20.201 Mechanisms of Drug Action

Lecture #18: Pharmacokinetics

October 31, 2005

Review

- Dose-response
- Protein binding, drug transport(ers)
- Metabolism
- NOW: PHARMACOKINETICS

Circulatory System and Drug Distribution

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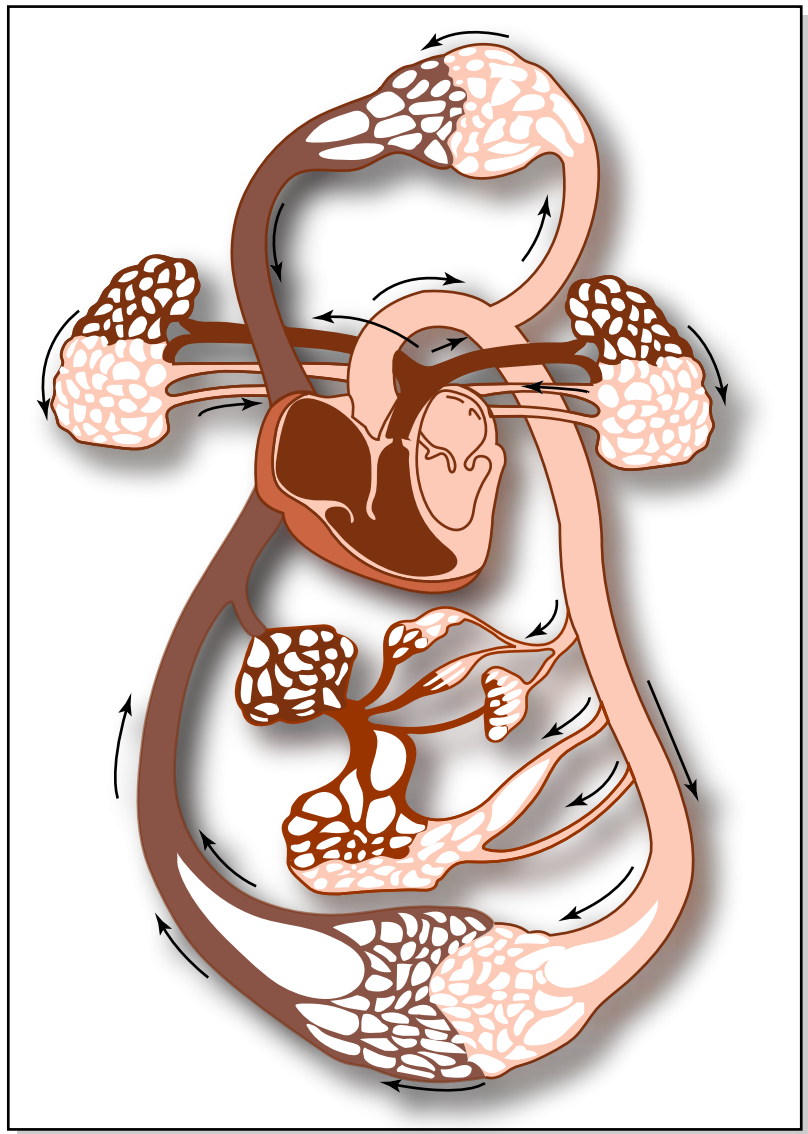

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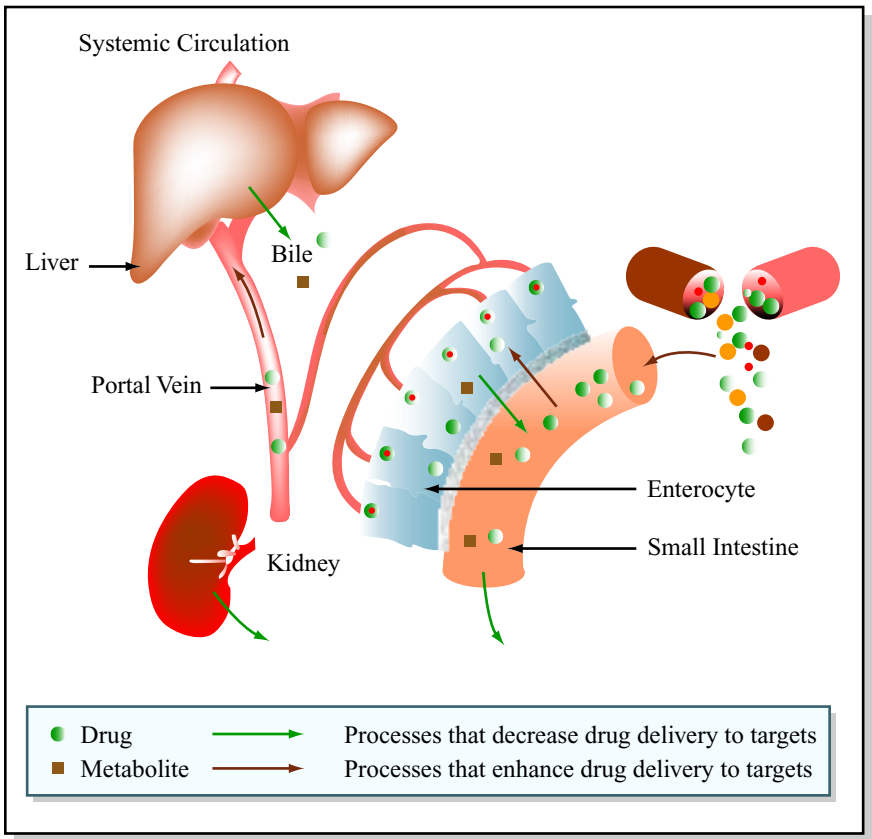
Portal Circulation and Enterohepatic Circulation

