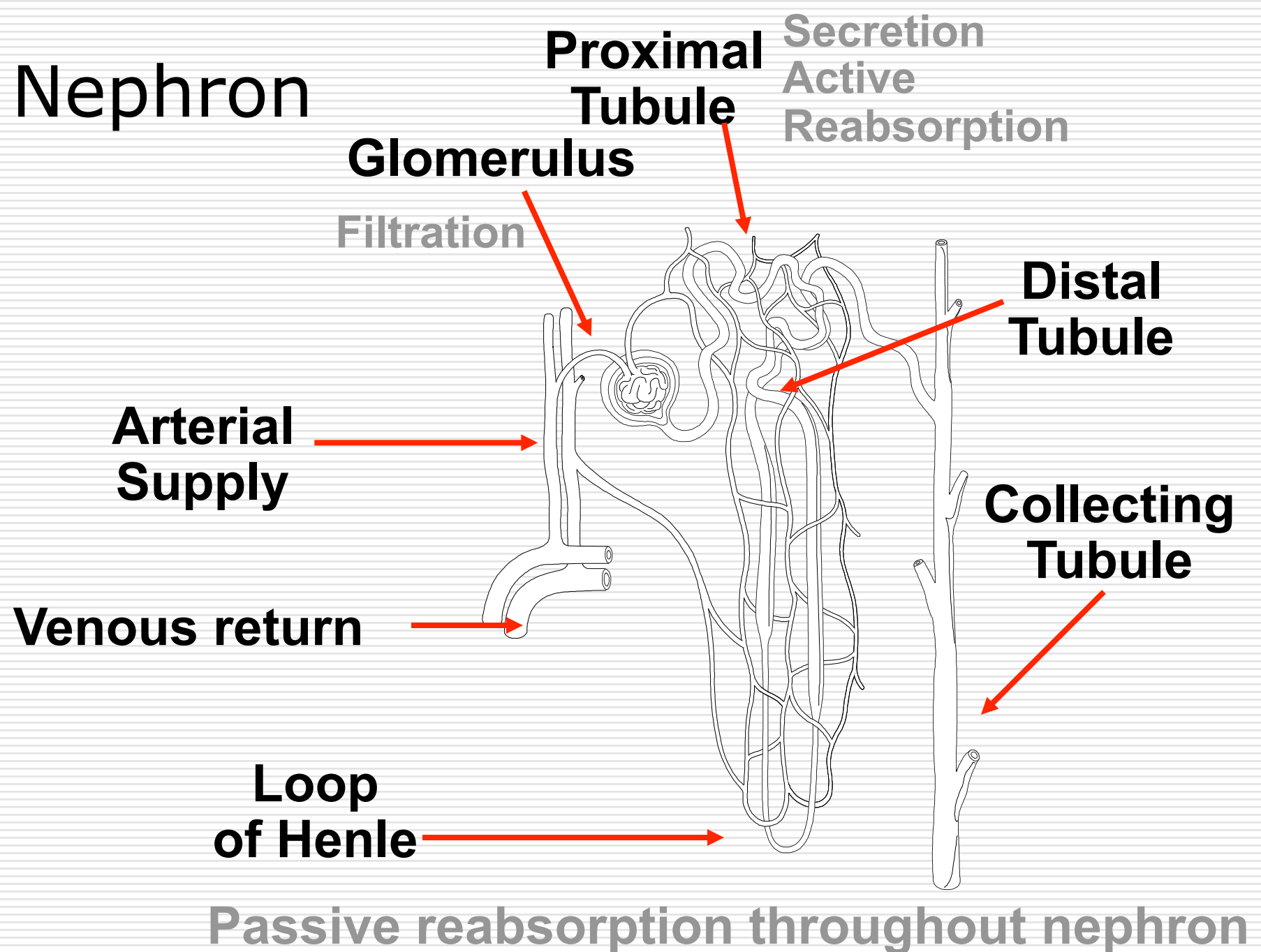
- **Exception: pulmonary clearance**

Serial blood flow relative to other organs

Total cardiac output through lungs

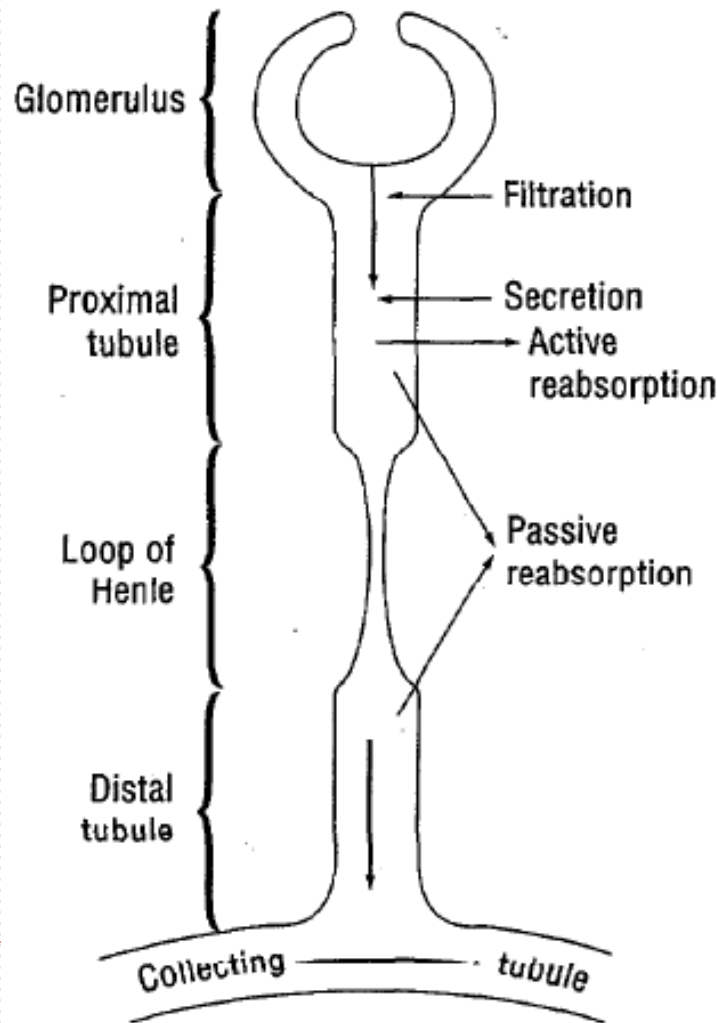
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# Nephron



# Filtration, secretion and reabsorption sites

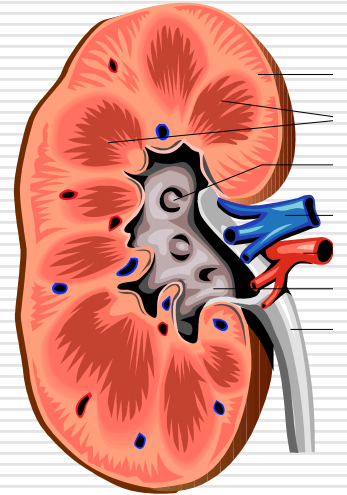
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# Renal Clearance

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- **Glomerular filtration**
- **Tubular reabsorption**
- **Tubular secretion**



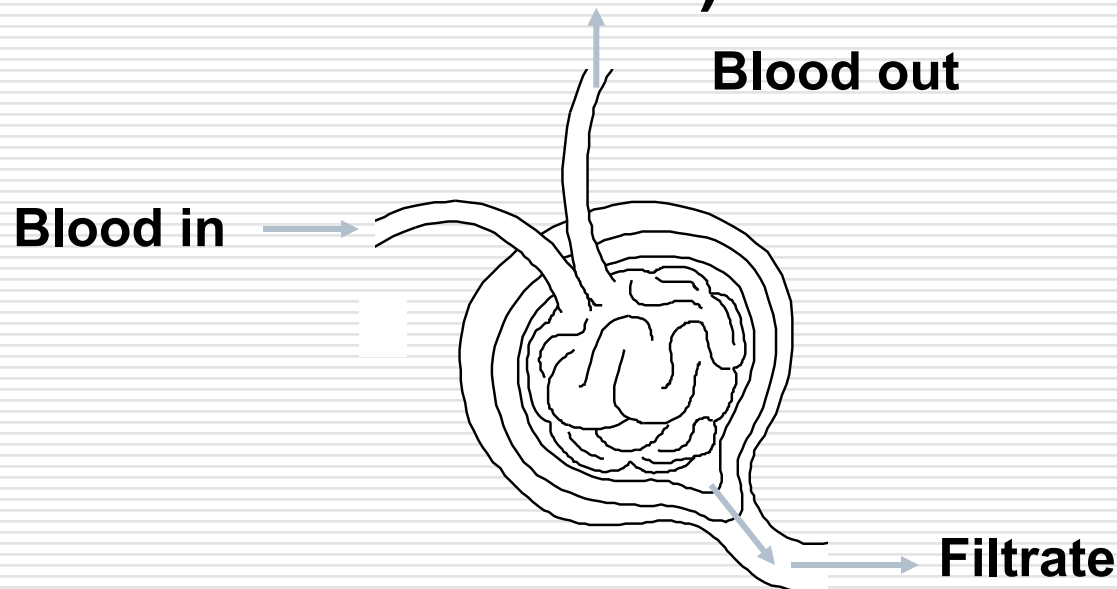
**All three will affect renal clearance**

$$Cl_{\text{ren}} = Cl_{\text{filtration}} - Cl_{\text{reabsorption}} + Cl_{\text{secretion}}$$

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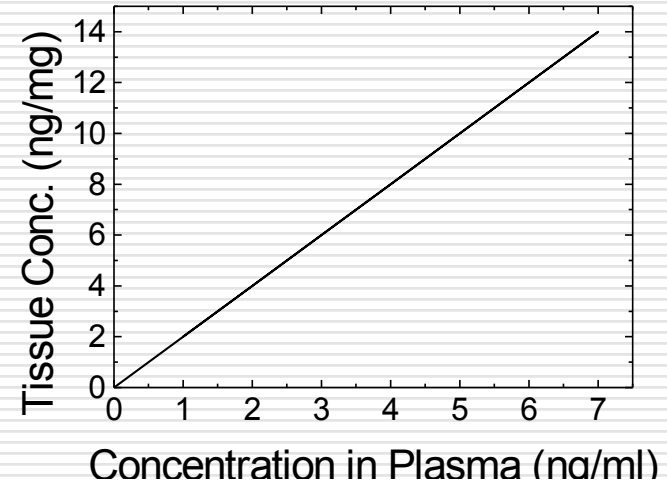
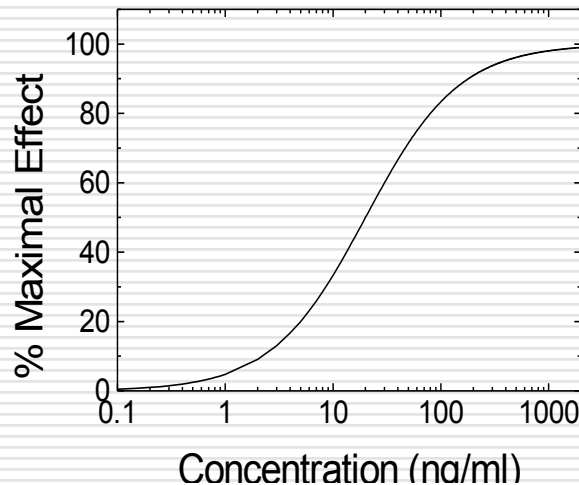
# Glomerular Filtration

- **Blood flows into capsule of the glomerulus**
- **There is passive filtration of fluids and solute across membrane**
- **Glomerula filtration rate 130 ml/min (about 10 % of blood flow 1.1 L/min)**



# Pharmacokinetics is important as:

- Often a correlation exists between drug concentration at the site of action (which we can't measure) and the pharmacological response



- However, quite often plasma levels are good predictors of concentration in tissue (they are not identical) but they can be used for dose optimization

# Introduction to Pharmacokinetics

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How the pharmacokinetics of a drug or metabolite is determined ?

## Invasive methods

Blood, Plasma, and CSF

## Non invasive methods

Urine, feces, saliva, breast milk etc.

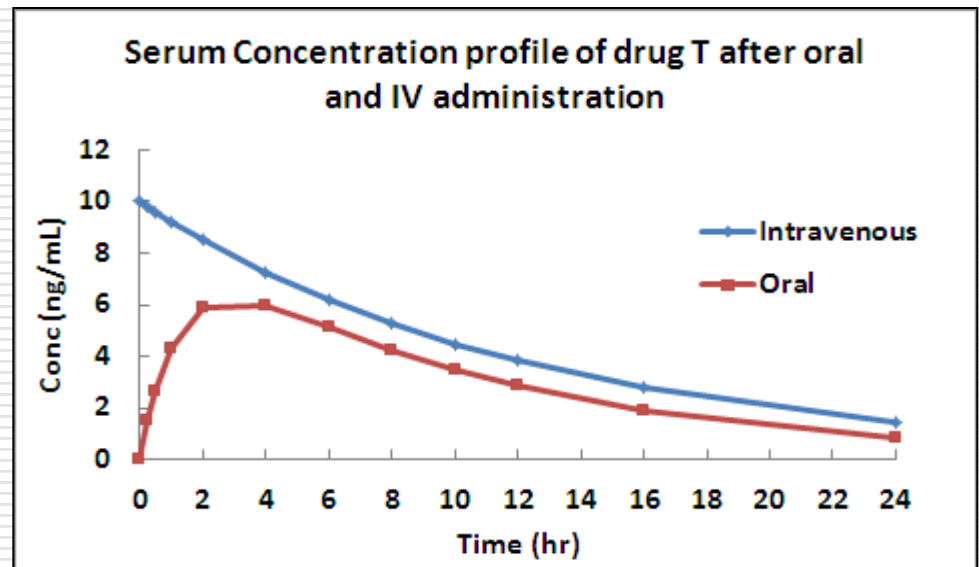
- Analyze these samples using LC/MS/MS or HPLC
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# Introduction to Pharmacokinetics

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- Tabulate Time vs Concentration
- Plot Time vs Concentration

| Time (hr) | Oral         | Intravenous  |
|-----------|--------------|--------------|
|           | Conc (ng/mL) | Conc (ng/mL) |
| 0         | 0.00         | 10.00        |
| 0.25      | 1.49         | 9.80         |
| 0.5       | 2.68         | 9.61         |
| 1         | 4.34         | 9.23         |
| 2         | 5.87         | 8.52         |
| 4         | 6.00         | 7.26         |
| 6         | 5.15         | 6.19         |
| 8         | 4.26         | 5.27         |
| 10        | 3.50         | 4.49         |
| 12        | 2.87         | 3.83         |
| 16        | 1.92         | 2.78         |
| 24        | 0.86         | 1.47         |



# Types of Kinetics Commonly Seen

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## ☐ Zero Order Kinetics

☐ Decreases at a constant rate

☐ Rate = k

☐  $C = C_0 - kt$

☐ C vs. t graph is LINEAR

## ☐ First Order Kinetics

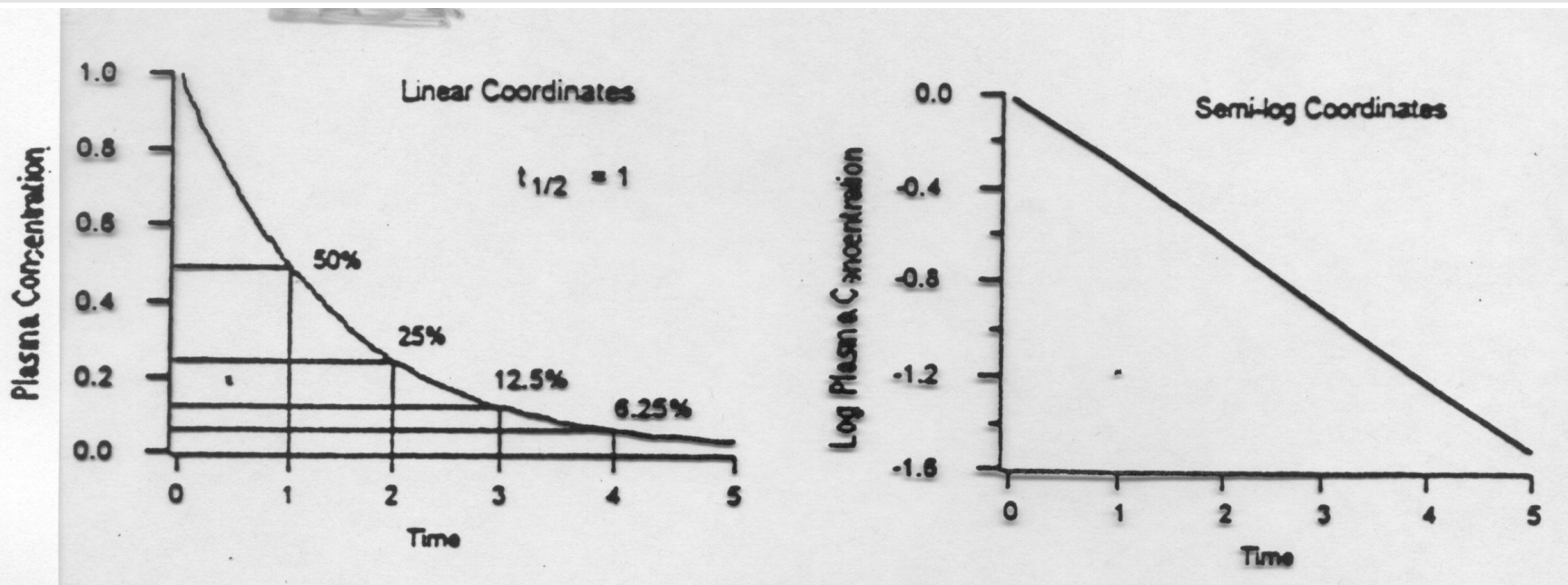
☐ Rate = k C

☐  $C = C_0 e^{-kt}$

☐ C vs. t graph is NOT linear, decaying exponential. Log C vs. t graph is linear.

