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Pharmacokinetic considerations in clinical and translational cancer research

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Acknowledgement

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University of Illinois, Chicago

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Outline

Pharmacokinetics

- Absorption
- Distribution
- Metabolism
- Elimination
- Concentration-time
- Practical resources for understanding PK profiles

Translational considerations

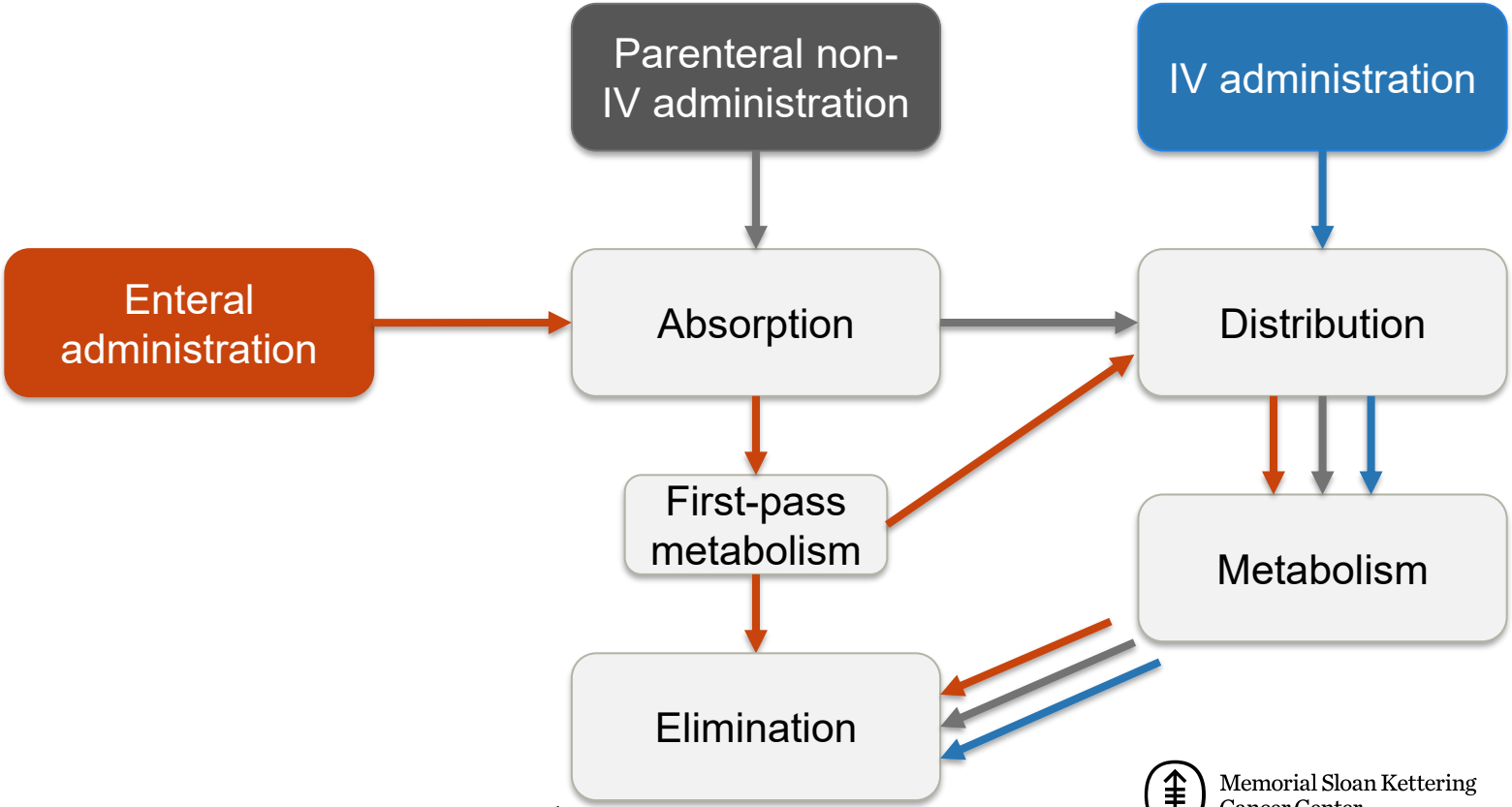
- Allometric scaling
- First in human studies

Pharmacokinetics vs pharmacodynamics

- Pharmacokinetics: mathematical representation of drug disposition over time
  - Absorption, distribution, metabolism, and/or elimination (“what the body does to the drug”)
  - Concentration-time profile representation of this processes
- Pharmacodynamics: mathematical representation of relationship between drug concentration/exposure, pharmacologic effect, and clinical effect (“what the drug does to the body”)
- Understanding drug disposition principles and being able to interpret related data can be crucial to a well-designed clinical study

Ernmyster K and Christam E. Nursing Pharmacology [2nd edition]. 2023.