• Unique circulation of blood from gut to liver: all venous blood from stomach and intestines proceeds via portal vein directly to liver.

• Poses problem for development of orally-active drugs: can achieve nearly complete removal of drug by metabolism in one pass through the liver.



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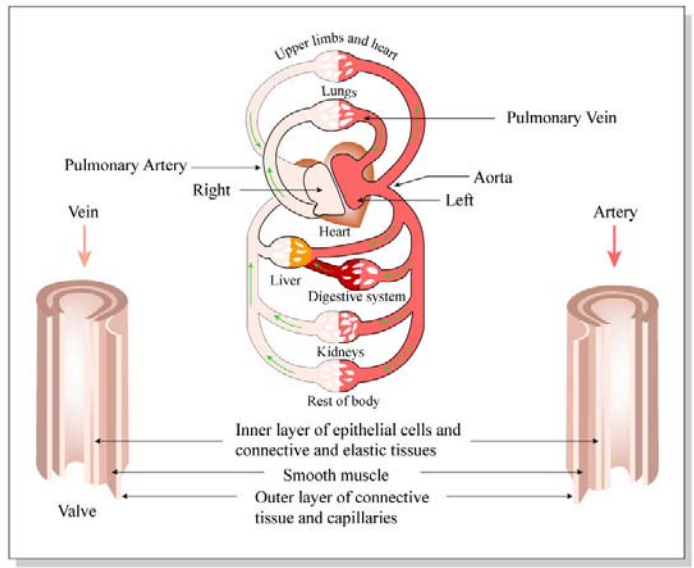

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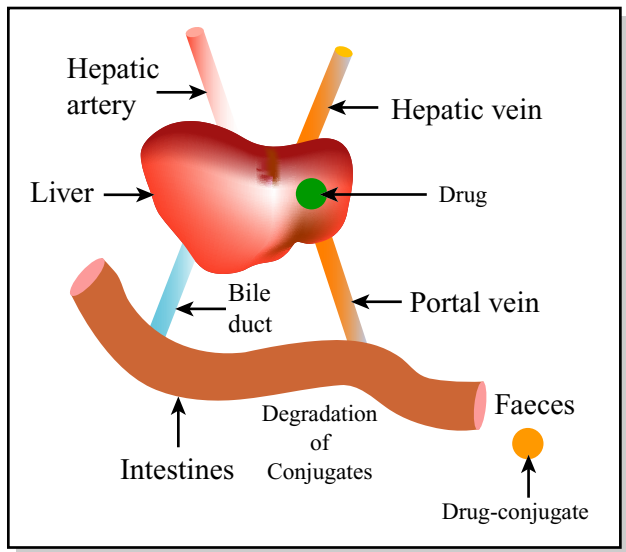


Figure by MIT OCW.

Distribution of Drugs

Process by which drug leaves site of absorption and enters tissues

(1) Blood flow: rate varies widely as function of tissue structure/function:

Organ/Tissue	Resting Blood Flow (ml/min)	Ml/min/100 g
Liver	1350 (27%)	95
Muscle	750 (15%)	4
Kidney	1100 (22%)	360
Heart	200 (4%)	70
Skin	300 (6%)	3
Brain	700 (14%)	50
Bronchi	100 (2%)	25
Other	500 (10%)	

(2) Capillary structure:

- Most capillaries are “leaky” and do not impede diffusion of drugs
- blood-brain barrier formed by high level of tight junctions between cells
- BBB is impermeable to most water-soluble drugs

(3) Plasma protein binding: Albumin!