# First-Order Kinetics

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# Comparison

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## □ First Order Elimination

- [drug] decreases exponentially w/ time
- Rate of elimination is proportional to [drug]
- Plot of  $\log$  [drug] or  $\ln$ [drug] vs. time are linear
- $t_{1/2}$  is constant regardless of [drug]

## □ Zero Order Elimination

- [drug] decreases linearly with time
- Rate of elimination is constant
- Rate of elimination is independent of [drug]
- No true  $t_{1/2}$

# Pharmacokinetic Models

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

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## Non-compartmental:

- Does not rely on any underlying assumptions on model development –
- Generally applies to first order linear models
- Most toxicokinetic, preclinical, phase I studies utilize this method
- Also appropriate for sparse data especially in toxicokinetic studies

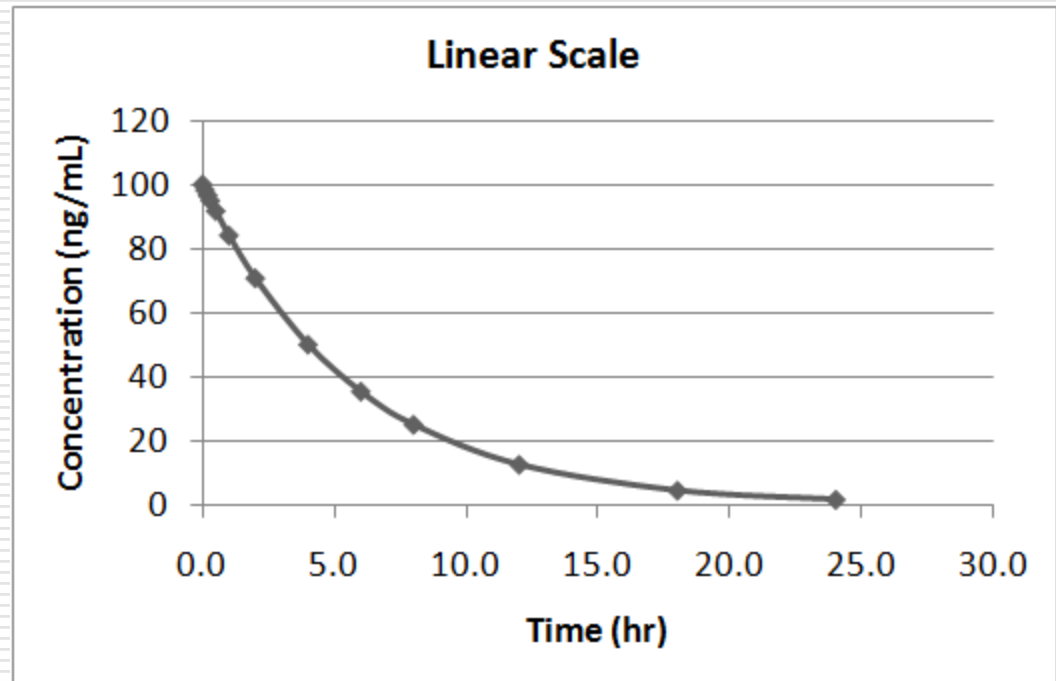
# Noncompartmental Pharmacokinetic Parameters

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- ☐ Bioavailability (F)
  - Absolute ( $F_{\text{abs}}$ ) and relative ( $F_{\text{rel}}$ )
- ☐ Elimination rate constant ( $k_{\text{el}}$ )
- ☐ Clearance (CL)
  - Total ( $CL_{\text{tot}}$ ), Renal ( $CL_{\text{ren}}$ ), Hepatic ( $CL_{\text{hep}}$ )
- ☐ Volume of distribution ( $V_d$ )
- ☐ Average steady-state concentration ( $C_{\text{avg,ss}}$ )
- ☐ AUC in a dosing interval ( $AUC_t$ )
- ☐ Minimum concentration ( $C_{\text{min}}$ )
- ☐ Average concentration ( $C_{\text{avg}}$ )
- ☐ Many others...
- ☐ AUMC- area under the first moment curve
- ☐ MRT- mean residence time
- ☐ MAT-mean absorption time
- ☐ MDT- mean dissolution time

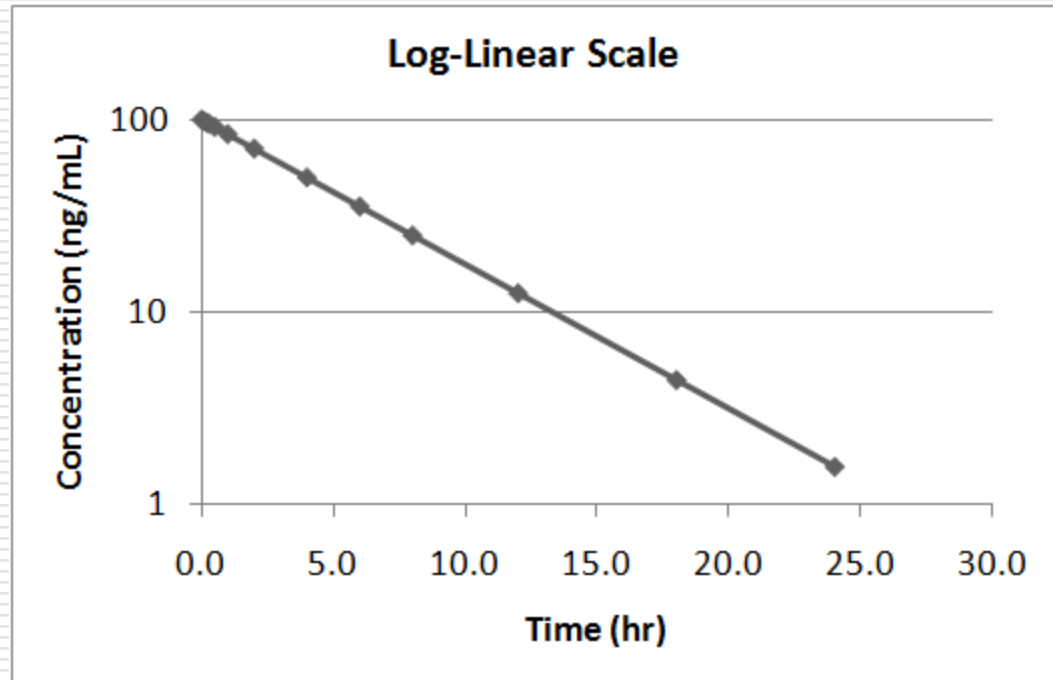
# Intravenous Bolus PK Profile

| Time (hr) | Conc (ng/mL) |
|-----------|--------------|
| 0.0       | 100          |
| 0.1       | 98           |
| 0.2       | 97           |
| 0.3       | 95           |
| 0.5       | 92           |
| 1.0       | 84           |
| 2.0       | 71           |
| 4.0       | 50           |
| 6.0       | 35           |
| 8.0       | 25           |
| 12.0      | 13           |
| 18.0      | 4            |
| 24.0      | 2            |



# Intravenous Bolus PK Profile

| Time (hr) | Conc (ng/mL) |
|-----------|--------------|
| 0.0       | 100          |
| 0.1       | 98           |
| 0.2       | 97           |
| 0.3       | 95           |
| 0.5       | 92           |
| 1.0       | 84           |
| 2.0       | 71           |
| 4.0       | 50           |
| 6.0       | 35           |
| 8.0       | 25           |
| 12.0      | 13           |
| 18.0      | 4            |
| 24.0      | 2            |



# First Order Process

Rate of change is proportional to initial amount

$$\frac{dA}{dt} \propto A$$

$$\frac{dA}{dt} = -k.A$$

$$\frac{dA}{A} = -k.dt$$

$$\int \frac{dA}{A} = \int -k.dt$$

$$\ln A + C = -kt$$

$$e^{\ln A + C} = e^{-kt}$$

$$e^{\ln A} . e^C = e^{-kt}$$

$$A . e^C = e^{-kt}$$

$$A = \frac{e^{-kt}}{e^C}$$

$$A_0 = \frac{e^0}{e^C} = \frac{1}{e^C}$$

At  $t=0$

$$A = A_0 e^{-kt} \quad C = C_0 e^{-kt}$$

$$\frac{d}{dx} \ln x = \frac{1}{x}$$

$$d \ln x = \frac{dx}{x},$$

$$\int d \ln x = \int \frac{dx}{x},$$

$$\ln x + C = \int \frac{dx}{x}.$$

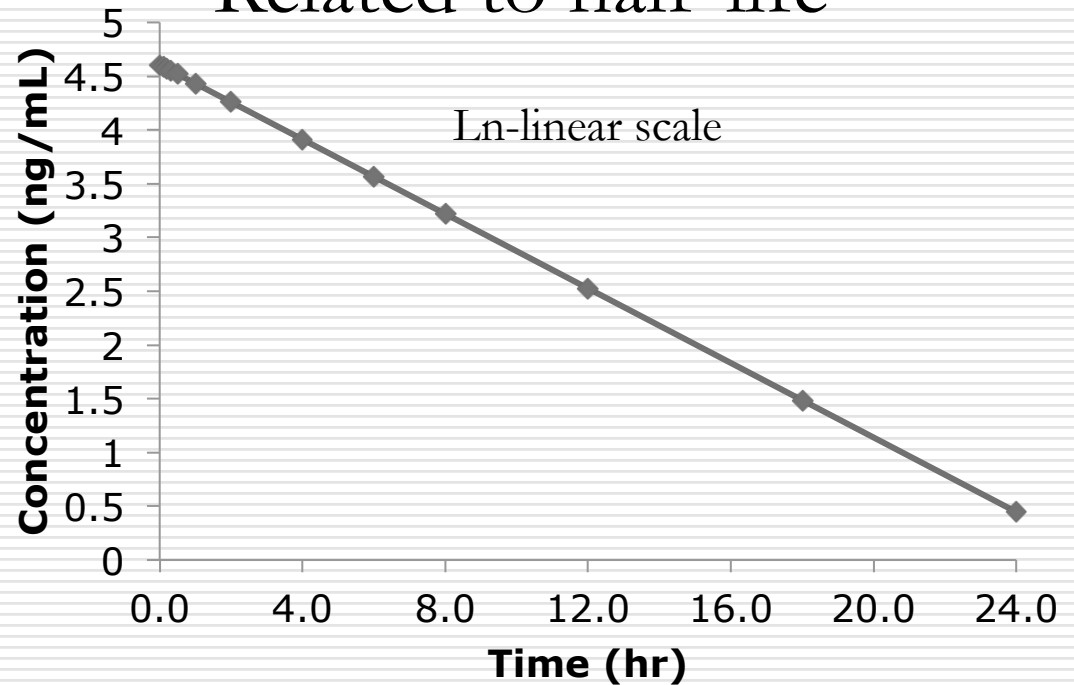
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$$C = C_0 e^{-kt}$$

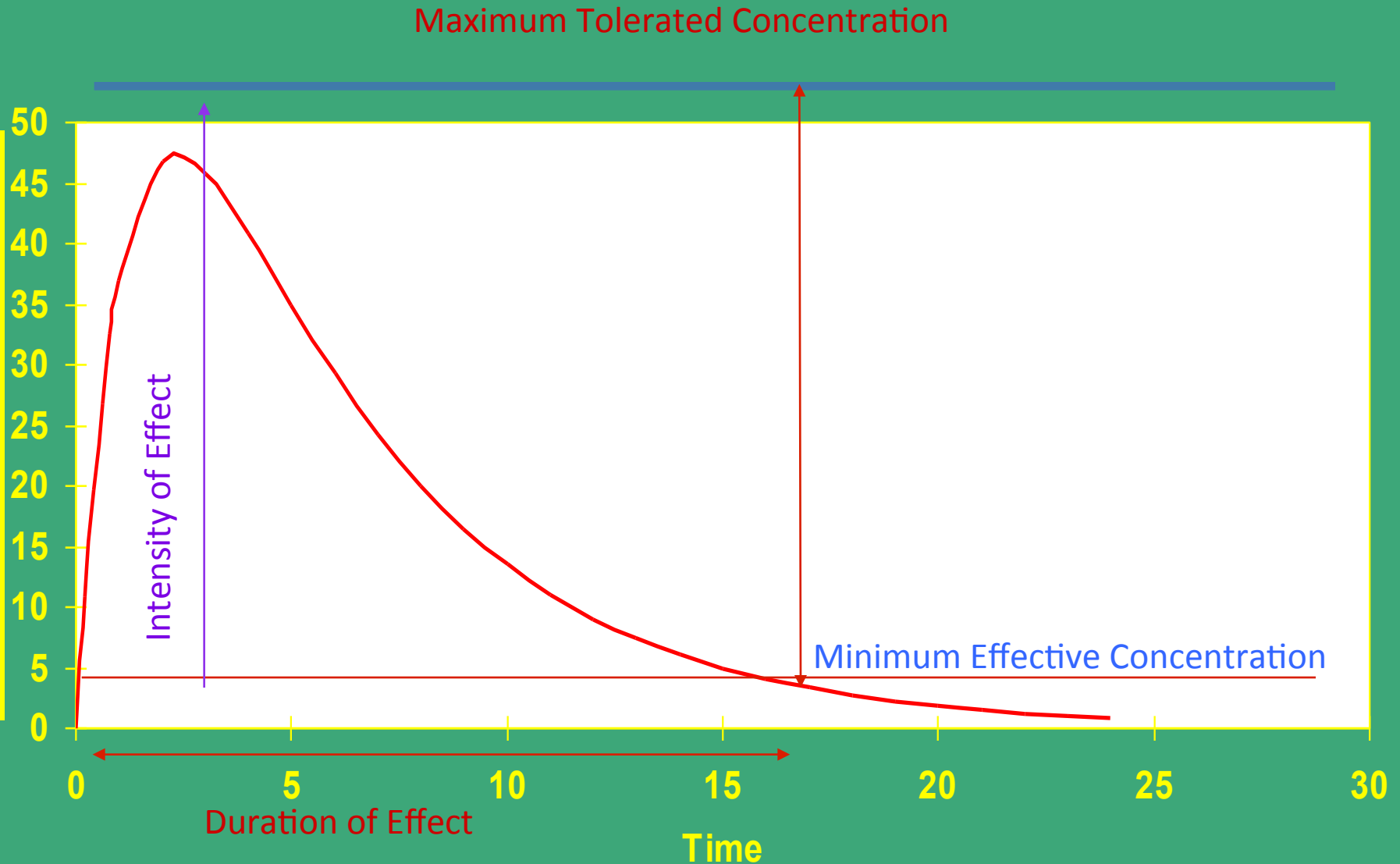
$$\ln C = -kt + \ln C_0$$

$$y = mx + b$$

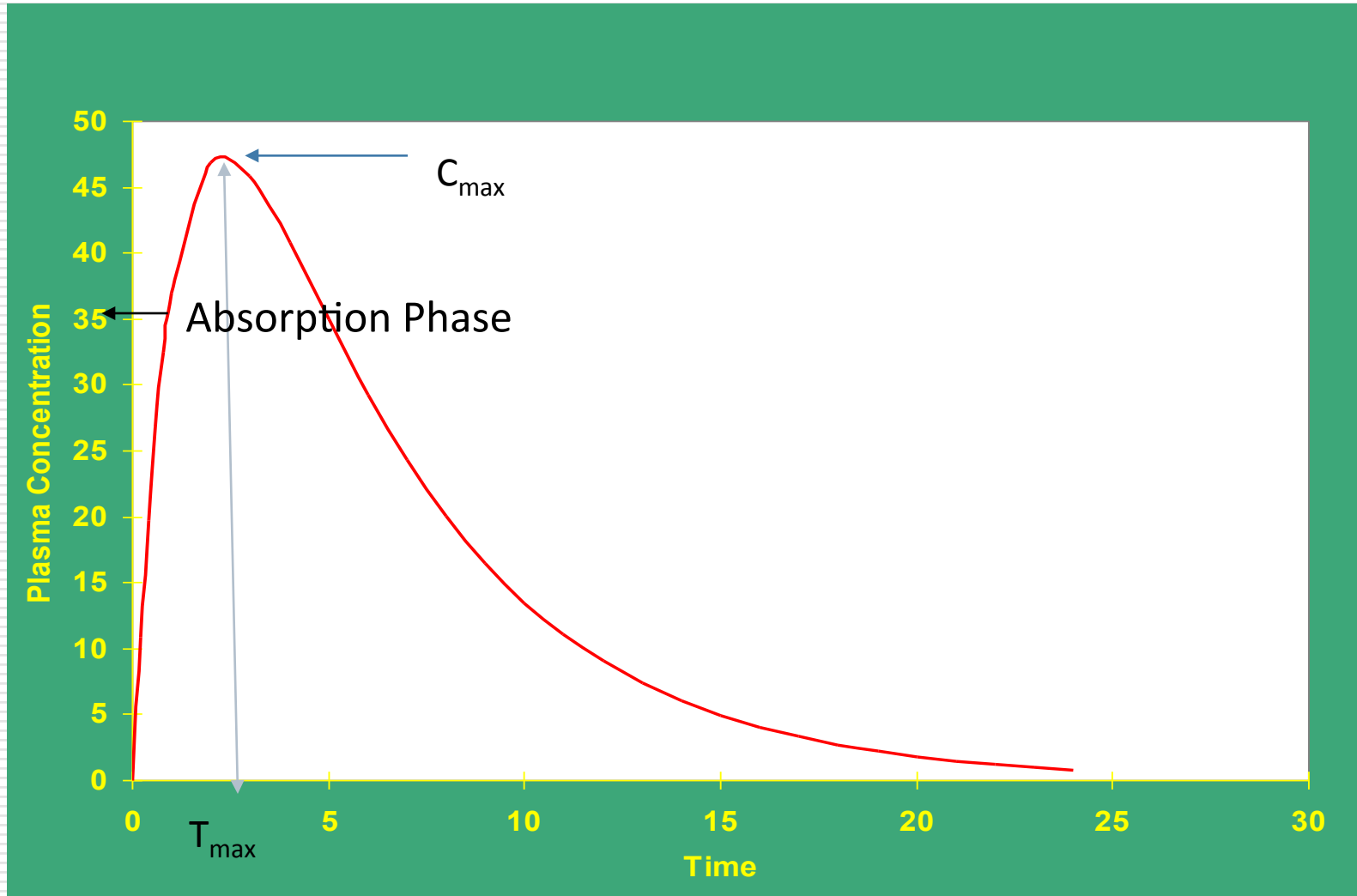
K is the elimination rate constant  
Related to half life