Drug fate (and action) depends on convoluted pathways



Ernmyster K and Christam E. Nursing Pharmacology [2nd edition]. 2023.

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Drug absorption

- Movement of drug from administration site to site of action (usually into circulation)
- Often described for orally-administered drugs, but also a vital factor for non-IV parenteral routes
  - Inhalational
  - Intramuscular
  - Subcutaneous/intradermal
  - Transdermal

Ernmyster K and Christam E. Nursing Pharmacology [2nd edition]. 2023.

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Key factors influencing absorption: disintegration/dissolution, diffusion

- Solid/semisolid drug solubility in the delivery compartment is vital in its ability to reach site of action (particularly for oral route)
- Factors influencing solubility and/or diffusion of a drug and/or dosage forms may include:
  - Drug/route physicochemical/biological properties
  - pH: do native pH or induced pH change affect dissolution?
  - Fed vs fasted state: effects of lipid and/or protein content, food influence on metabolism (eg, small intestinal CYP3A4 inhibition by grapefruit juice)
  - Passive permeability, facilitated diffusion/active transport (eg, P-glycoprotein), and saturability
  - Expression of metabolizing enzymes, microbiota
  - Disease-related changes in any of the above, altered anatomy

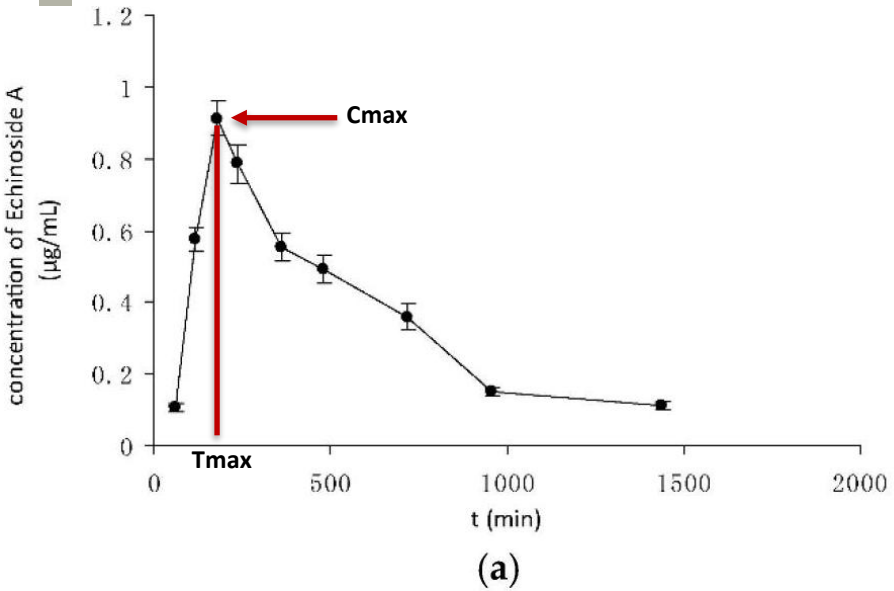
Eur J Pharm Sci. 2019;134(153-75).
Pharm Res. 1998;7(7)756-61.
Pharm Res. 1997;14(4):497-502.
Pharm Res. 2006;23(1):165-76.
J Physiol Biochem. 2007;63(1):75-81.
N Engl J Med. 1981;305(14):789-94.
Drug Discov Today. 2017;22(5):761-75.
J Clin Invest. 1997;99(10):2545-53.