Blood Cells

Classes		Cell Type	Products	Function	Size	Number	Lifetime
Erythrocytes		Erythrocytes	Hemoglobin	O_2 transport	7.5x2.5 um	$5x10^6$/ul (M) $4x10^6$/ul (F)	120 days
Leukocytes	Granulocytes	Neutrophils	Oxidative chemicals	Bacterial phagocytosis	15 um	5000/ul	6-7 hr blood 1-4 d tissues
		Eosinophils	Inflamm. modulating chemicals	Parasite defense, mod. of inflamm.	15 um	300/ul	
		Basophils	Histamine, heparin	Allergic reactions	15 um	100/ul	
	Mononuclear Leukocytes	Monocytes	Lysosomal enzymes	Phagocytosis of viruses, protozoa, dead cells	20 um	500/ul	12-100 hr blood
		B-Lymphocyte T-Lymphocyte Killer Cells	Antibodies (IgG, IgM, IgE) Cytokines Cytokines, etc.		6-18 um 6-18 um 6-18 um	2-3000/ul	
Platelets		Platelets	Blood clotting elements	Clot formation	2-4 um	$3x10^5$/ul	10 days

Proteins in blood

Molecule	*Mol. Wt.*	*G/dL*	*μM*	*Function*
Albumin	66,500	4.5	670	Chemical transport, plasma oncotic pressure
Globulins (α, β, γ)				
immunoglobulins (IgG, etc.)	150,000	1.5-2	130	Humoral Immunity
lipoproteins				Lipid and chemical transport
transferrin	79,000	0.2	17	Iron transport
ceruloplasmin	150,000	0.3	20	Copper transport
gluco/mucoprotein:haptoglobin				Binds to hemoglobin
coagulation factors (~10)				Clot formation
steroid-bindfing globulin	53,000	0.05	0.8	Transport of steroid hormones
thyroid hormone-binding globulin				Transport of thyroxine
macroglobulins				
α1-acid glycoprotein	42,000	0.4-1	9	Acute phase reactant, chemical transport
Fibrinogen	400,000	0.5	12	Clot formation
Complement proteins(~12)				Antibody-dependent responses and bacterial immunity

Pharmacokinetics and the Distribution of Chemicals in the Body

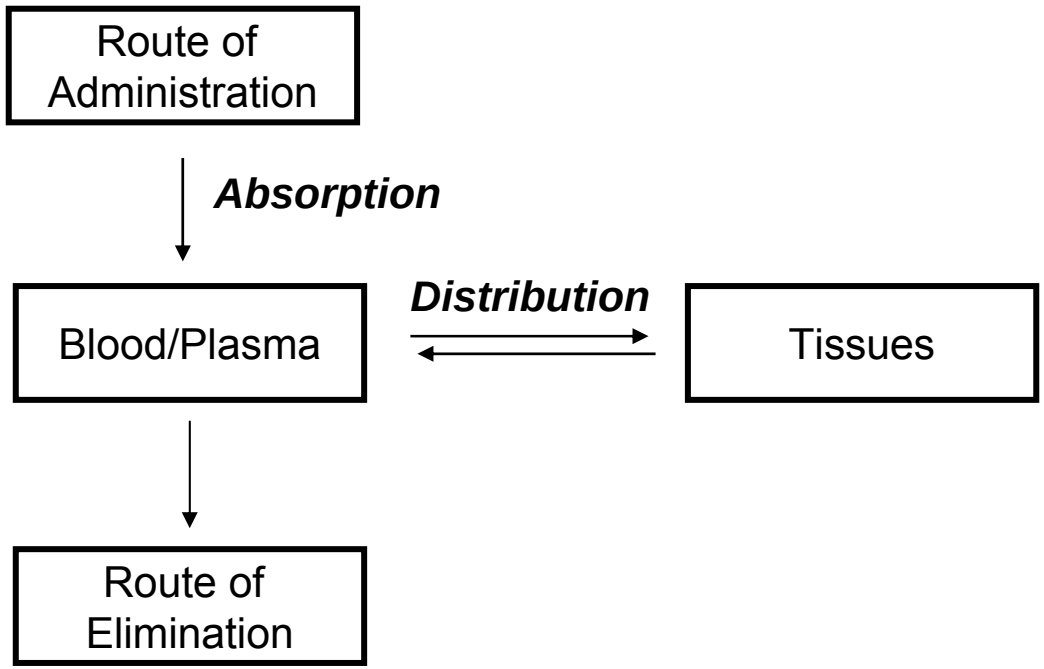
- Definition of Pharmacokinetics/Toxicokinetics: quantitative temporal analysis of the processes of absorption, distribution, metabolism and elimination of a chemical in the body

- Compare to pharmacodynamics: mechanism by which a chemical or agent exerts its effects (*e.g.*, binding to receptor, interfering with cell wall formation)

- Uses:
  - ~ Pharmacology: need to determine how often to administer a drug to maintain therapeutic concentration in the blood
  - ~ Toxicology: need to define the association between the concentration of a chemical in the blood or in a tissue and the progression of disease

- Approaches to pharmacokinetic analysis:
  - ~ Simple compartment models
  - ~ Physiologically-based pharmacokinetic models

Pharmacokinetics: Basic Concepts



Routes of administration

(1) Enteral -
- oral
- sublingual
- rectal

(2) Parenteral -
- intravenous (iv)
- intramuscular (im)
- subcutaneous (sc)

(3) Other -
- inhalation
- topical
- transdermal

Pharmacokinetics: Absorption

Quantitative aspects of absorption are important for GI, pulmonary and topical administration.