# Why Are Plasma Concentrations Important?

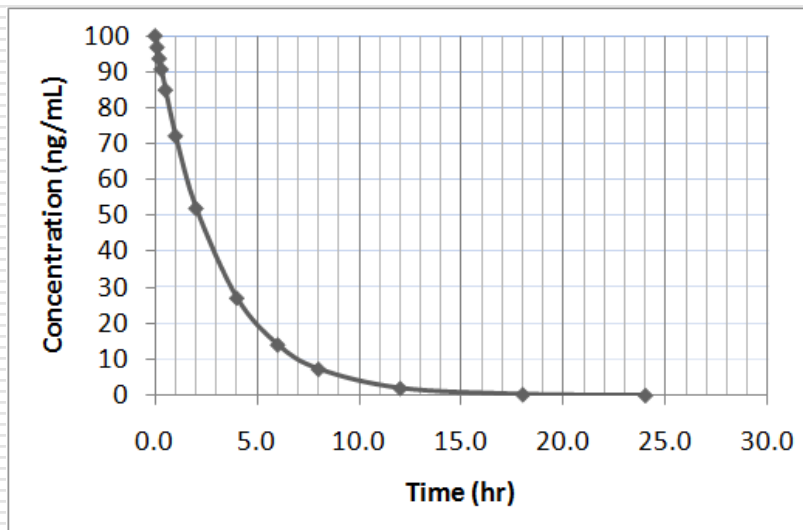


# What is $C_{\max}$ ?

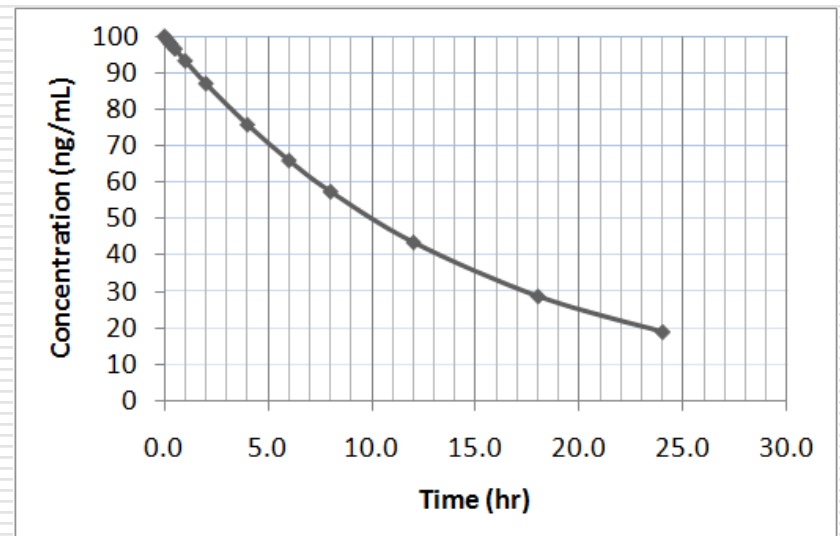


# Half-Life

Half-life is the time taken to reach half of the initial concentration



2-hr half life



10-hr half life

$$C = C_0 e^{-kt}$$

$$\ln C = -kt + \ln C_0$$

---

Lets consider the situation where the concentration is equal to half of the initial concentration

$$\ln(C_0/2) = -kt + \ln C_0$$

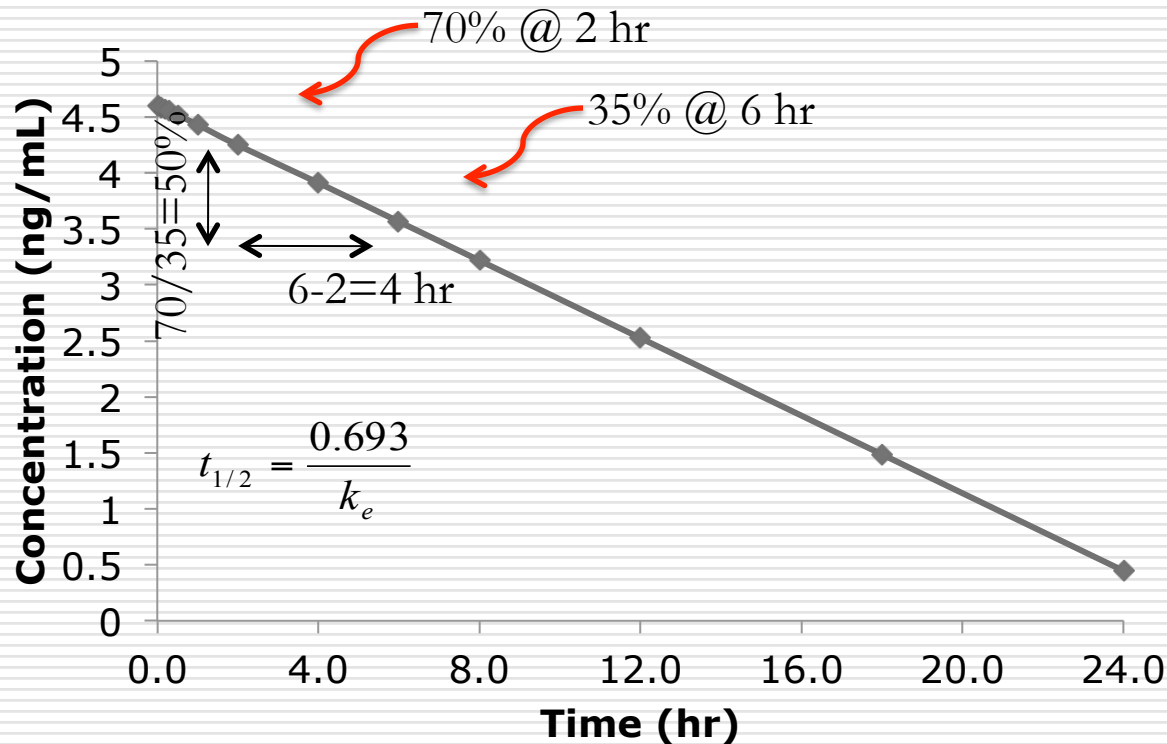
$$kt = \ln C_0 - \ln(C_0/2)$$

$$kt = \ln(2)$$

$$t = \frac{\ln(2)}{k} = \frac{0.693}{k}$$

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

# Determining $T_{1/2}$



$$K_e = \text{Slope} = (y_2 - y_1) / (x_2 - x_1) = (3.5657 - 4.2485) / (6 - 2) = 0.6828 / 4 = 0.1707$$

$$T_{1/2} = 0.693 / 0.1707 = 4 \text{ hr}$$

# Volume of distribution ( $V_d$ )

---

- $V_d$  is the apparent volume of distribution
- Not a 'real' volume but a theoretical volume that has no real physiological meaning
- Defined as that volume of plasma in which the total amount of drug in the body would be required to be dissolved in order to reflect the drug concentration attained in plasma.

# Volume of Distribution

---

$$A = A_0 e^{-kt} ; \quad C = \frac{A}{V}$$

$$\therefore C = C_0 e^{-kt}$$

$$C_0 = \frac{A_0}{V_d} = \frac{D}{V_d}$$

Volume of distribution is the theoretical volume of plasma in which the drug is distributed

# Clearance

---

- Clearance is the theoretical volume of plasma that is completely cleared of the drug per unit time
- Related to  $V_d$  and elimination rate

$$Cl = k_e * V_d$$

$$Cl = \frac{0.693 * V_d}{T_{1/2}}$$

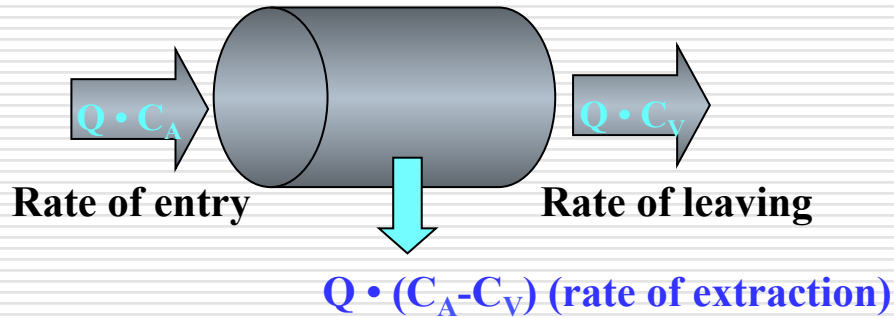
# Concept of clearance

---

- Clearance has the greatest potential for clinical applications among all PK concepts.
  - Clearance is the most useful parameter for the evaluation of an elimination mechanism.
  - Clearance is the proportionality factor relating rate of drug elimination to the plasma (drug) concentration, i.e.  $\frac{dA_e}{dt} = CL \cdot C$ .
-

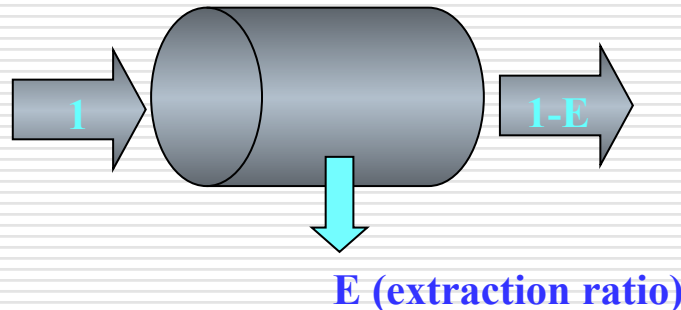
# Loss across an organ of elimination

## 1. Mass balance



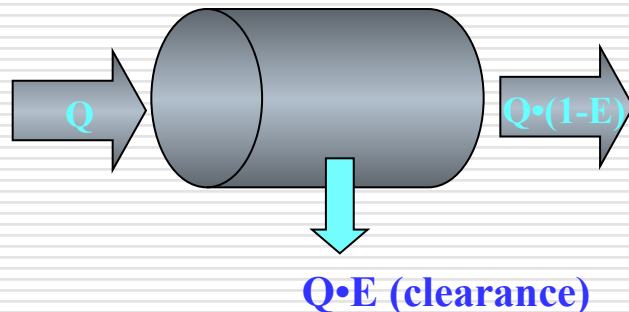
$$\text{Rate of extraction} = Q \cdot (C_A - C_V)$$

## 2. Mass balance normalized to rate of entry



$$E = \frac{\text{Rate of extraction}}{\text{Rate of presentation}} = \frac{C_A - C_V}{C_A}$$

## 3. Mass balance normalized to entering concentration



$$\text{Clearance} = \frac{Q \cdot (C_A - C_V)}{C_A} = Q \cdot E \leq Q$$

# Additive Clearance

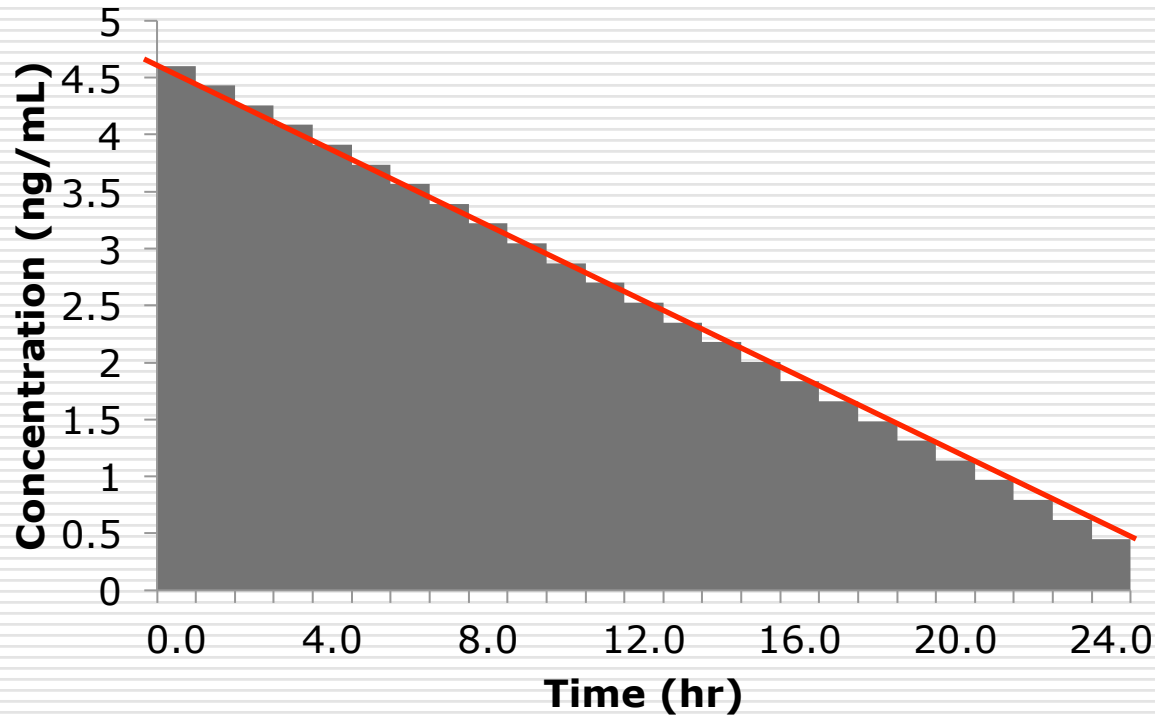
---

- Clearance is the theoretical volume of plasma that is completely cleared of the drug per unit time
- Plasma clearance is a sum of various clearance mechanisms

$$Cl_{total} = Cl_{metabolism} + Cl_{renal} + Cl_{biliary} + Cl_{expired} + Cl_{salivary} \dots$$