Bioavailability is a function of multiple co-occurring processes

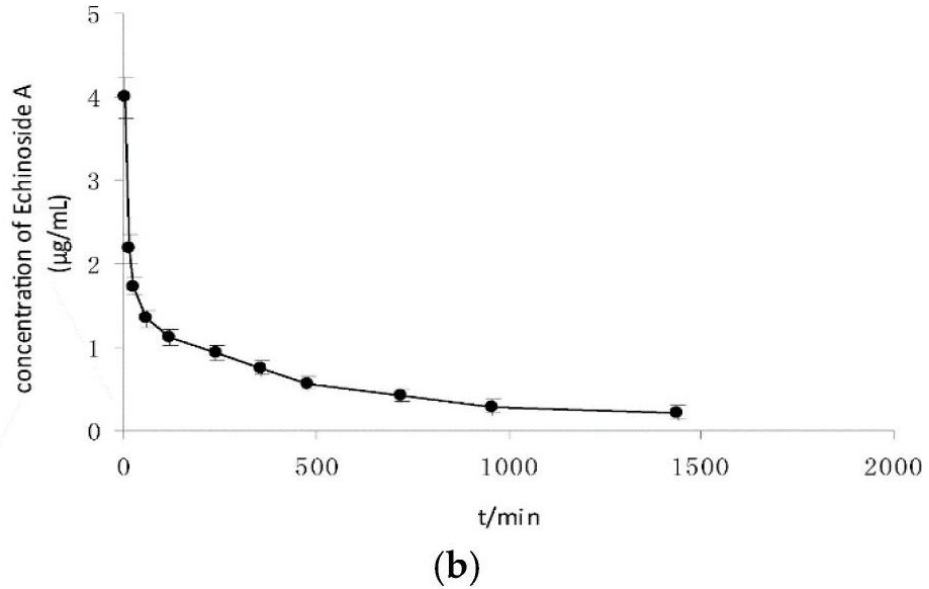
- Factors determining absorption influence bioavailability (*F*), defined by FDA as the rate and extent to which the active ingredient or active moiety is absorbed and becomes available at the site of action
- For a given drug, bioavailability may depend on:
  - Rate and extent of absorption
  - Extent of first-pass hepatic metabolism
  - Elimination for drugs undergoing first-pass metabolism
  - Rate and extent of distribution to site of action
- While surrogate data can be used in specific situations, bioavailability testing comparing IV exposure to planned route exposure is crucial for many new drugs

Biochem Pharmacol. 2014;87(1):93-120.
Tomlin M, editor. Pharmacology & Pharmacokinetics: A Basic Reader. London, United Kingdom: Springer-Verlag London Limited; 2010.

Example of bioavailability study: IV vs PO



(a)



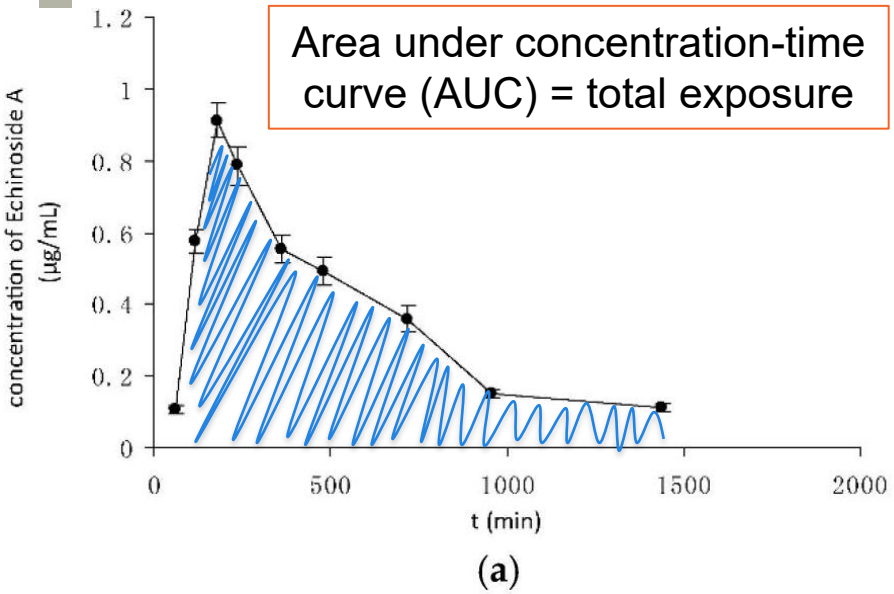
(b)