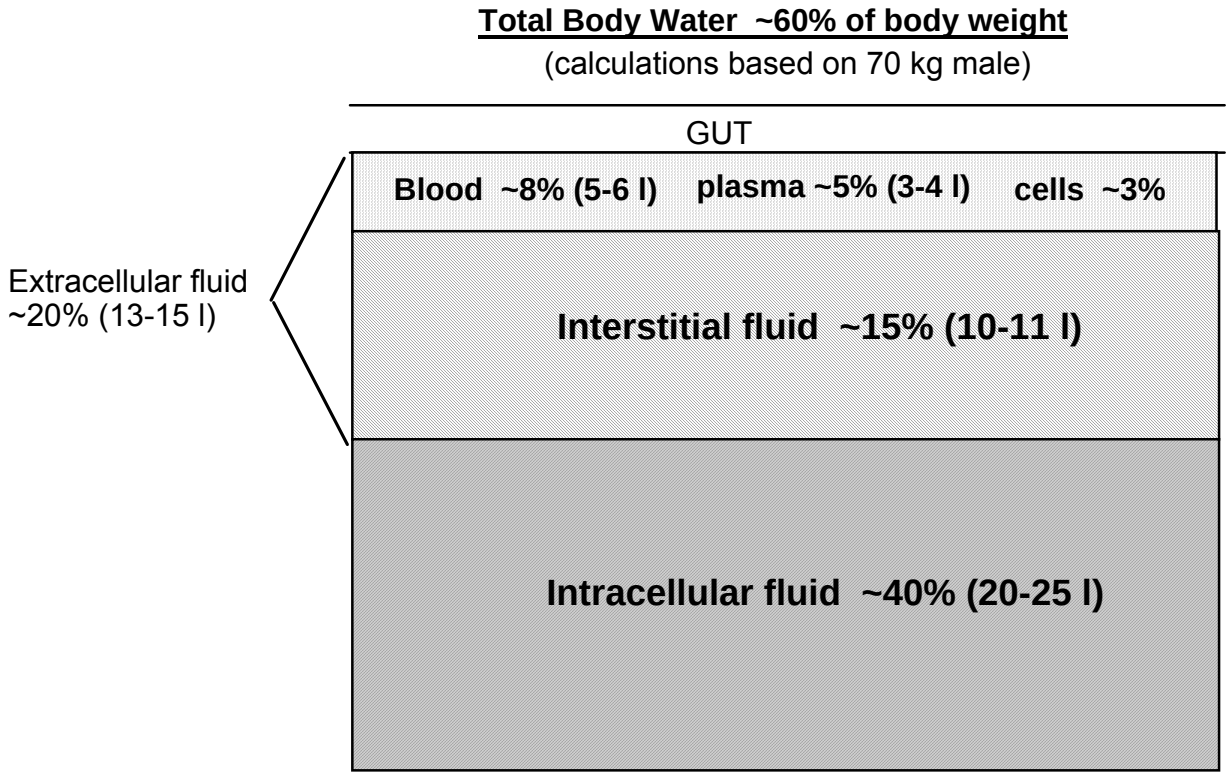
(1) Transport
- passive
- active

(2) pH effects

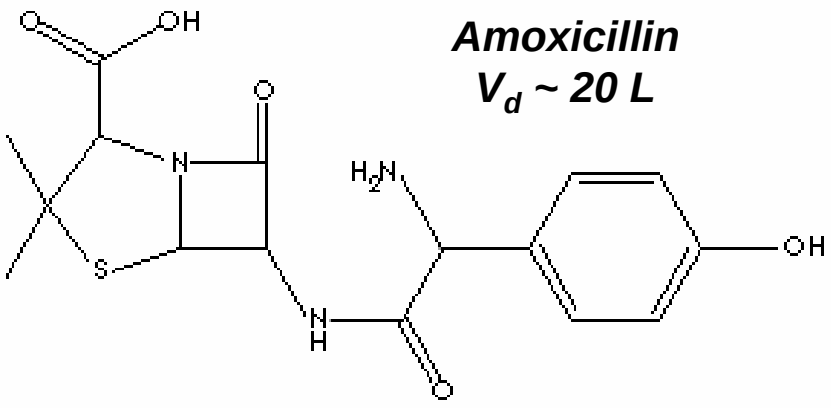
(3) Physical factors
- blood flow:
- surface area: lungs, 140 m^2; GI tract, 300 m^2 (small intestine); skin, 1.5-2 m^2
- contact time