# Exposure (AUC)

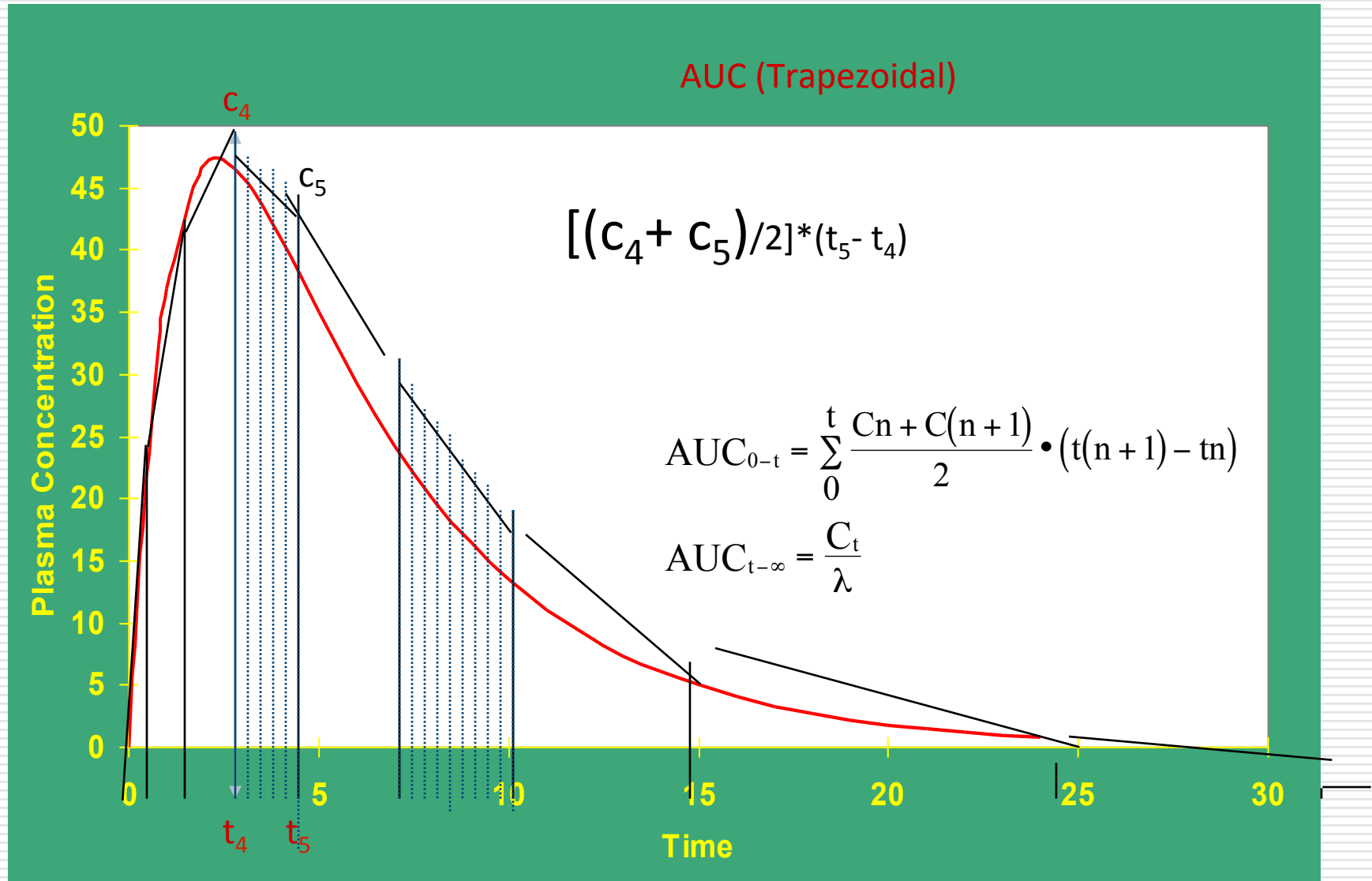
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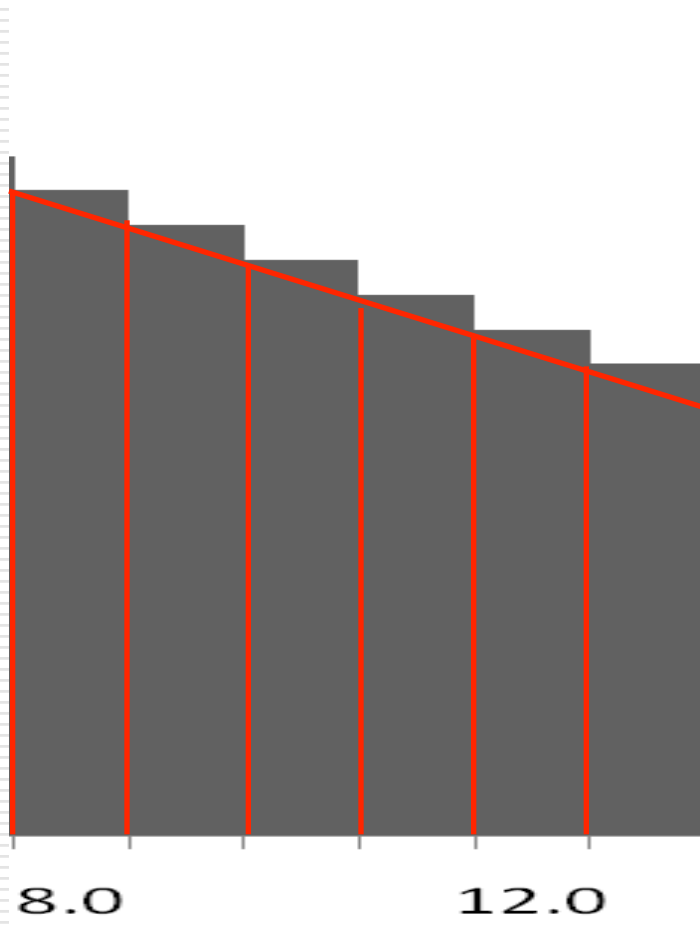
AUC= Area Under the Curve  
Signifies the extent of absorption

---

# What is Area Under the Curve (AUC, ng\*h/mL)?



- AUC (ng\*h/mL) signifies the extent of absorption*



Area of Rectangle = Length\*Breadth

$$\text{Area of a trapezoid} = \frac{(L_1 + L_2)}{2} * B$$

$$\sum_0^t \text{Area of trapezoid} = AUC_{0-t}$$

$$AUC_{0-t}$$

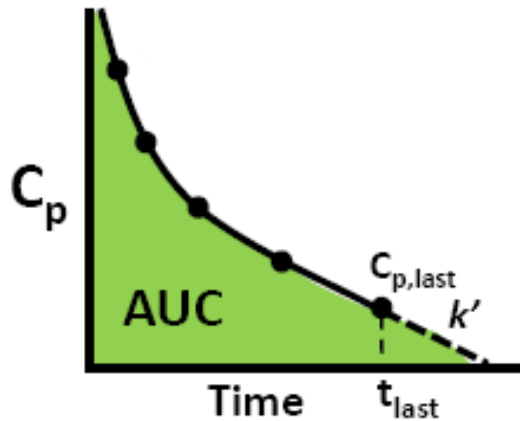
$$AUC_{0-24}$$

$$AUC_{0-\tau}$$

$$AUC_{0-\infty}$$

# AUC (extrapolated to infinity)

## □ Numerical Calculation:



$$AUC = \underbrace{AUC_{0-t_{last}}}_{\text{Calculated Interval Areas (Trapezoidal Rule)}} + \underbrace{\frac{C_{P,last}}{k'}}_{\text{AUC}_{(last-\infty)} \text{ (Extrapolate from } t_{last} \text{ to } t=\infty)}$$

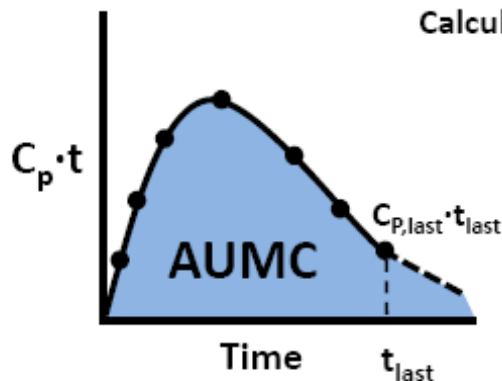
where  $k'$  is the terminal slope from semi-log graph of  $C_p$  vs. time

# Area under the first moment curve (AUMC)

$$M_1 = \int_0^{\infty} t \cdot C_p dt = AUMC$$

## □ Numerical Calculation:

$$AUMC = AUMC_{0-t_{last}} + \frac{C_{P,last} \cdot t_{last}}{k'} + \frac{C_{P,last}}{k'^2}$$



Calculated Interval Areas  
(Trapezoidal)

$AUMC_{(last-\infty)}$   
(Extrapolation)

where  $k'$  is the terminal slope from  
semi-log graph of  $C_p$  vs. time  
(Same  $k'$  used for  $AUC_{(last-\infty)}$ )

AUMC: Area under the first moment curve

# Utility of AUMC

---

$$MRT = \frac{AUMC}{AUC}$$

- MRT: Mean Residence Time, the average time that drug molecules remain in the body after dosing.
- Apparent elimination rate constant ( $kel'$ )

$$kel' = \frac{1}{MRT} \quad \text{for an IV dose of drug}$$

- Used for calculation of other parameters, particularly  $V_{ss} = MRT \cdot CL$

---

# ORAL PHARMACOKINETICS

# Bioavailability

---

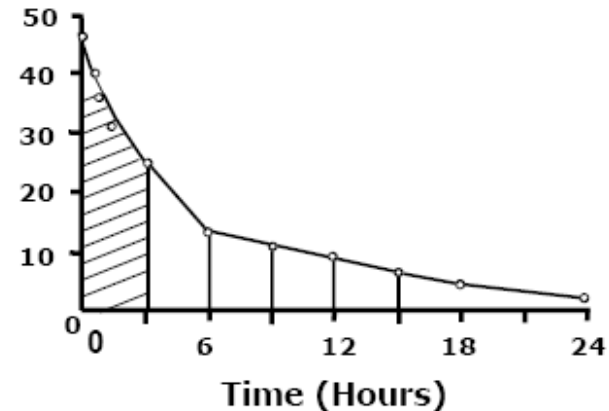
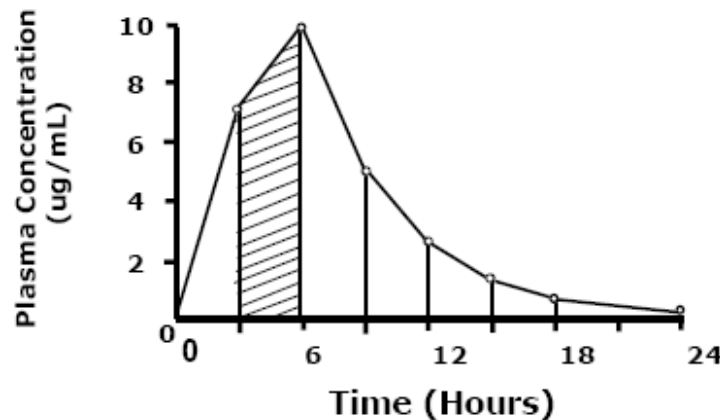
- ❑ **Bioavailability** (designated as **F**) is defined as the fraction of the administered drug reaching the systemic circulation intact (i.e., not metabolized or chemically altered in any way).
- ❑  $F = 100\%$  for intravenously administered drugs
- ❑  $F \leq 100\%$  for orally administered drugs
- ❑  $F$  affected by metabolism, reduced absorption (efflux transporters, poor solubility, etc.)

---

**Bioavailability:** Fraction of drug that reaches systemic circulation

- Solubility, Permeability, First pass metabolism
  - Blood flow to site of absorption
  - Degradation
  - Gastric emptying and intestinal transit time
-

# Pharmacokinetics



- Characterize the rate and extent of drug movement in the body
- Absolute bioavailability
- Concentrations in effect compartment or surrogate
- Determine PK parameters such as volume of distribution, clearance,  $T_{1/2}$ , bioavailability

# Oral Clearance

---

$$\frac{CL_{app}}{F} = \frac{Dose}{AUC}$$

- Is an apparent clearance estimated after oral dosing
- Frequently greater than “systemic clearance” since F can be less than “1”
- Highly dependent on bioavailability

# Utility of AUC

---

- Determination of Absolute Bioavailability (F)

$$F = \frac{AUC_{PO} \times Dose_{IV}}{AUC_{IV} \times Dose_{PO}}$$

- Total Clearance (CL)  
 $CL = Dose/AUC$

$$CL = \frac{dA_e / dt}{C_p} = \frac{\text{Elimination Rate}}{C_p}$$

$$\text{Thus : } \frac{dA_e}{dt} = CL \cdot C_p \quad \text{Rearrange}$$

$$\text{Integrate : } \int_0^{\infty} dA_e = CL \cdot \int_0^{\infty} C_p \cdot dt$$

$$A_e^{\infty} = Dose = CL \cdot AUC$$

# Compartmental Modeling

---

- Compartmental: uses intensive phase I and II data to develop and establish model - applications to PK/PD and population pharmacokinetic research
-

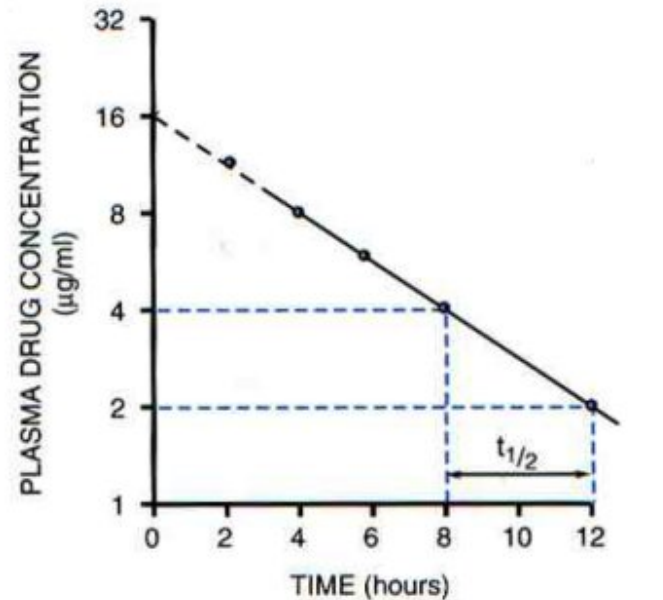
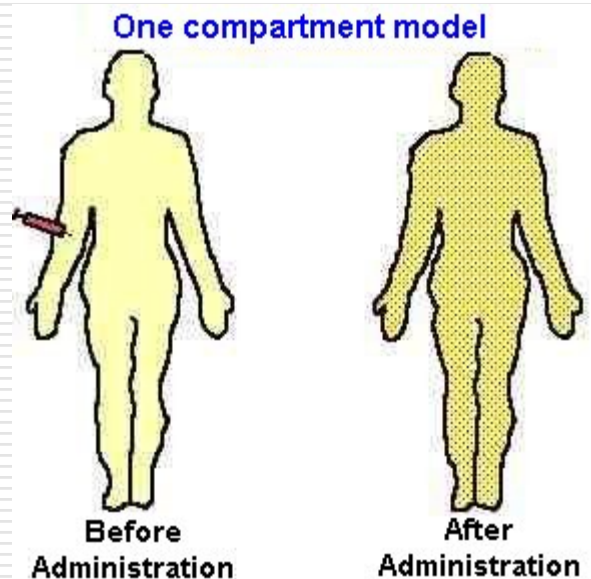
# Uses of Compartmental Modeling

---

- Obtain good estimates of physiological parameters, e.g.  $K_a$ ,  $Cl$
- Do simulations to estimate administered dose necessary to achieve a therapeutic range of plasma levels
- Predict concentrations in a compartment which can't be measured directly
- Predict how differing drug release characteristics will affect bioavailability
- Determine the relationship between PK and PD
- Predict the effect of a loading dose on plasma concentrations

# Pharmacokinetic Models

## □ One compartment model



A **one-compartment model** may be used for drugs which rapidly equilibrate with the tissue compartment,  
e.g, aminoglycosides.

A log scale plot of the serum level decay curve of a 1-compartment model yields a **straight line**.

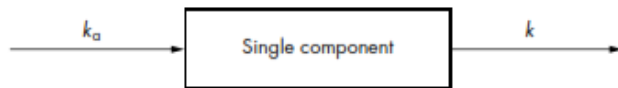
*EduCater*

*Building Knowledge - Inspiring Minds*

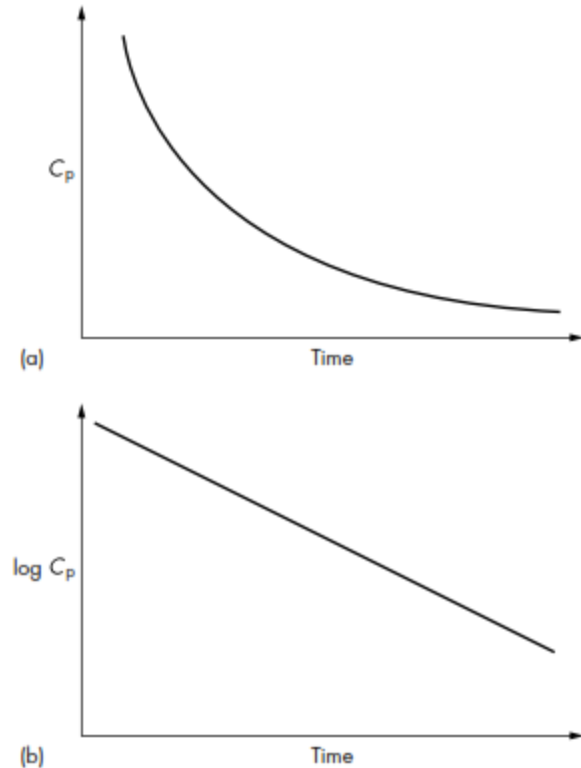
[http://www.rxkinetics.com/pktutorial/1\\_5.html](http://www.rxkinetics.com/pktutorial/1_5.html)

# One compartment model

- Body is depicted as kinetically homogenous unit
- Achieves instantaneous distribution throughout body
- Shows monophasic response
- Plasma concentration quantitatively reflects the changes in tissues



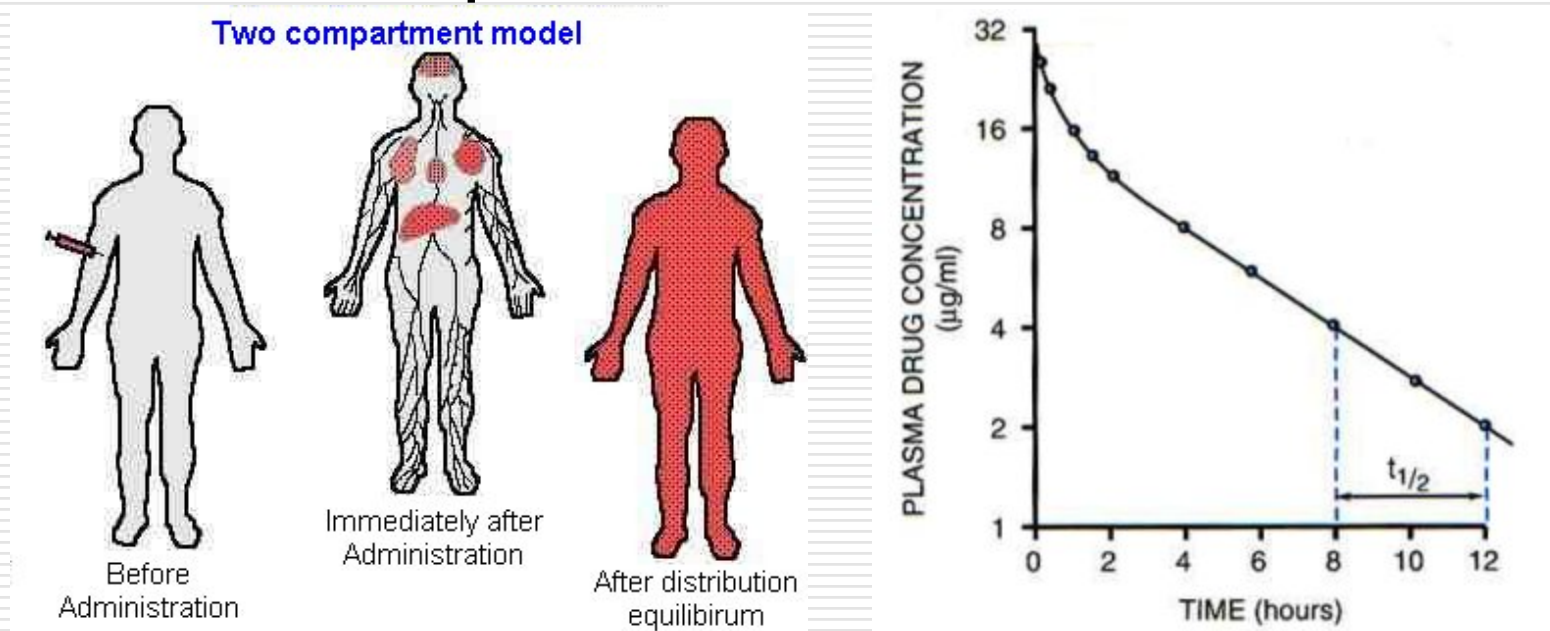
**Figure 1.1** One-compartment model.  $k_a$  = absorption rate constant ( $\text{h}^{-1}$ ),  $k$  = elimination rate constant ( $\text{h}^{-1}$ ).