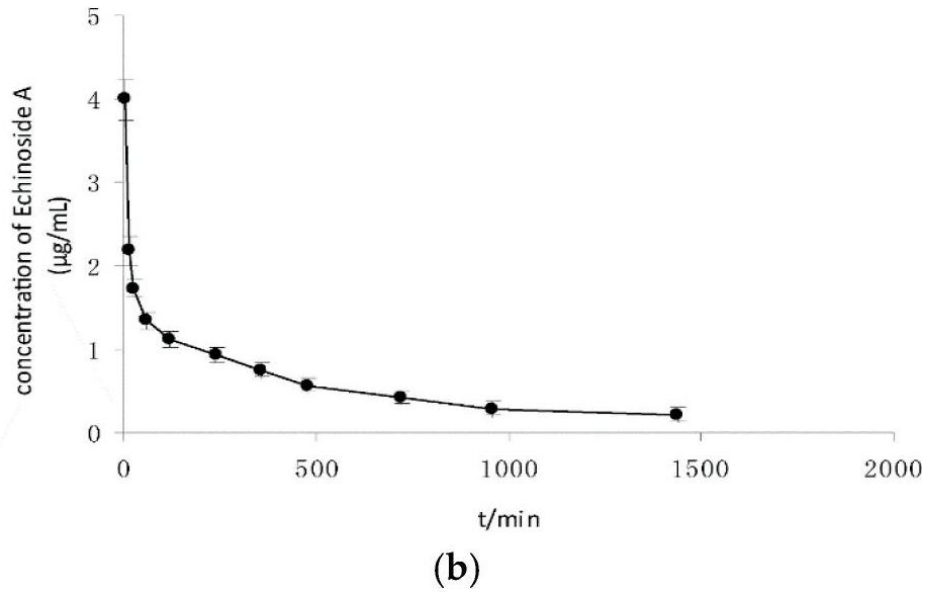
Enteral administration

Derivative of: Mar Drugs. 2016;14(6):114.
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Concentration-time AUC defines exposure



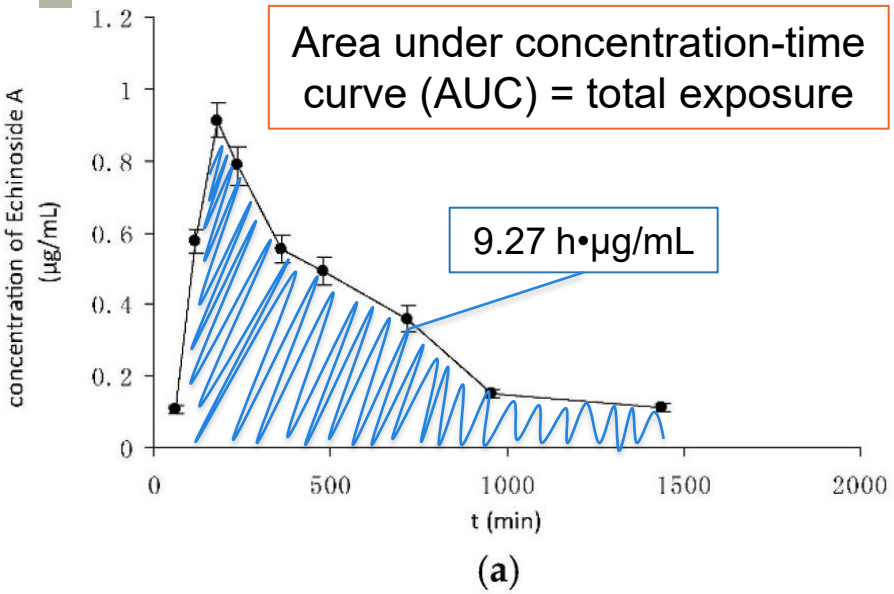


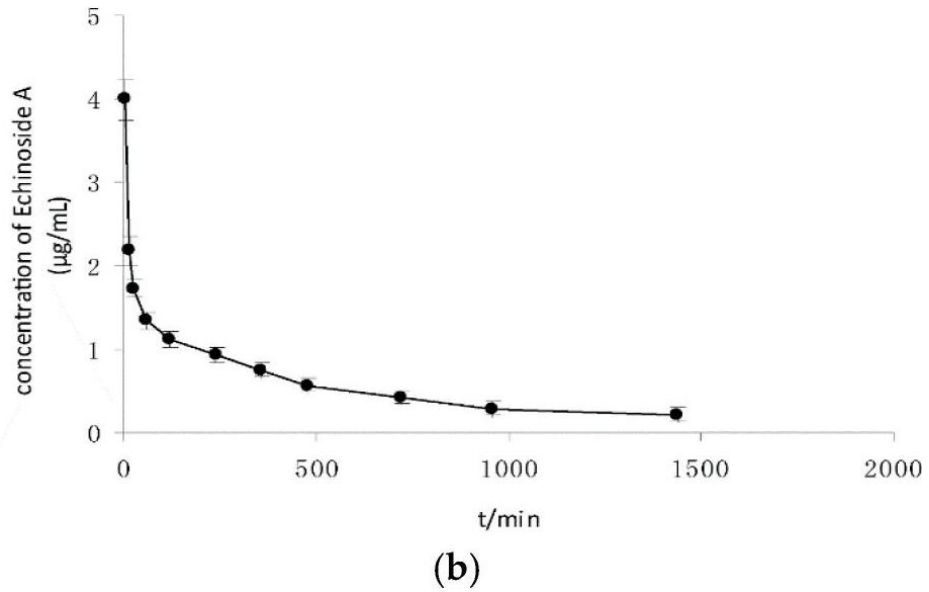
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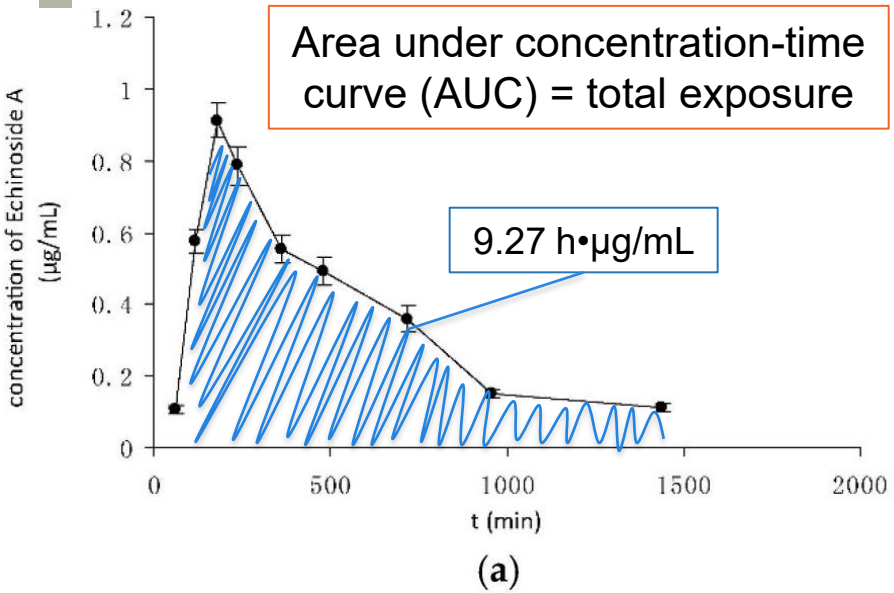