Apparent Volume of Distribution

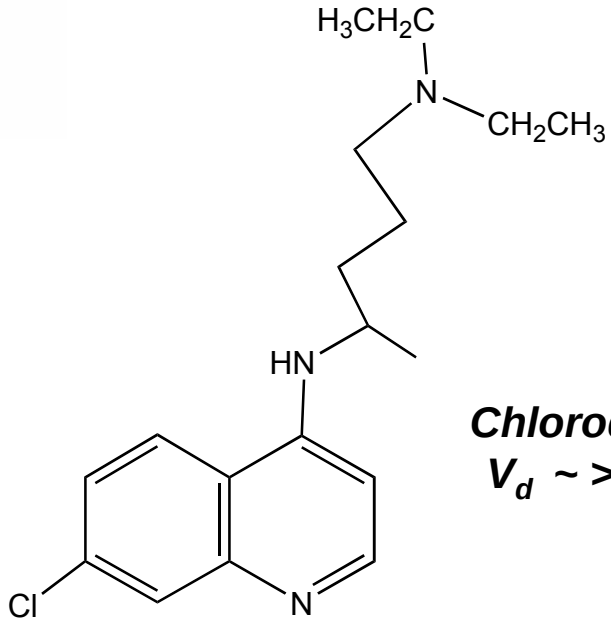
Hypothetical volume into which the drug is dissolved or distributed. Limited physical interpretation but useful concept to understand water compartments



- Definition - **V_d = (total amount of drug)/(plasma concentration)**
- Lipid soluble drugs have a high apparent volume of distribution



Amoxicillin
V_d ~ 20 L



Chloroquine
V_d ~ >10^4L

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Basic Kinetics

• Use the example of chemical kinetics to develop concepts of pharmacokinetics

• Basic rate law for a reaction in which molecule A is converted to molecule B:

A ➔ B $\qquad -\frac{dA}{dt} = \frac{dB}{dt} = k \bullet [A]^n$

• **Zero-order kinetics: n = 0**

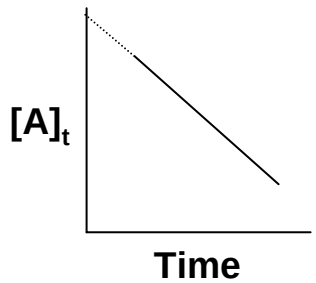
~ -dA/dt = k•$[A]^n$ becomes -dA/dt = k•1

~ Rearrange and integrate rate equation:

$$\int -dA = k \bullet dt$$

$$[A]_t = -k \bullet t + C \qquad t = 0 \Rightarrow C = [A]_0$$

$$[A]_t = -k \bullet t + [A]_0$$



~ Rate of the reaction is independent of substrate concentration

~ Rate constant k has units of concentration per unit time

~ Concentration versus time plot is linear

Basic Kinetics: Zero Order

- Processes subject to zero order kinetics:
  - ~ "Saturable" process: ligand molecules completely occupy available binding sites
  - ~ Metabolic enzymes
  - ~ Transport proteins

- Metabolic enzymes
  - ~ Michaelis-Menten rate equation considerations:

$$V = dP/dt = \frac{V_{max} \bullet [S]}{(K_m + [S])}$$

  - ~ When [S] >> K_m, all substrate binding sites occupied and enzyme operates at V_{max}

$$V = dP/dt = \frac{V_{max} \bullet \cancel{[S]}}{\cancel{[S]}}$$

- Examples of substrate/enzyme pairs frequently subject to zero-order kinetics in humans
  - ~ Aspirin - glycine conjugation and phenolic glucuronidation
  - ~ Ethanol - alcohol/aldehyde dehydrogenase
  - ~ Phenytoin - CYP2C9; K_m~ 5 mg/L; therapeutic range 10-20 mg/L

- Transport proteins are just enzymes, the product of which is movement of the substrate
  - ~ Glucose transporter in renal tubule cells (exceed filtered load of 320 ng/min)
  - ~ Acid transporters that handle salicylates

Basic Kinetics: First Order

- **First-order kinetics: n = 1**

~ $-dA/dt = k \bullet [A]^n$ becomes $-dA/dt = k \bullet [A]$

~ Rearrange and integrate rate equation:

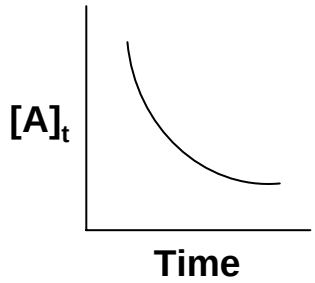
$$\int -\frac{dA}{[A]_t} = k \bullet dt$$

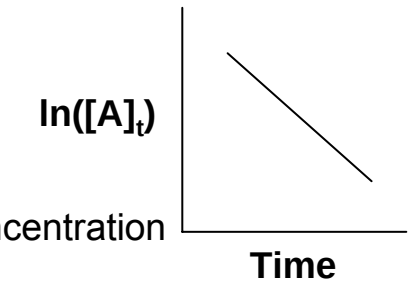
$$\ln([A]_t) = -k \bullet t + C \qquad t = 0 \Rightarrow C = \ln([A]_0)$$

$$\ln([A]_t) = -k \bullet t + \ln([A]_0)$$

$$\ln\left(\frac{[A]_t}{[A]_0}\right) = -k \bullet t$$

$$[A]_t = [A]_0 e^{-kt}$$





~ Rate of the reaction is dependent on substrate concentration
~ Rate constant k has units of reciprocal time
~ ln(Concentration) versus time plot is linear

~ Half-life - time to decrease concentration by one-half

$$\ln\left(\frac{[A]_t}{[A]_0}\right) = \ln\left(\frac{1}{2}\right) = -0.693 = -k \bullet t \qquad t_{1/2} = \frac{-0.693}{k}$$

First-Order Processes in the Body

- Definition of a first-order process: a reaction or activity, the rate of which depends on the concentration of reactants or the chemical of interest

- Most of the processes of absorption, distribution, metabolism, elimination are first-order

- Absorption: Rate of diffusion depends on the concentration gradient, i.e., the concentration of the "reactant."

$$-\frac{dQ}{dt} = P \bullet A \bullet \Delta C$$

- Metabolism and transport proteins: Enzyme kinetics generally first -order, except under conditions of substrate saturation:

$$\frac{dProduct}{dt} = V = \frac{V_{max} \bullet [S]}{K_m + [S]}$$

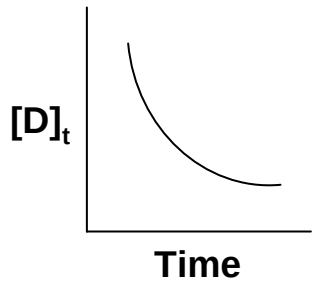
when Km>>[S], then $\frac{dProduct}{dt} = V = \frac{V_{max}}{K_m} \bullet [S] = k_{met} \bullet [S]$

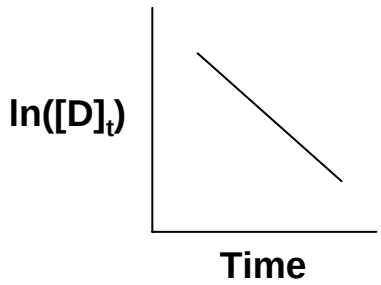
Pharmacokinetic Behavior

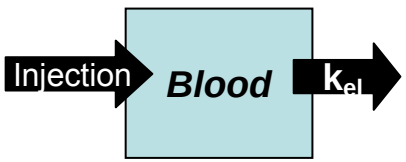
- Build an understanding of PK'S with simple models
- More complicated physiologically-based models combine many simple models
- Generally always consider elimination from blood with simple models
- Contributions to "elimination"
- **Single compartment with I.V. injection**

  ~ Considers the body as a single box
  ~ Rapid injection and presumed rapid ("instantaneous") distribution
  ~ Sample compartment (blood) and quantify drug as a function of time

  ~ Zero-order - strongly linear region of concentration vs time plot
  ~ First-order - linear plot of ln(concentration) vs time
  ~ The rate constant, k, is now the elimination rate constant, k_{el}
  ~ Half-life = $0.693/k_{el}$





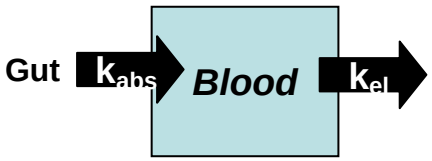


$$\ln\left(\frac{[D]_t}{[D]_0}\right) = -k \bullet t$$

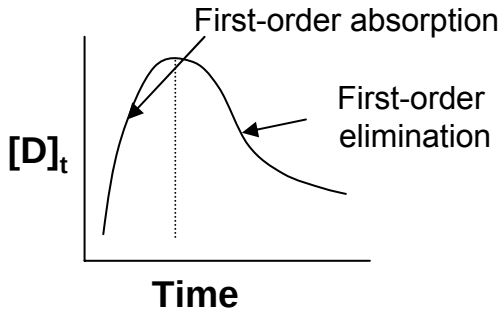
Pharmacokinetic Behavior

- **Single compartment with absorption from gut**

~ Factor in kinetics of absorption from gut with kinetics of elimination from blood
~ Distribution no longer instantaneous
~ Assume first-order absorption from gut (why?)
~ How to prove both first-order absorption and elimination?