**Figure 1.2** (a) Plasma concentration ( $C_p$ ) versus time profile of a drug showing a one-compartment model. (b) Time profile of a one-compartment model showing  $\log C_p$  versus time.

# Pharmacokinetic Models

## □ Two compartment model

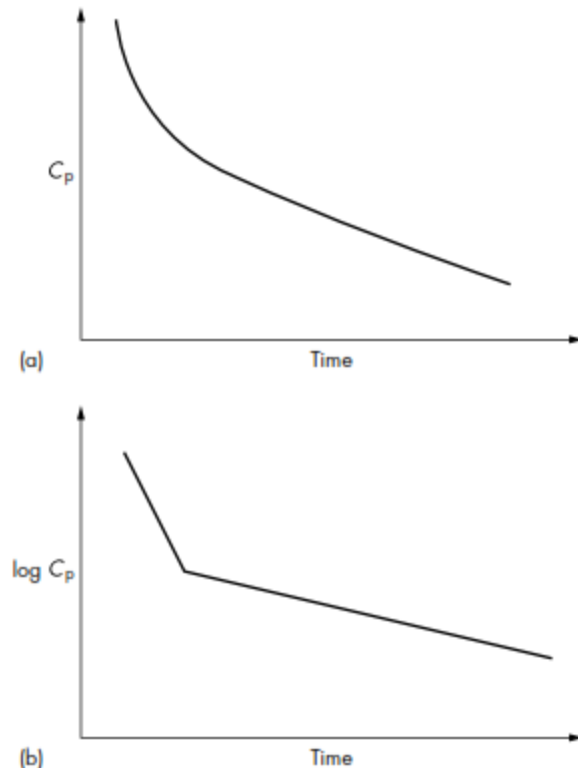
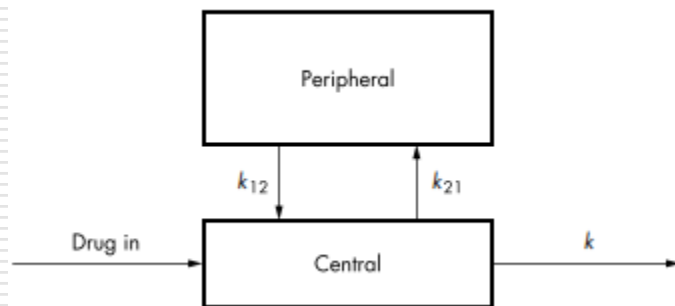


A **two-compartment model** should be used for drugs which slowly equilibrate with the tissue compartment, e.g, vancomycin.

A log scale plot of the serum level decay curve of a 2-compartment model yields a **biphasic line**.

# Two compartment model

- Body is depicted as central and peripheral compartment
  - Compartments have no physiological or anatomical meaning
- Central: highly perfused (heart, kidney, lungs, liver and brain)
- Peripheral: less well-perfused (skin, muscle, fat)
- Shows biphasic response



**Figure 1.4** (a) Plasma concentration versus time profile of a drug showing a two-compartment model. (b) Time profile of a two-compartment model showing  $\log C_p$  versus time.

# Recommended Steps for Compartmental PK analysis

---

- 1) Explore concentration-time data visually
  - 2) Select compartmental model(s) to fit to the data using non-linear regression
  - 3) Determine initial values of the PK parameters
  - 4) Estimate the PK parameters using a computer programme with nonlinear regression.
  - 5) Re-run the nonlinear regression with different initial values of the PK parameters to ensure the programme has converged at the global minimum not a local minimum.
  - 6) Assess how well the compartmental PK model(s) explains the individual's concentration-time data:
    - a) Visually – Observed and predicted concentrations versus time, Residuals versus predicted concentrations;
    - b) Precision of parameter estimates
    - c) Goodness of fit – Akaike Information Criteria (AIC) for comparing different compartmental models
-

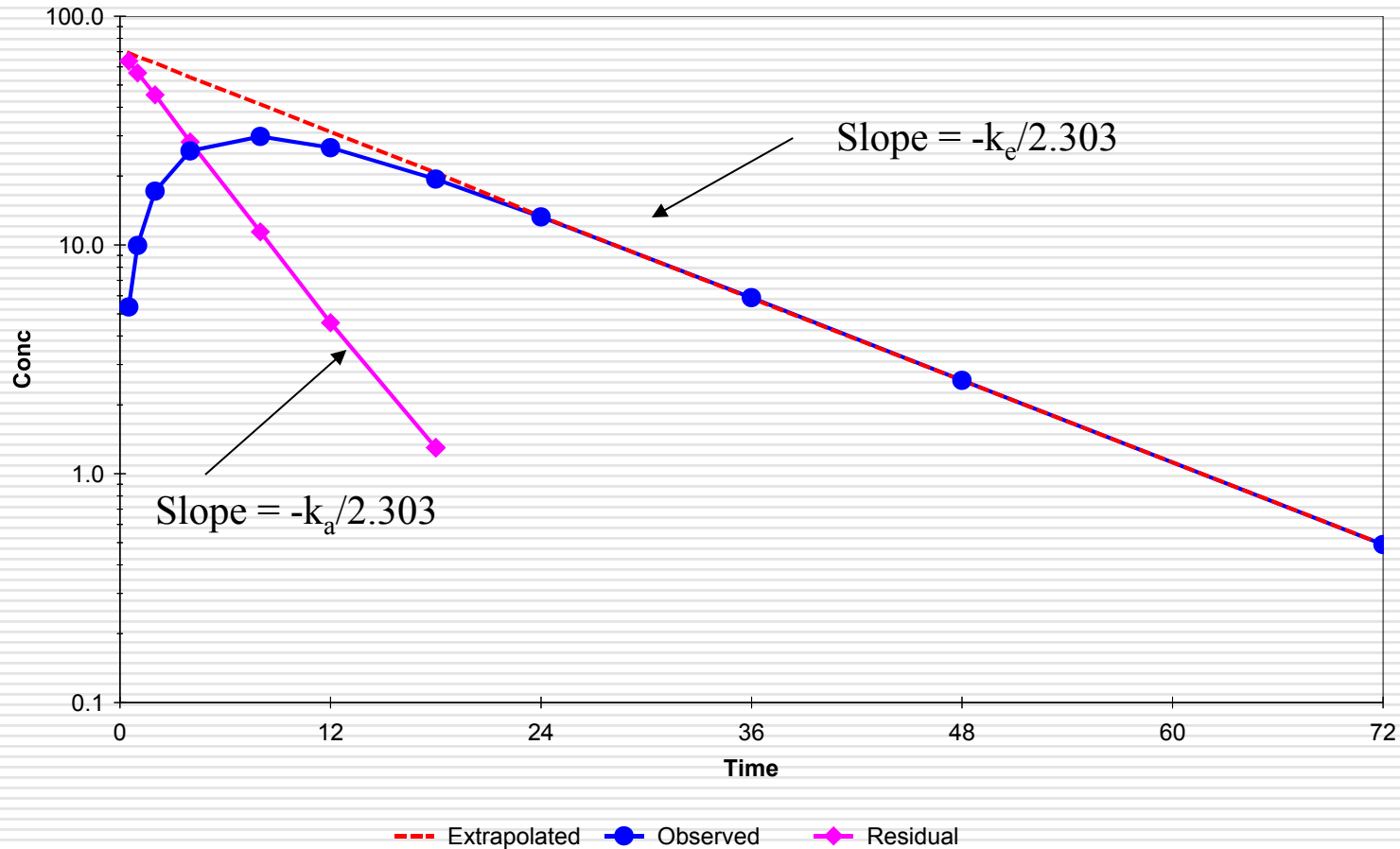
# Compartmental Models:– Initial Parameter Estimates

---

- ❑ PK compartment models are parameter-based
  - ❑ Parameters are variables in the model equation, for example a one-compartment IV-bolus model:
  - ❑  $C(t) = D/V \cdot \exp(-k_{10} \cdot t)$ 
    - $D$  = Dose, a constant
    - $T$  = time
    - $V$  = volume of distribution (parameter)
    - $K_{10}$  = elimination rate constant (parameter)
  - ❑ More complex models, e.g. with more compartments will have more parameters
  - ❑ The use of boundaries (either User supplied or WinNonlin supplied) is recommended for Initial Estimates
-

# Obtaining Initial Estimates

$$C = A e^{-\alpha t} + B e^{-\beta t}$$



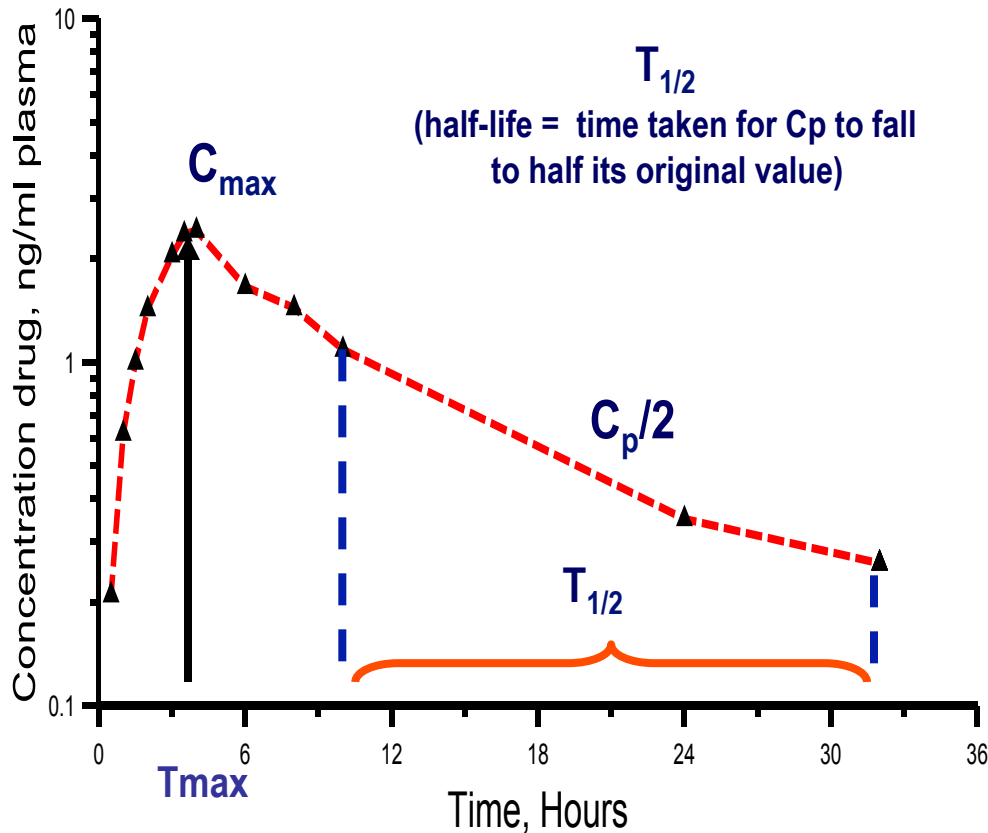
A and B are coefficients ;  $\alpha$  and  $\beta$  are exponents

# Compartmental Modeling - Minimization

---

- ❑ During modeling, Phoenix starts with initial PK parameter estimates, and goes through an iterative process of re-estimating the parameters.
- ❑ Curve fitting – optimal fit with minimal residual sum of squares (RSS) of differences between observed and predicted data
- ❑ Minimization methods to converge to true parameter values: obtain parameter estimates such that the difference between the observed concentrations and predicted concentrations are minimal.
  - Model Comparison: When using AIC and SBC, note that the weighting scheme of the models being compared must be the same.
  - Every time you increase the number of parameters, WRSS will decrease. AIC adds a penalty to increased number of parameters.
  - Degrees of freedom should be at least 6-8. Degrees of freedom =  $n \text{ obs} - n \text{ parameters}$ .
- ❑ Convergence is achieved when two consecutive iterations do not reduce the SS by more than the convergence criterion (0.0001 by default). The parameters used in the last iteration are reported as Final Parameters.

# Recap

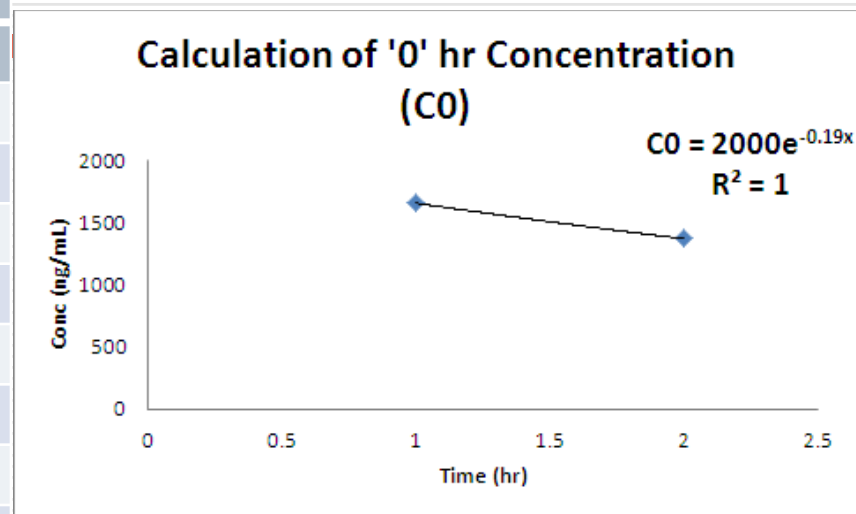


- ☐ AUC: area under the curve
- ☐  $C_{max}$  : Maximum observed concentration
- ☐  $T_{max}$ : Time of  $C_{max}$
- ☐ Elimination Half-life ( $T_{1/2}$ ): amount of time to eliminate 50% of the drug from the body at terminal data time points

# Calculation of NCA PK parameters

Compound A dosed by oral and IV route at 10 mg in a cross-over design

| Time (hr) | 10 mg IV     | 10 mg oral   |
|-----------|--------------|--------------|
|           | Conc (ng/mL) | Conc (ng/mL) |
| 0         | 2000.00      | 0.00         |
| 1         | 1653.92      | 707.33       |
| 2         | 1367.72      | 1008.14      |
| 3         | 1131.05      | 1085.60      |
| 4         | 935.33       | 1046.65      |
| 6         | 639.64       | 838.02       |
| 8         | 437.42       | 611.94       |
| 10        | 299.14       | 428.66       |
| 24        | 20.92        | 27.41        |
| 36        | 2.14         | 2.49         |
| 48        | 0.22         | 0.23         |