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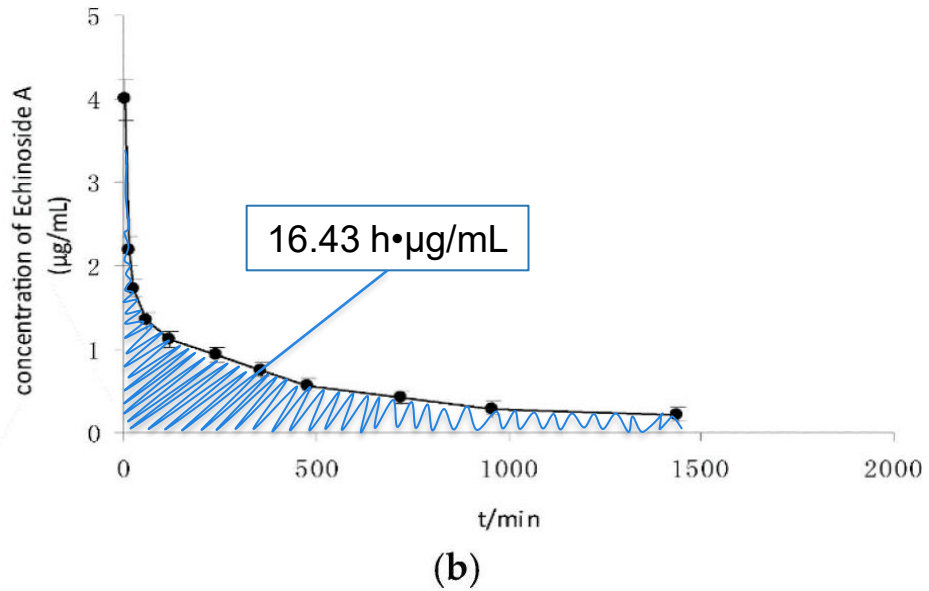
Derivative of: Mar Drugs. 2016;14(6):114.
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$AUC_{non\text{-}IV}$ relative to AUC_{IV} defines bioavailability