$$d\frac{[D]_p}{dt} = k_{abs}[D]_{gut} - k_{el}[D]_p$$



$$d\frac{[D]_p}{dt} = k_{abs}[D]_{gut} - k_{el}[D]_p = k_{abs}\left([D]_{gut0}e^{-k_{abs}t}\right) - k_{el}[D]_p$$

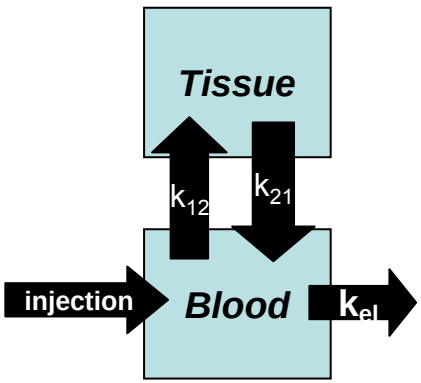
$$Integrate \Rightarrow [D]_{p_t} = [D]_{gut_0}\left(\frac{k_{abs}}{k_{abs}-k_{el}}\right)\left(e^{-k_{el}t} - e^{-k_{abs}t}\right)$$

~ As drug absorbed from gut, e^{-kabst} goes to zero and $[D]_p$ dominated by k_{el}

Pharmacokinetic Behavior

- **Two compartments with I.V. injection**

~ Injected drug distributes in blood "instantaneously"
~ Drug moves out of blood into tissue compartment: first-order (why?)
~ As blood concentration falls, higher tissue concentration drives return to blood (why?)
~ Examine plasma concentration versus time plot in this model

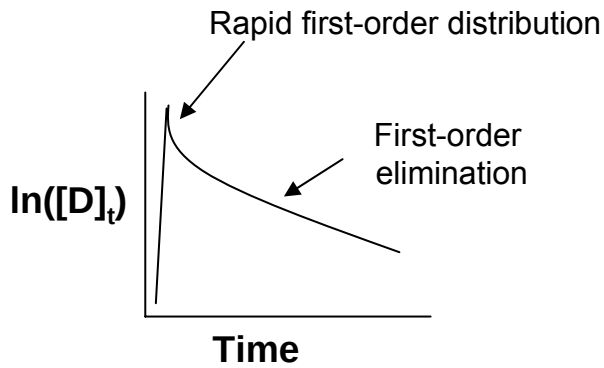


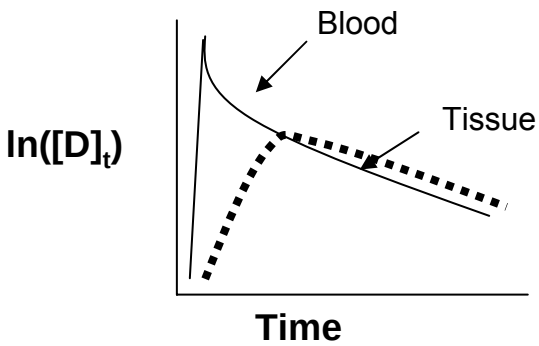
$$d\frac{[D]_p}{dt} = k_{21}[D]_{tis} - k_{12}[D]_p - k_{el}[D]_p$$

$$Integrate \Rightarrow [D]_{p_t} = Ae^{-\alpha t} + Be^{-\beta t}$$

$$\alpha + \beta = k_{12} + k_{21} + k_{el} \qquad A = [D]_{p_0}\left(\frac{\alpha - k_{21}}{\alpha - \beta}\right)$$

$$\alpha \bullet \beta = k_{21} \bullet k_{el} \qquad B = [D]_{p_0}\left(\frac{k_{21} - \beta}{\alpha - \beta}\right)$$