Assuming first order decay:  $C = C_0 * e^{-K_{el} * t}$

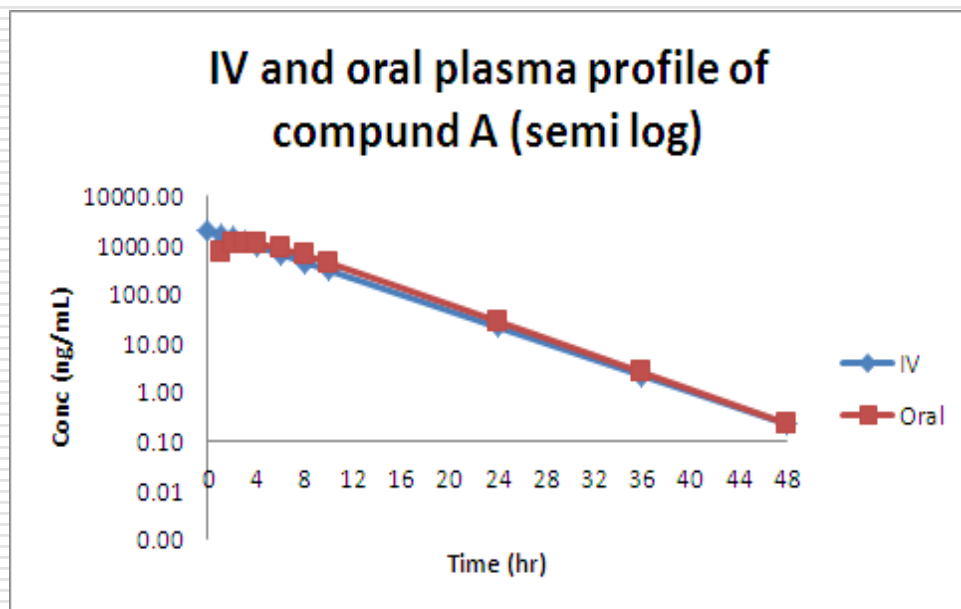
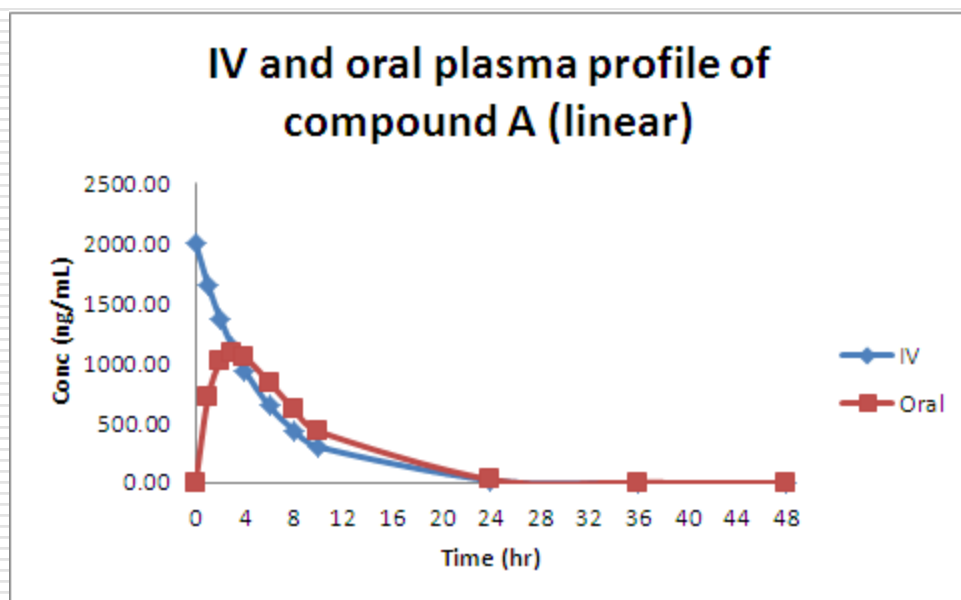
A exponential regression line drawn between the first two time points.

The Y intercept of the line is C<sub>0</sub>: 2000 ng/mL

# Calculation of NCA PK parameters

| Time (hr) | 10 mg IV     | 10 mg oral   |
|-----------|--------------|--------------|
|           | Conc (ng/mL) | Conc (ng/mL) |
| 0         | 2000.00      | 0.00         |
| 1         | 1653.92      | 707.33       |
| 2         | 1367.72      | 1008.14      |
| 3         | 1131.05      | 1085.60      |
| 4         | 935.33       | 1046.65      |
| 6         | 639.64       | 838.02       |
| 8         | 437.42       | 611.94       |
| 10        | 299.14       | 428.66       |
| 24        | 20.92        | 27.41        |
| 36        | 2.14         | 2.49         |
| 48        | 0.22         | 0.23         |

- **Oral route:**
- **C<sub>max</sub>:** 1085.60 ng/mL
- **T<sub>max</sub>:** 3 hrs
- **Both IV and oral elimination seem to be comparable**



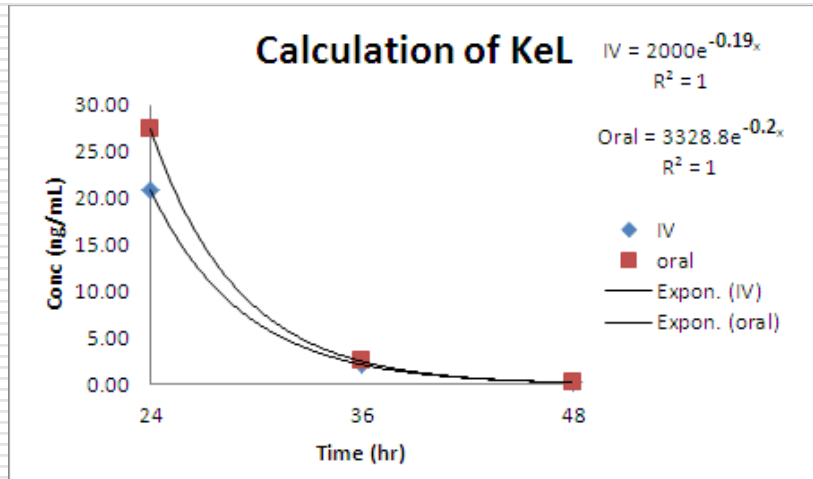
# Calculation of AUC

| Time (hr) | 10 mg IV     | 10 mg oral   | IV AUC   | Oral AUC |
|-----------|--------------|--------------|----------|----------|
|           | Conc (ng/mL) | Conc (ng/mL) | ng.hr/mL | ng.hr/mL |
| 0         | 2000.00      | 0.00         | 1826.96  | 353.67   |
| 1         | 1653.92      | 707.33       | 1510.82  | 857.73   |
| 2         | 1367.72      | 1008.14      | 1249.39  | 1046.87  |
| 3         | 1131.05      | 1085.60      | 1033.19  | 1066.13  |
| 4         | 935.33       | 1046.65      | 1574.97  | 1884.67  |
| 6         | 639.64       | 838.02       | 1077.06  | 1449.96  |
| 8         | 437.42       | 611.94       | 736.56   | 1040.59  |
| 10        | 299.14       | 428.66       | 2240.43  | 3192.49  |
| 24        | 20.92        | 27.41        | 138.39   | 179.40   |
| 36        | 2.14         | 2.49         | 14.15    | 16.29    |
| 48        | 0.22         | 0.23         |          |          |

- **Calculate individual trapezoid areas  $(t_2 - t_1) * (c_1 + c_2 / 2)$ ,**
- **Add individual trapezoid together to get total AUC**

| Parameter           | Linear trapezoid                     | Unit     | IV: AUC <sub>0-48</sub> | Oral: AUC <sub>0-48</sub> |
|---------------------|--------------------------------------|----------|-------------------------|---------------------------|
| AUC <sub>0-48</sub> | $\sum (t_2 - t_1) * (c_1 + c_2) / 2$ | ng.hr/mL | <b>11401.92</b>         | <b>11087.80</b>           |

# Calculation of $AUC_{0-\infty}$ , CL, Vz and $t_{1/2}$



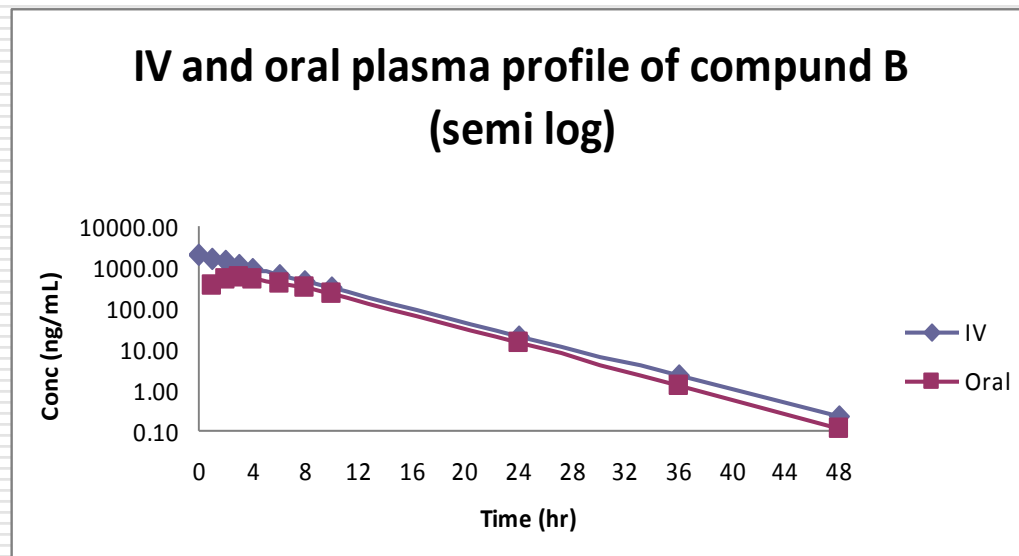
Assuming first order decay:  $C = C_0 * e^{-KeL * t}$

Fitting the terminal points (atleast 3 data points) to exponential regression using Excel gives '**KeL**'

| KeL (hr <sup>-1</sup> ) |                                |       |
|-------------------------|--------------------------------|-------|
| IV                      | $e^{-KeL.t}$                   | -0.19 |
| Oral                    | $e^{-KeL.t}$                   | -0.2  |
| t <sub>1/2</sub> (hr)   |                                |       |
| IV                      | $0.693/KeL$                    | 3.64  |
| Oral                    | $0.693/KeL$                    | 3.46  |
| CL (mL/hr)              |                                |       |
| IV                      | Dose/AUC <sub>inf</sub>        | 877   |
| Oral                    | Dose/AUC <sub>inf</sub>        | 902   |
| Vz (mL)                 |                                |       |
| IV                      | Dose/(AUC <sub>inf</sub> *KeL) | 4616  |
| Oral                    | Dose/(AUC <sub>inf</sub> *KeL) | 4509  |

| AUC <sub>0-∞</sub> | AUC <sub>0-48</sub> + C <sub>last</sub> /keL                              | IV: 11403.07 | Oral: 11088.93 |
|--------------------|---------------------------------------------------------------------------|--------------|----------------|
| Bio availability   | (AUC <sub>inf</sub> oral * Dose IV) / (AUC <sub>inf</sub> iv * Dose oral) | 0.97         |                |

|           | 10 mg IV       | 10 mg oral   |
|-----------|----------------|--------------|
| Time (hr) | Conc (ng/mL)   | Conc (ng/mL) |
| 0         | <b>2000.00</b> | 0.00         |
| 1         | 1653.92        | 353.67       |
| 2         | 1367.72        | 504.07       |
| 3         | 1131.05        | 542.80       |
| 4         | 935.33         | 523.32       |
| 6         | 639.64         | 419.01       |
| 8         | 437.42         | 305.97       |
| 10        | 299.14         | 214.33       |
| 24        | 20.92          | 13.71        |
| 36        | 2.14           | 1.24         |
| 48        | 0.22           | 0.11         |



- **Oral route:**
- **C<sub>max</sub>:** 542.80 ng/mL
- **T<sub>max</sub>:** 3 hrs
- **Both IV and oral elimination seem to be comparable**

|                           |                                             |              |              |
|---------------------------|---------------------------------------------|--------------|--------------|
| AUC <sub>0-inf</sub>      | AUC <sub>0-48</sub> +C <sub>last</sub> /keL | IV: 11403.07 | Oral:5544.46 |
| Bio availability          | (AUCinf oral*Dose IV)/(AUCinf iv*Dose oral) | 0.49         |              |
| <b>CL (mL/hr)</b>         |                                             |              |              |
| IV                        | Dose/AUCinf                                 | 877          |              |
| Oral (CL <sub>app</sub> ) | Dose/AUCinf                                 | 1804         |              |
| Oral (CL <sub>app</sub> ) | Dose/AUCinf *F                              | 884          |              |

---

# **Non Compartmental Analysis - Urine**

---

# Non-Compartmental Analysis

---

## Analysis of urine data

Interested parameters

- Amount excreted through urine ( $A_e$ )
- Percent/Fraction of dose excreted through urine ( $f_{A_e}$ )
- Renal clearance ( $CL_R$ )
- Contribution of renal clearance in Total clearance

For the maximum utility, the urine data need to be interpreted in conjunction with the plasma PK data

---

# Non-Compartmental Analysis

## Plasma and Urine data analysis

---

**Let us take a hypothetical example assuming 100% BA**

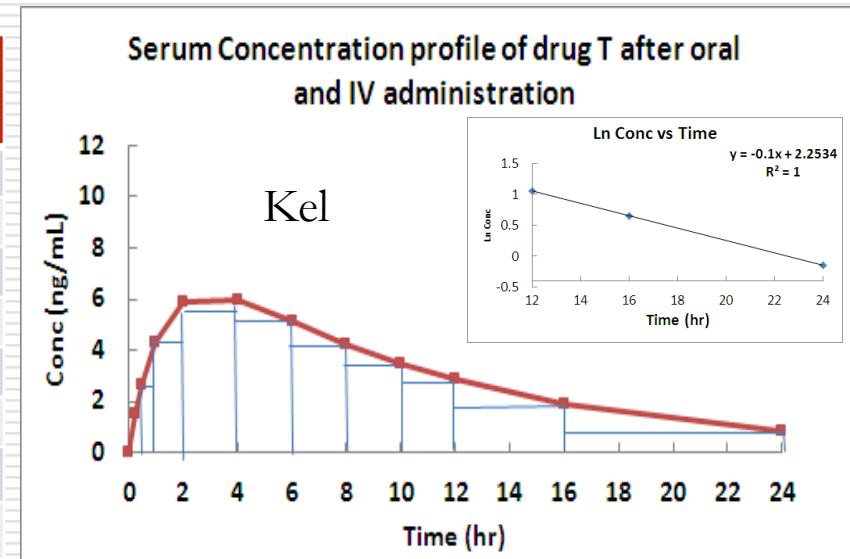
A healthy volunteer received single 100 µg of drug T by oral route. Urine samples were collected at specified intervals for a duration of 24 hours. Plasma samples were also collected serially for 24 hours post dose at specified time points.

- The concentration of drug in each aliquot were estimated using LC/MS/MS
-

# Non-Compartmental Analysis

## Plasma Theoretical example

| Time (hr) | Conc (ng/mL)  | AUC (ng.hr/mL) |
|-----------|---------------|----------------|
| 0         | 0.0000        | 0.1864         |
| 0.25      | 1.4912        | 0.5208         |
| 0.5       | 2.6753        | 1.7534         |
| 1         | 4.3382        | 5.1064         |
| 2         | 5.8746        | 11.8704        |
| <b>4</b>  | <b>5.9958</b> | 11.1442        |
| 6         | 5.1484        | 9.4119         |
| 8         | 4.2635        | 7.7639         |
| 10        | 3.5004        | 6.3683         |
| 12        | 2.8679        | 9.5814         |
| 16        | 1.9228        | 11.1472        |
| 24        | 0.8640        | -              |



Calculation of AUC = Sum of individual trapezoid area:  $(C_2 - C_1) * (T_1 + T_2) / 2$   
 For the first trapezoid:  $(1.4912 - 0.00) * (0 + 0.25) / 2 = 0.1864$

Sum of all the trapezoids:  $AUC_{0-24} = 74.8543 \text{ ng.hr/mL}$

$AUC_{0-\infty} : AUC_{0-24} + C_{\text{last}} / k_{el} = 74.8543 + (0.8640 / 0.1) = 83.49 \text{ ng.hr/mL}$

Clearance = Dose /  $AUC_{0-\infty} = 1115.4 \text{ mL/hr}$

Total clearance = Metabolic clearance + Excretion clearance

# Urine data analysis

| Time (hr)  | Concentration (ng/mL) | Urine Volume (mL) | Xu (ng)      |
|------------|-----------------------|-------------------|--------------|
| 0-4 hr     | 10                    | 200               | 2000         |
| 4-6 hrs    | 20                    | 500               | 10000        |
| 6-8 hrs    | 10                    | 250               | 2500         |
| 8-12 hrs   | 15                    | 450               | 6750         |
| 12- 24 hrs | 5                     | 650               | 3250         |
|            |                       |                   | <b>24500</b> |

Amount excreted during each duration  $X_u = \text{Concentration} \times \text{Volume}$

Cumulative amount excreted through urine ( $A_e$ ) =  $\sum X_u = \mathbf{24500}$  ng

Percent of dose excreted =  $(24500/100000) \times 100 = \mathbf{24.5\%}$

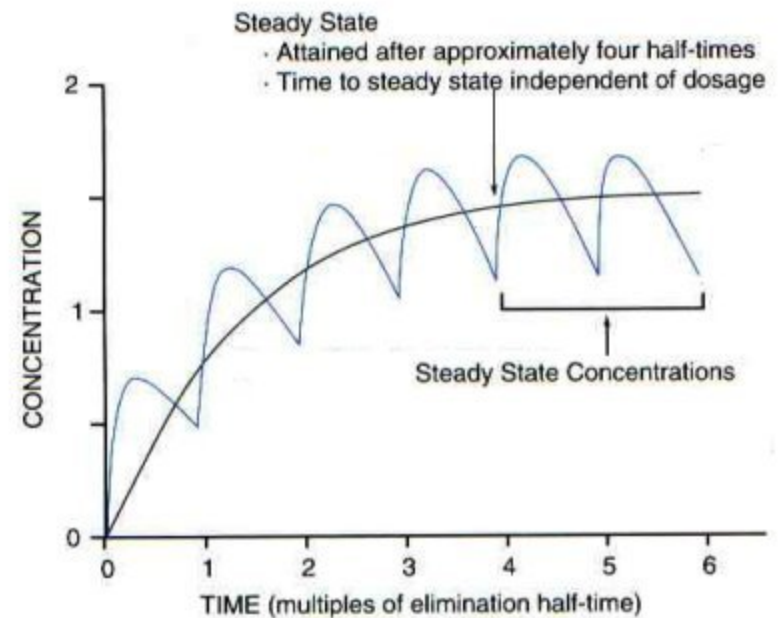
Renal clearance ( $CL_R$ ) =  $A_e/AUC = 24500/83.49 = \mathbf{293.5}$  mL/hr