Enteral administration

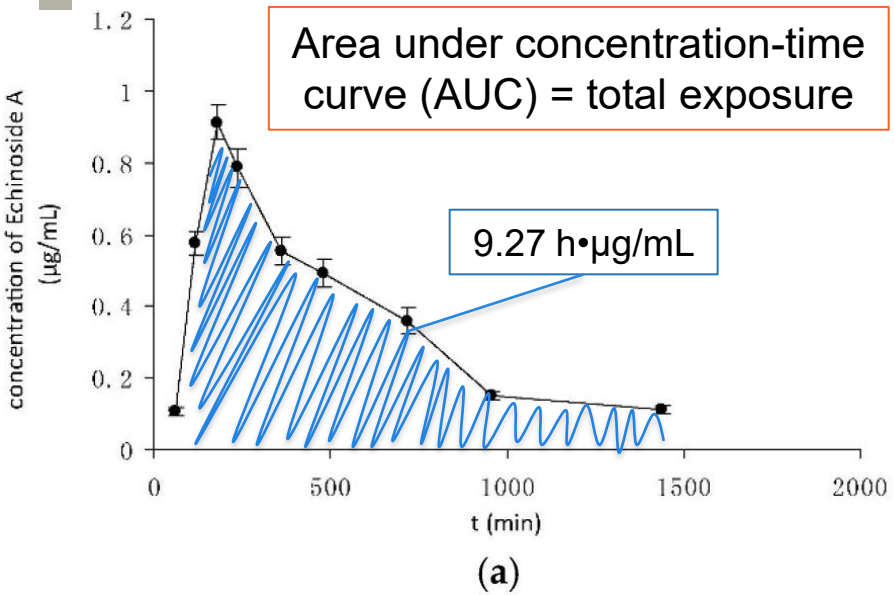


IV administration

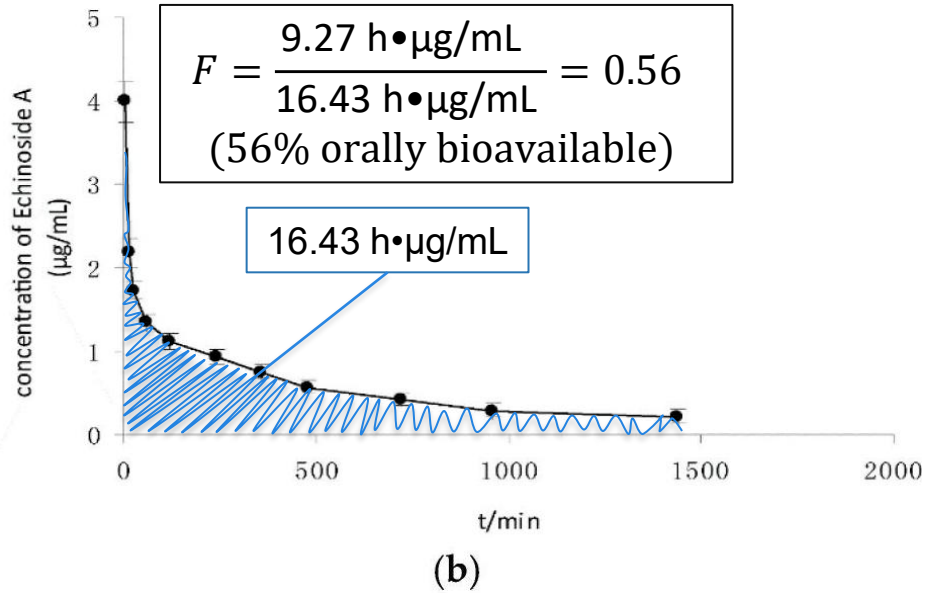
Derivative of: Mar Drugs. 2016;14(6):114.
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$AUC_{non\text{-}IV}$ relative to AUC_{IV} defines bioavailability



Enteral administration



IV administration

Derivative of: Mar Drugs. 2016;14(6):114.
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Absorption-related questions to consider in study design

- What is the bioavailability of the drug, if non-IV? Is it known or estimated, and are these data in humans?
- Is absorption mediated by transporters (influx or efflux)? Is it saturable?
- Is drug absorption impacted by:
  - Fed/fasted state? Meal content?
  - Antacid use? If so, do all vs some antacids need to be avoided (eg, PPIs vs H_2RAs vs short-acting antacids)?
  - Chelation (eg, avoidance of heavy metals, dairy)?
  - Disease features in target population?

Case #1

Compound X is being evaluated in a phase II clinical trial. The investigational brochure lists the following information for clinical PK data: “After oral administration of compound X to healthy subjects on an empty stomach, bioavailability was determined to be 90% and Cmax was reached within 1 hour. After administration with a high-fat meal, Cmax had decreased by 2% with no change in mean time to Cmax or AUC.” Which of the following statements would be true regarding the administration of compound X based on the information above?

1. Compound X needs to be administered with a high fat meal
2. Compound X should be administered on an empty stomach
3. Compound X can be taken with or without food
4. Compound X needs to be administered with a high protein meal

Drug distribution and V_D

- Distribution: drug movement between body compartments
- Apparent volume of distribution (V_D):
  - Intended to represent (not approximate) fluid volume containing drug and understand the extent of extravascular distribution
  - Calculated using dose administered and extrapolated concentration at t_0
- V_D is often difficult to reconcile physiologically due to protein binding (plasma/extracellular fluid proteins, tissue)
  - High plasma/ECF protein binding generally produces a low V_D, whereas high tissue binding typically produces very high V_D
  - For example, V_D of ibrutinib is ~10,000L
- Kinetic modeling using concentration-time data is generally needed to evaluate drug distribution and calculate V_D

Biochem Pharmacol. 2014;87(1):93-120.
Cancer Chemother Pharmacol. 2015;75(1):111-21

Tomlin M, editor. Pharmacology & Pharmacokinetics: A Basic Reader. London, United Kingdom: Springer-Verlag London Limited; 2010.