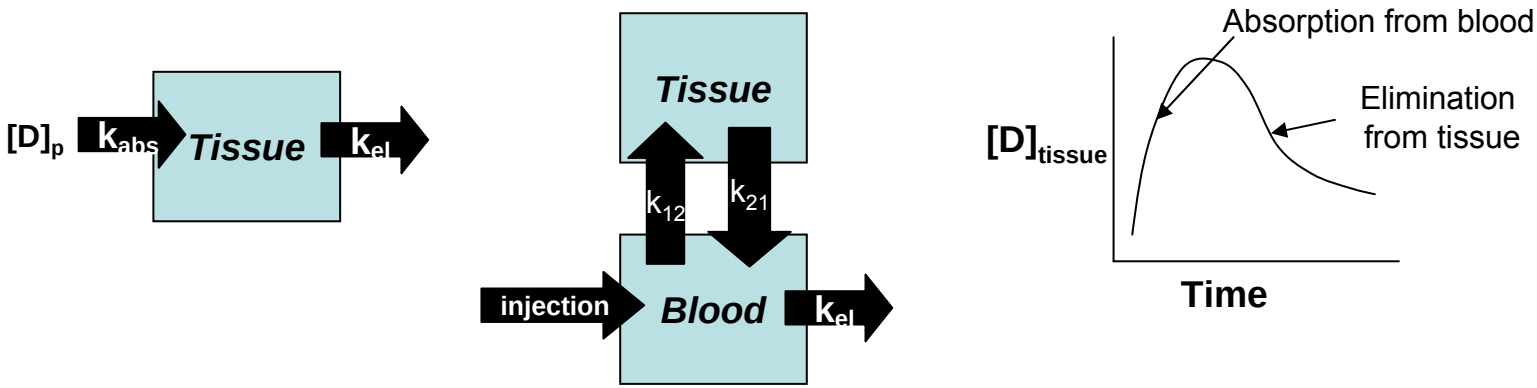
Pharmacokinetic Behavior

- **Correlate single- and multi-compartment models**

  ~ Graph of $[D]_{tissue}$ versus time from two compartment model is identical to graph of single compartment model with 1° absorption and 1° elimination

  ~ Thus, string together single compartment models for each entry and exit component

  ~ Don't hassle with the complexity of ≥ 2 compartment models



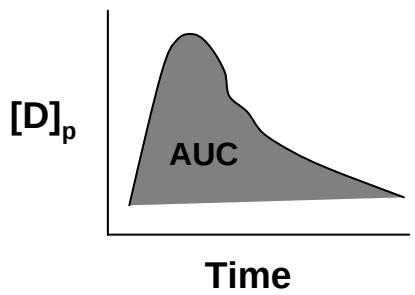
Clearance

- Important concept in toxico- and pharmacokinetics
- Clearance represents the rate of removal of a chemical from blood, tissue, compartment or entire body
- Physical interpretation: volume of blood/tissue from which the chemical is removed in a set time period. Example: Cl = 100 ml/min means that the chemical is completely removed from 100 ml of blood every minute.
- Parameter is independent of the mechanism of removal (*i.e.*, excretion, equilibrium binding in tissue, metabolism, *etc*.)
- Definitions:

$CL = k_{el} \bullet V_d$ where k_{el} is the first-order rate constant for elimination of a chemical from the blood or tissue; V_d is the apparent volume of distribution of the chemical.

$$CL = \frac{\text{Dose}}{AUC_0^\infty}$$ where AUC is the area under the blood/tissue concentration versus time curve over the time period t = 0 to t = ∞.

$$CL_{organ} = Q\left(\frac{C_A - C_V}{C_A}\right) = Q \bullet E$$ where Q is blood flow to the organ, C_A is the arterial blood concentration, C_V is the venous blood concentration and E is the extraction ratio



Bioavailability

(1) Defined as the percentage (fraction) of administered drug entering the blood.

- AUC: area under the plasma concentration versus time curve
- Ratio of oral (or other route) AUC to intravenous AUC

$$CL_{organ} = Q\left(\frac{C_A - C_V}{C_A}\right) = Q \bullet E$$

$$F_{max} = 1 - E_H$$

where F_{max} is the maximum oral bioavailability for a drug given by mouth, and E_H is the hepatic extraction ratio

(2) Influences

- First pass metabolism
- solubility - hydrophilic implies poor diffusion; hydrophobic implies insoluble in aqueous media
- chemical stability - penicillin and acid pH
- drug formulation - salt form, particle size, "excipients" all affect rate of dissolution

(3) Bioequivalence - relative bioavailability of two drugs

How to administer a drug

- Need to determine how frequently to give a drug so that we maintain blood concentration in the therapeutic range and below the toxic range

- Define the concept of steady-state concentration of drug in blood ($\mathbf{C_{ss}}$):
  - ~ balance between dose rate (how many times a day), rate of absorption from gut and rate of elimination blood
  - ~ eventually reach a state in which drug concentration fluctuates within a narrow window (akin to chemical kinetics with formation balancing degradation)

- Achieve Css at ~4 half-lives: quantify average $[D]_p$ at $t > 4 \times t_{1/2}$

- Solve equation below for T

$$C_{ss} = \frac{F \bullet dose}{CL \bullet T}$$

C_{ss} = steady-state concentration (mg/mL)
F = fractional bioavailability
CL = blood clearance (mL/min)
T = dosage interval (min)
Dose in mg