Metabolic clearance =  $1115.4 - 293.5 = \mathbf{821.9}$  mL/hr

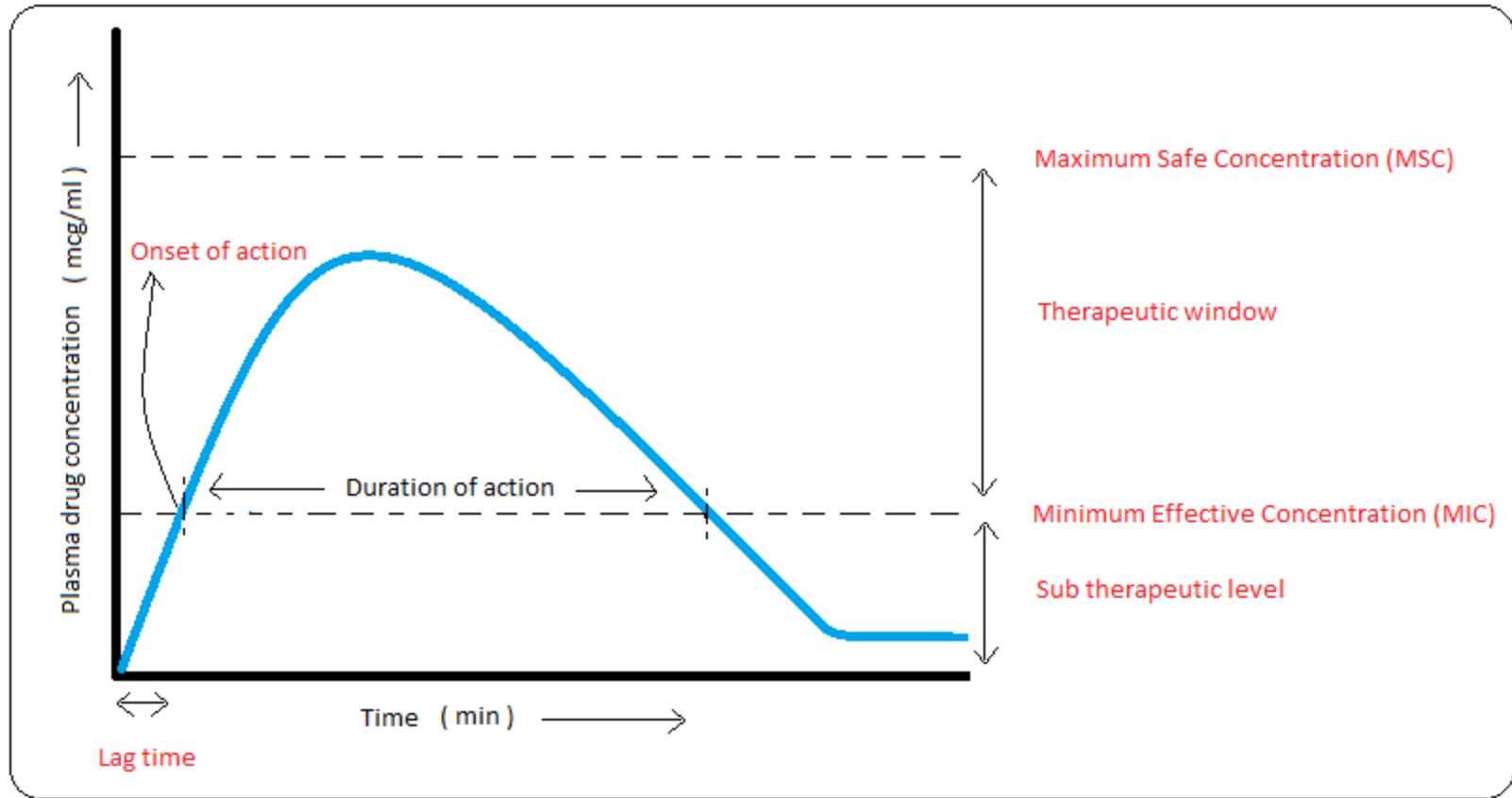
- Metabolic clearance (**74%**) and Renal clearance (**26%**)

# Steady-State

- With first order elimination, at a certain point in therapy, the amount of drug administered during a dosing interval exactly replaces the amount of drug excreted
- Rate in = Rate out
- The time required to reach steady-state is approximately 4 to 5 half-lives

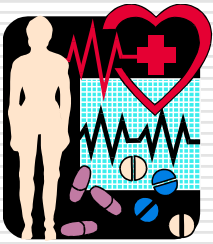


# Therapeutic Index



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

**Excessive levels will lead to toxicity and tissue damage**



# Therapeutic Drug Monitoring



- 
- ☐ Narrow Therapeutic Window Drugs (digoxin, aminoglycosides, lidocaine, lithium, phenobarbital, phenytoin, theophylline)
  - ☐ Allows rapid and safe delivery of drugs as these drugs can be easily over or under dosed
  - ☐ Give drug, measure plasma concentrations
  - ☐ Use concentration data to develop safe dosing regimen for individual patient.
-

# Determination of pharmacokinetic parameters in "normal" subjects

---

1. Measure drug and metabolite concentrations in blood, urine and other body fluids as a function of time.
2. Set up models to describe the time course and to predict the drug levels at times not studied.
3. Determine parameters from model which can be related to physiological, clinical, physical or chemical properties of the drug.

# Pharmacodynamics

---

Pharmacodynamics is the study of  
what the drug does to the body  
dynamics = change

# Drug Receptors

---

- Most drugs bind to cellular receptors
    - Initiate biochemical reactions
    - Pharmacological effect is due to the alteration of an intrinsic physiologic process and not the creation of a new process
  - Proteins or glycoproteins
    - Present on cell surface, on an organelle within the cell, or in the cytoplasm
    - Finite number of receptors in a given cell
      - Receptor mediated responses plateau upon saturation of all receptors
  - Action occurs when drug binds to receptor and this action may be:
    - Ion channel is opened or closed
    - Second messenger is activated
      - cAMP, cGMP,  $\text{Ca}^{++}$ , inositol phosphates, etc.
      - Initiates a series of chemical reactions
    - Normal cellular function is physically inhibited
    - Cellular function is “turned on”
-

# Drug Receptor

---

## □ Affinity

- Refers to the strength of binding between a drug and receptor
- Number of occupied receptors is a function of a balance between bound and free drug

## □ Dissociation constant ( $K_D$ )

- Measure of a drug's affinity for a given receptor
  - Defined as the concentration of drug required in solution to achieve 50% occupancy of its receptors
-

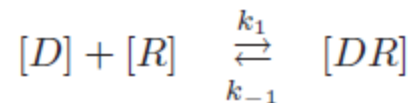
# PD Model: Definitions

---

- Efficacy
    - Degree to which a drug is able to produce the desired response
  - Potency
    - Amount of drug required to produce 50% of the maximal response the drug is capable of inducing
    - Used to compare compounds within classes of drugs
  - Effective Concentration 50% ( $ED_{50}$ )
    - Concentration of the drug which induces a specified clinical effect in 50% of subjects
  - Lethal Dose 50% ( $LD_{50}$ )
    - Concentration of the drug which induces death in 50% of subjects
  - Therapeutic Index
    - Measure of the safety of a drug
    - Calculation:  $LD_{50}/ED_{50}$
  - Margin of Safety
    - Margin between the therapeutic and lethal doses of a drug
-

# Understanding Pharmacodynamics

- ❑ Drug molecule binds to target receptors/enzymes to elicit a pharmacological action
- ❑ The drug binding to the receptor initiates a change in the structure of the receptor and thereby changing the cell membrane.
- ❑ The set of unoccupied receptors  $[R]$  placed on the target cells that potentially can bind with drug molecules  $[D]$  and their relation to the bound drug/receptor complex  $[DR]$  can be stated as



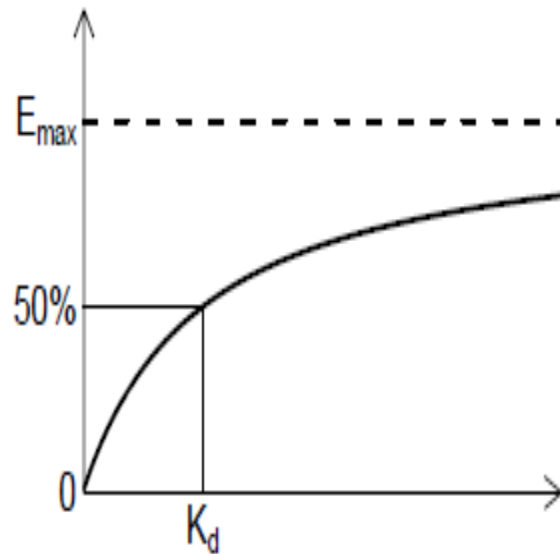
- ❑ It is possible to derive a model for the relation between drug concentration and effect based on receptor theory. The effect response  $E$  is assumed proportional to the occupancy of the receptors and thus that the maximal effect is achieved if all receptors  $[R_{tot}]$  are occupied.

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

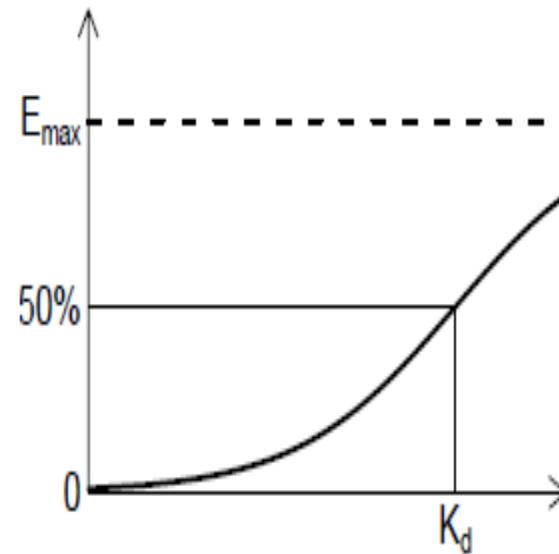
MM model correlating drug conc vs effect

# MM model correlating drug concentration vs effect

---



(a) Response vs. Conc.



(b) Response vs.  $\log(\text{Conc})$ .

# Pharmacodynamic Models (Direct Response)

Under pharmacokinetic steady-state conditions, concentration-effect relationships can be described by several relatively simple pharmacodynamic models, which comprise the **fixed effect model**, the **linear model**, the **log-linear model**, the **E<sub>max</sub>-model** and the **sigmoid E<sub>max</sub>-model**

- ❑ Fixed effect model – A defined effect is present or not

$$E = E_{fixed} \text{ if } C > C_{threshold}$$

- ❑ Linear model

$$Effect = m \cdot [Drug] + E_0$$

- ❑ Log-linear model

$$Effect = I + m \cdot \text{Log}([Drug])$$

- ❑ E<sub>max</sub> model

$$Effect = \frac{E_{max} \cdot [Drug]}{EC_{50} + [Drug]}$$

- ❑ Sigmoid E<sub>max</sub> model

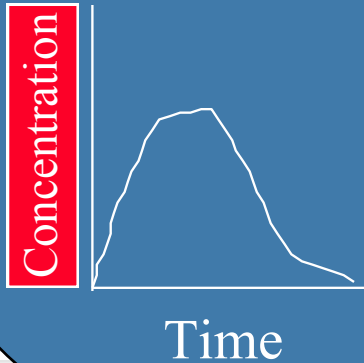
$$Effect = \frac{E_{max} \cdot [Drug]^H}{EC_{50}^H + [Drug]^H}$$

Usually applied to characterize the relationship between drug concentrations and pharmacological effects when the pharmacological effects are functions of drug concentration

# PK / PD Modeling

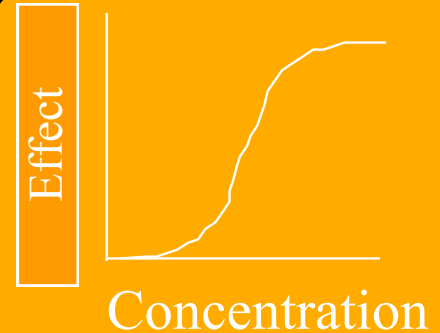
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# PK/PD Modeling



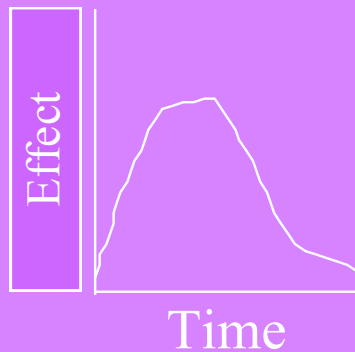
**Pharmacokinetics  
(PK)**

*What the body does to the  
drug*



**Pharmacodynamics  
(PD)**

*What the drug does to the body*



**Pharmacokinetics/Pharmacodynamic Modeling  
(PK/PD)**

**MODEL**  
*Simplified description of some  
aspect of reality*  
**HELPS IN PREDICTION**

# Why do PK/PD modeling?

---

- ❑ A huge gap between the number of candidate drug compounds in testing and the ones that actually get approved.
  - ❑ < 10% from phase I get to approval phase
  - ❑ Failure to understand the relationship between dose – concentration response
  - ❑ Unanticipated safety events
  - ❑ PK/PD modeling can help optimize dosing regimens, thereby decreasing risk of failure at the final stage.
  - ❑ PK/PD modeling approaches are proving useful in determining relationships between biomarker response, drug levels, and dosing regimens.
  - ❑ Helps to streamline the process
  - ❑ Instead of sequential drug development, can do parallel drug development
-

# PK/PD Basic assumptions

---

- ☐ There is an “effect site ” where drug will have its effect
  - ☐ Magnitudes of response and toxicity depend on drug concentration at the effect site
  - ☐ Drug cannot be placed directly at effect site, must move there
  - ☐ Concentrations at the effect site are determined by ADME
  - ☐ Concentrations must be kept high enough to produce a desirable response, but low enough to avoid toxicity - “Therapeutic window”
  - ☐ (Usually ) cannot measure concentration at effect site directly, but can measure in blood/plasma/serum; reflect those at site
-

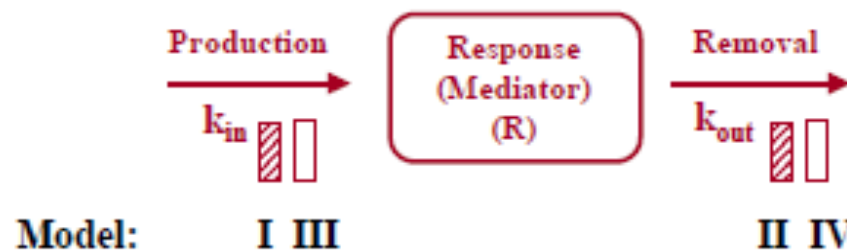
# PK / PD Link Models

---

- Four basic attributes of PK/PD Models to be considered during the selection of appropriate modeling approach
    - Direct Link vs Indirect Link
    - Direct Response vs Indirect Response
    - Soft Link vs Hard Link
    - Time Invariant vs Time Variant
-

# PD Models

- ❑ **Direct Link** – Plasma concentrations and drug concentration at the effect site (biophase) are proportional
- ❑ For some drugs, responses takes time for their development and are not apparently related to plasma concentrations because of an equilibrium delay between the plasma concentration and the Biophase
- ❑ In such cases, an hypothetical effect compartment (link) type approach can account for the equilibration delay
- ❑ **Indirect link (Indirect response models)** - There is a lag time for development of a response even after drug reaches the target site – Require time for their elaboration because of processes such as inhibition or stimulation of the production or dissipation of factors controlling the response
- ❑ The time pattern of the mediator or response variable (R) is affected by drugs which can alter the production ( $k_{in}$ ) or dissipation ( $k_{out}$ ) process normally controlling endogenous levels of R. Drugs can inhibit or stimulate any of these processes.