Plasma protein binding

- Albumin and α_1-acid glycoprotein (AAG) are predominant drug-binding proteins in extracellular fluid
- Albumin is abundant and is most likely to bind weak acids; AAG is less abundant but carries higher/broader binding affinity
- Importantly, protein binding is known to vary between species
- Protein binding is reversible and typically non-saturable, however:
  - Some drugs can be competitively displaced by other drugs with affinity for binding site, leading to changes in free/active drug concentrations
  - If binding is saturable, increasing dose will have unpredictable PK effects

Biochem Pharmacol. 2014;87(1):93-120.
Adv Biol Skin. 1972;12:61-3.

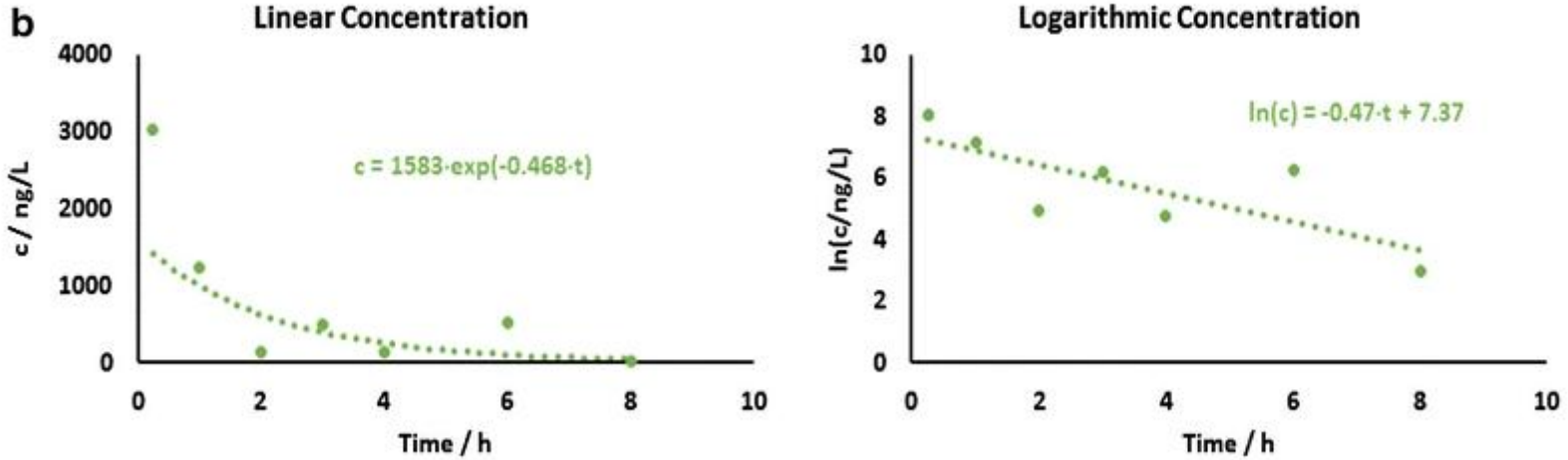
Compartmental analysis

- Several pharmacokinetic modeling systems exist
  - Non-compartmental – empirical estimation of pharmacokinetic parameters based on assumptions of linearity
  - Compartmental – construction of system of ≥ 1 compartments to describe drug concentrations over time, assuming each compartment represents a distinct and kinetically homogeneous ‘mixture’
  - Physiologic – individual organs are assigned literature-defined model parameters in a large multicompartmental model
- Compartmental models are frequently used to understand drug distribution without invasive/impractical monitoring

Trends Pharmacol Sci. 1991;12(3):96-101.