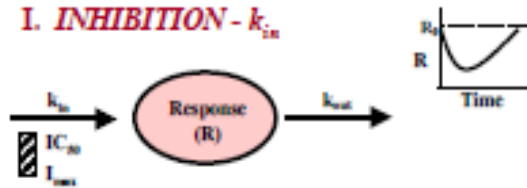


- ❑ IDR models are more appropriate for drugs that produces responses with a lag time between biophase drug concentrations and the time course of responses

# Indirect link (Indirect response models)

May be relevant for

## I. INHIBITION - $k_{in}$



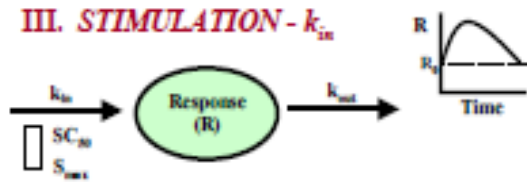
$$\frac{dR}{dt} = k_{in} \cdot \left( 1 - \frac{I_{max} \cdot C_p}{IC_{50} + C_p} \right) - k_{out} \cdot R$$

## II. INHIBITION - $k_{out}$



$$\frac{dR}{dt} = k_{in} - k_{out} \cdot \left( 1 - \frac{I_{max} \cdot C_p}{IC_{50} + C_p} \right) \cdot R$$

## III. STIMULATION - $k_{in}$



$$\frac{dR}{dt} = k_{in} \cdot \left( 1 + \frac{S_{max} \cdot C_p}{SC_{50} + C_p} \right) - k_{out} \cdot R$$

## IV. STIMULATION - $k_{out}$



$$\frac{dR}{dt} = k_{in} - k_{out} \cdot \left( 1 + \frac{S_{max} \cdot C_p}{SC_{50} + C_p} \right) \cdot R$$

| Class                                   | Model |
|-----------------------------------------|-------|
| Anticoagulants                          | I     |
| H1 antagonists                          | I     |
| Cholinesterase inhibitors               | II    |
| Diuretics                               | II    |
| Dopamine antagonists                    | III   |
| $\beta$ – antagonists (Bronchodilation) | III   |
| $\beta$ – antagonists (Hypokalemia)     | IV    |
| Insulin sensitizers (PPAR $\gamma$ )    | IV    |

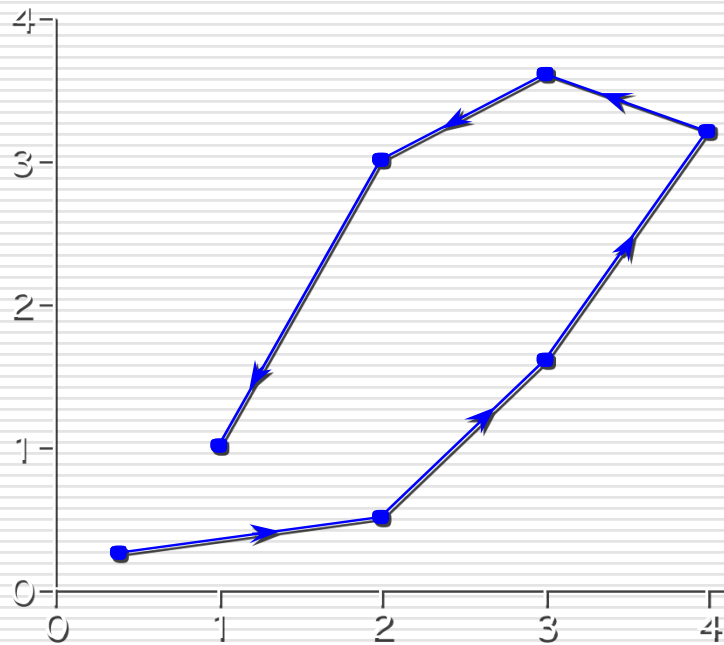
# Hysteresis and Proteresis Loops

A situation in which concentration-effect curves do not always follow the same pattern of serum concentrations. Can result from tolerance to a drug (clockwise hysteresis) or accumulation of active metabolites (counterclockwise hysteresis).

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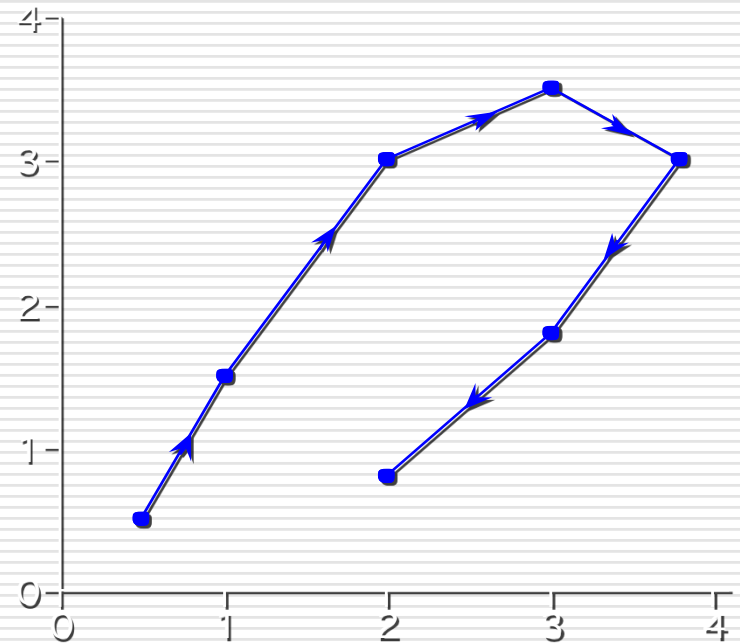
Intensity of  
Drug Effect

**Hysteresis Loop  
(Counterclockwise)**



Intensity of  
Drug Effect

**Proteresis Loop  
(Clockwise)**



Plasma Drug Concentration

Pattern of a  $C_p(t)$  vs.  $E(t)$  plot  
connected in time sequence

Factors causing the time-related discrepancies in the apparent  
concentration–effect relationship

*Proteresis*

Development of tolerance: a dampened response to the drug, after prolonged or repeated exposure (diazepam, morphine)  
Formation of antagonistic metabolites: antagonistic metabolites competing with the drug for the same binding sites on the receptor (pentobarbital)  
Down-regulation: decrease in the number of receptors after the prolonged exposure of the drug (isoproterenol)  
Biofeedback regulation (almitrine, nifedipine, tyramine)

*Hysteresis*

Distribution delay<sup>a</sup>: the nonequilibrium condition of drug concentrations between the plasma and the effect site owing to slow drug distribution from the plasma, sampling site, to the effect site (9-tetrahydrocannabinol, thiopental)  
Response delay: the delayed pharmacological response resulting from a series of biological events upon the initial stimulus by the drug interacting with a specific receptor at the effect site (corticosteroids, warfarin)  
Sensitization of receptors (angiotensin, propranolol)  
Formation of agonistic (active) metabolites (fenfluramine, camazepam, midazolam)  
Up-regulation: increase in the number of receptors after the prolonged exposure of the drug (propranolol)



# PK/PD Modeling

---

## □ Procedure:

- Estimate exposure and examine correlation between PD other endpoints (including AE rates)
- Use mechanistic models

## □ Purpose:

- Estimate therapeutic window
  - Dose selection
  - Identify mechanism of action
  - Model probability of AE as function of exposure (and covariates)
  - Inform the label of the drug
-

# PK/PD

---

## ☐ **Preclinical:**

- Affinities of active drug molecules for the binding site (in vitro, in situ, in vivo)
- Mechanism between binding and measurable effect including auto-regulation (feedback, synthesis)
- In vivo: dose (time) – concentration (time) – measurable effect (time)

## ☐ **Clinical:**

- Ideally everything measured in the preclinical program (in vivo affinities will be difficult to obtain), but at least the following:
  - Dose (time)
  - Concentration (time)
  - Effect (time)
  - In addition, drug response data as a function of time
-

# PK/PD

- 
- ❑ Pharmacokinetic-Pharmacodynamic (PK/PD) modeling - Scientific mathematical tool which integrates relationship with PK model (describing the relationship between dose, systemic drug concentrations, and time) to that of PD model (describing the relationship between systemic drug concentration and the effect *vs* time profile) and a statistical model (particularly, the intra- and inter-individual variability of PK and/or PD origin)
  - ❑ PK/PD-modeling establish and evaluate dose-concentration-response relationships and subsequently describe and predict the effect-time courses resulting from a drug dose.
  - ❑ Applications of PK/PD have been extended to virtually all phases of drug development, which has resulted in the current Guidance for Industry on ***Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications from the Food and Drug Administration***
-

# Process of PK/PD Modeling

---

- ☐ Build a PK model
  - ☐ Build a PD model
  - ☐ Link PKPD models
  - ☐ Simulate treatment regimens or trials for useful predictions
-

# Reference Text

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- ❑ Clinical Pharmacokinetics, 3rd Edition, M. Rowland, T.N. Tozer, Lippincott Williams, and Williams, Philadelphia, 1994
  - ❑ Pharmacokinetics, 2<sup>nd</sup> Revised and Expanded Edition, M. Gibaldi and D. Perrier, Marcel and Dekker Inc., New York, USA 1982
  - ❑ PK/PD Data Analysis: Concepts and Applications, 4<sup>th</sup> Edition, Johan Gabrielson and Dan Weiner
-

# Thank You

---

- PhUSE
  - PhUSE organizing team
  - Quintiles
  - Attendees
-

---

# **Demonstration of Phoenix<sup>®</sup> WinNonlin<sup>®</sup>**

---

# WinNonLin: Classical PK Models

- First Plot Data
  - Exploratory Analysis
- Fit data to a simple model
  - Pick out of 19 Classical WNL Models
  - Obtain initial estimates (or let WinNonLin provide initial estimates)

The screenshot displays the WinNonLin software interface. The 'Options' tab is active, showing a table of 13 models. The first model is selected. To the right, a diagram illustrates a bolus IV model with a single compartment (1) and a first-order elimination rate (K10). Below the diagram, the 'Clearance' checkbox is checked, and the equation  $C(T) = D/V \cdot \exp(-K_{10} \cdot T)$  is shown. The 'Simulation' checkbox is unchecked.

| Selected                            | Number | Input       | Compartments | MicroMacro | LagTime | EliminationRate |
|-------------------------------------|--------|-------------|--------------|------------|---------|-----------------|
| <input checked="" type="checkbox"/> | 1      | IV-Bolus    | 1            | -          | No      | 1st order       |
| <input type="checkbox"/>            | 2      | IV-Infusion | 1            | -          | No      | 1st order       |
| <input type="checkbox"/>            | 3      | 1st Order   | 1            | -          | No      | 1st order       |
| <input type="checkbox"/>            | 4      | 1st Order   | 1            | -          | Yes     | 1st order       |
| <input type="checkbox"/>            | 5      | 1st Order   | 1            | K10=K01    | No      | 1st order       |
| <input type="checkbox"/>            | 6      | 1st Order   | 1            | K10=K01    | Yes     | 1st order       |
| <input type="checkbox"/>            | 7      | IV-Bolus    | 2            | micro      | No      | 1st order       |
| <input type="checkbox"/>            | 8      | IV-Bolus    | 2            | macro      | No      | 1st order       |
| <input type="checkbox"/>            | 9      | IV-Infusion | 2            | micro      | No      | 1st order       |
| <input type="checkbox"/>            | 10     | IV-Infusion | 2            | macro      | No      | 1st order       |
| <input type="checkbox"/>            | 11     | 1st Order   | 2            | micro      | No      | 1st order       |
| <input type="checkbox"/>            | 12     | 1st Order   | 2            | micro      | Yes     | 1st order       |
| <input type="checkbox"/>            | 13     | 1st Order   | 2            | macro      | No      | 1st order       |

**bolus IV** → **1** → **K10**

☒ Clearance  
 $C(T) = D/V \cdot \exp(-K_{10} \cdot T)$   
☐ Simulation

# Using a PK Library Model

---

- ☐ **Import the file 'compartment model.csv'**
  - ☐ **Plot the data to decide on a model selection**
  - ☐ **Fit a PK model to the data**
  - ☐ **Review Results**
-

# PK Library Model Step-by-Step

---

## Purpose

- Using WinNonlin to run a PK model for Compartmental Analysis
- Assume a 1-compartmental, IV Bolus (plasma)
- IV Dose = 10mg given at Time = 0

Import File: Compartment Model.csv

Plot Concentration-Time data (semi-log scale)

Do WNL5 Classic compartmental modeling

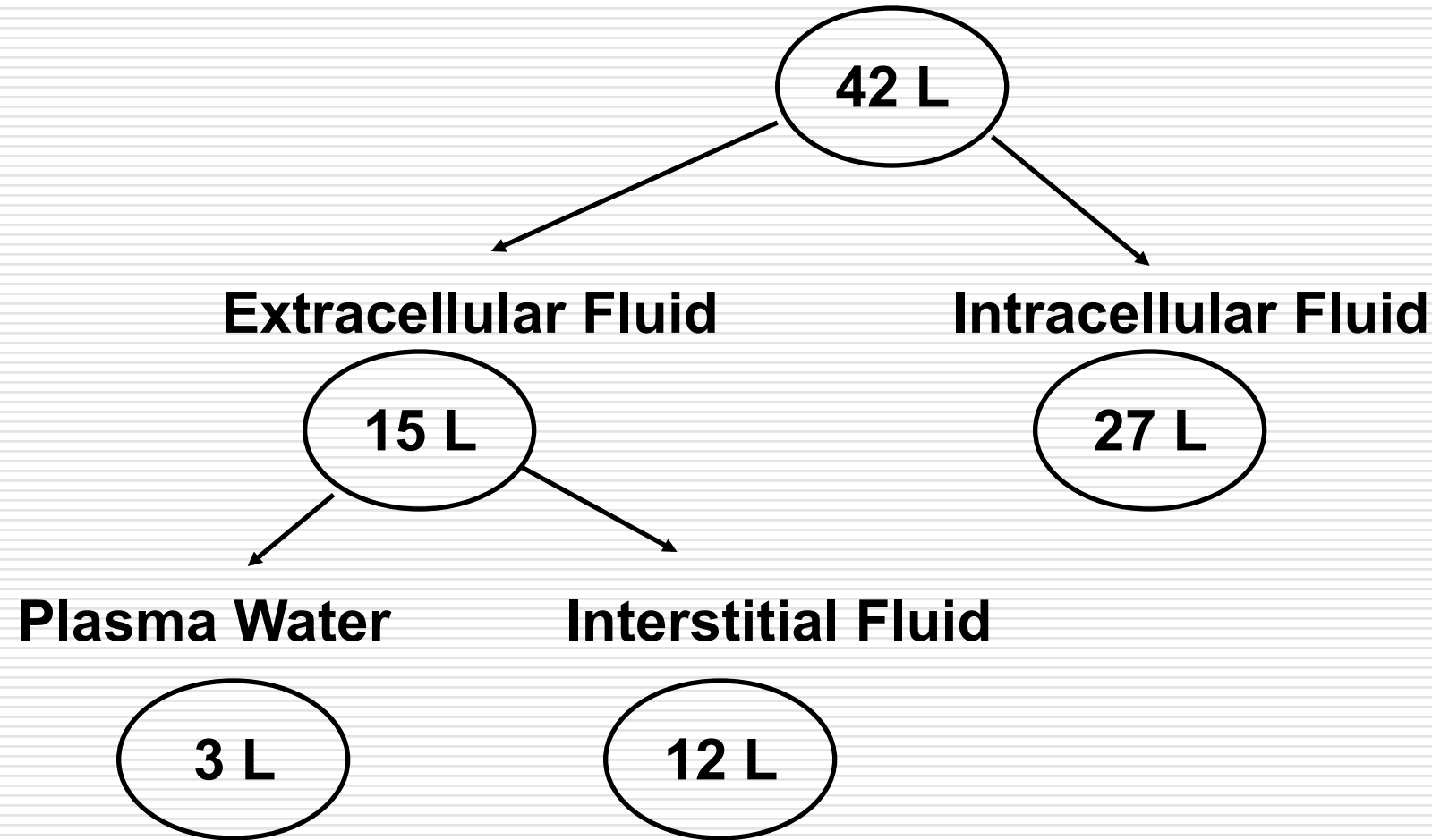
Enter dose and route information

Run Model

Choose different Weighting Options and Compare ( $1/Y$ ,  $1/\hat{Y}$ ,  $1/\hat{Y}^2$ )

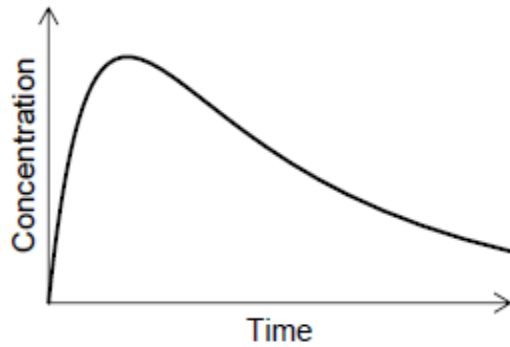
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# Total Body Water

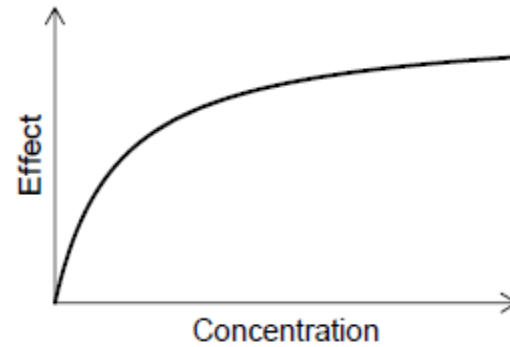


**Most hydrophilic drugs will be able to distribute within the extracellular fluid, unless they are too big. Lipophilic substances will be able to distribute throughout the body (entire extra- and intracellular space)**

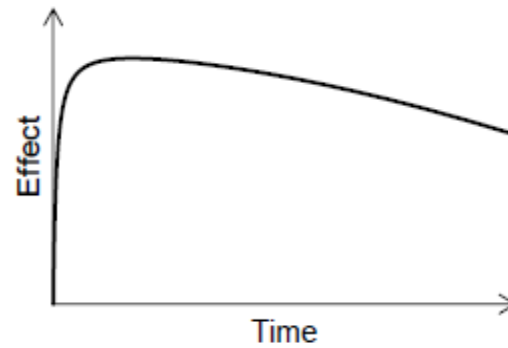
# PK-PD



(a) PK model



(b) PD model



(c) Combined PK/PD model

# What happens? Filtration