Example: Monophasic (one-compartment) distribution

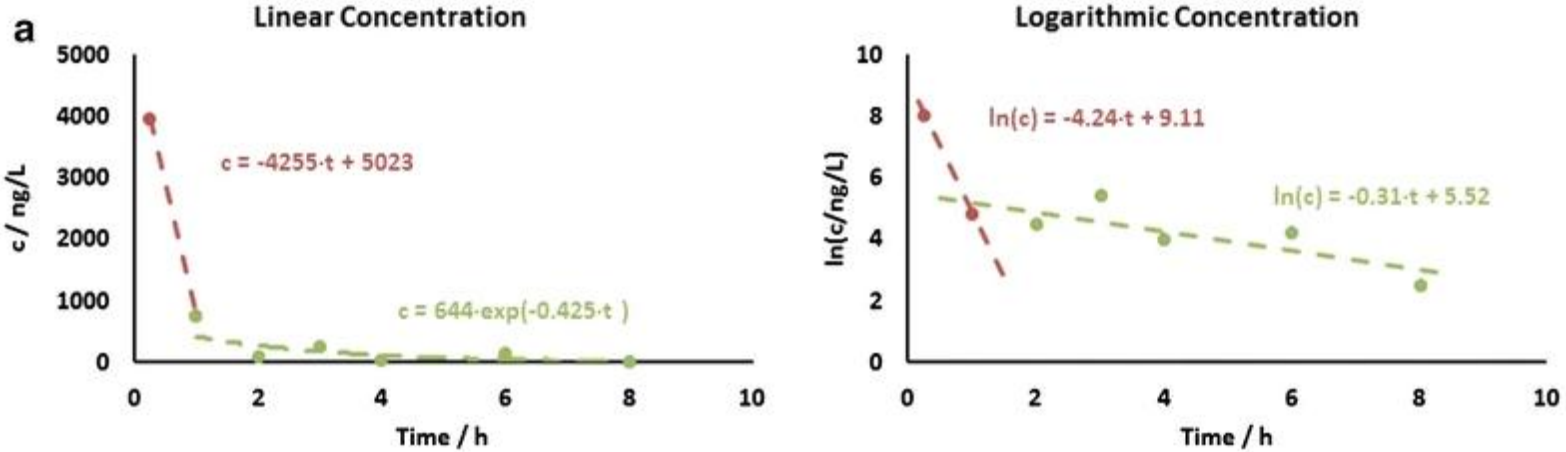
- Drug distributes rapidly and the V_D represents a single, pharmacokinetically homogeneous compartment
- On a semilogarithmic plot, concentration-time appears linear



Derivative of: J Nanobiotechnology. 2016;14(1):57.
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Example: Biphasic (two-compartment) distribution

- Plasma concentration drops rapidly due to simultaneous distribution outside central compartment and elimination (alpha phase, red line)
- Upon distributional equilibrium, rate of elimination predominates (beta phase, green line)



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Drug distribution across BBB

- Understanding whether a drug crosses the blood-brain barrier (BBB) is increasingly important for both efficacy and toxicity
- Cerebral endothelial and glial cells form tight junctions without fenestrations, making penetration dependent on transporters for many drugs
- Factors influencing BBB penetration include:
  - Whether drug is a substrate of relevant influx/efflux transporter(s)
  - Lipophilicity/ionization and molecular weight
  - Induced changes in BBB permeability (eg, increased permeability in meningitis)
- Measuring BBB penetration in humans is difficult and the validity of surrogate measures (eg, CSF concentrations) is controversial

Nat Rev Neurosci. 2006;7(1):41-53.
J Pharmacol Exp Ther. 2011;339(3):935-44.
Drug Metab Pharmacokinet. 2014;29(5): 419-26.

Distribution-related questions to consider in study design

- Is V_D known? How was it estimated?
- Is plasma protein binding (and/or tissue binding) characterized? If so, is it:
  - Based on human data?
  - Saturable?
- Is there a known model of drug distribution? If so, is it:
  - Estimated non-compartmentally vs compartmentally (vs another model)?
  - Based on human drug sampling vs animal or simulated/surrogate data?
- Does the drug penetrate the BBB? To what degree? How was this evaluated?
- Is the drug known to get to the desired site of action?

Clearance is a function of metabolism and excretion

- Clearance and elimination are often used interchangeably and generally refer to drug removal from the body (or, more often, plasma volume)
- For non-protein drugs, clearance is predominantly mediated by the liver, kidneys, or both
  - Note, with the exception of biliary excretion, hepatic clearance refers to removal of a given compound (via metabolism) from circulation
  - In other words, clearance does not necessarily refer to removal of a drug and all of its byproducts
- Metabolism occurs principally (not exclusively) in the liver and functions to increase hydrophilicity to allow for elimination
- Other sites of metabolism include (not limited to):
  - Intestines (eg, fentanyl)
  - Lung (eg, propranolol)
  - Brain/BBB (eg, alprazolam)
  - Plasma (hydrolysis, eg, protein drugs, bendamustine)

Curr Drug Metab. 2007;8(7):658-75.
Br J Anaesth. 2003;91(1):50-60.
PLoS One. 2008;3(6):e2337.

Phase I & II metabolic reactions

- Coined by Richard Tecwyn Williams based on the hypothesis that drug metabolism was reliably sequential
- Phase I: Catabolic, function to polarize compound by adding or exposing a functional group (eg, hydroxyl, amine, sulfhydryl)
- Phase II: Anabolic, function to further increase hydrophilicity by conjugation (eg, to glucuronide, glutathione, N-acetyl groups)
- Contrary to nomenclature implication, metabolic reactions may occur in any order or not at all

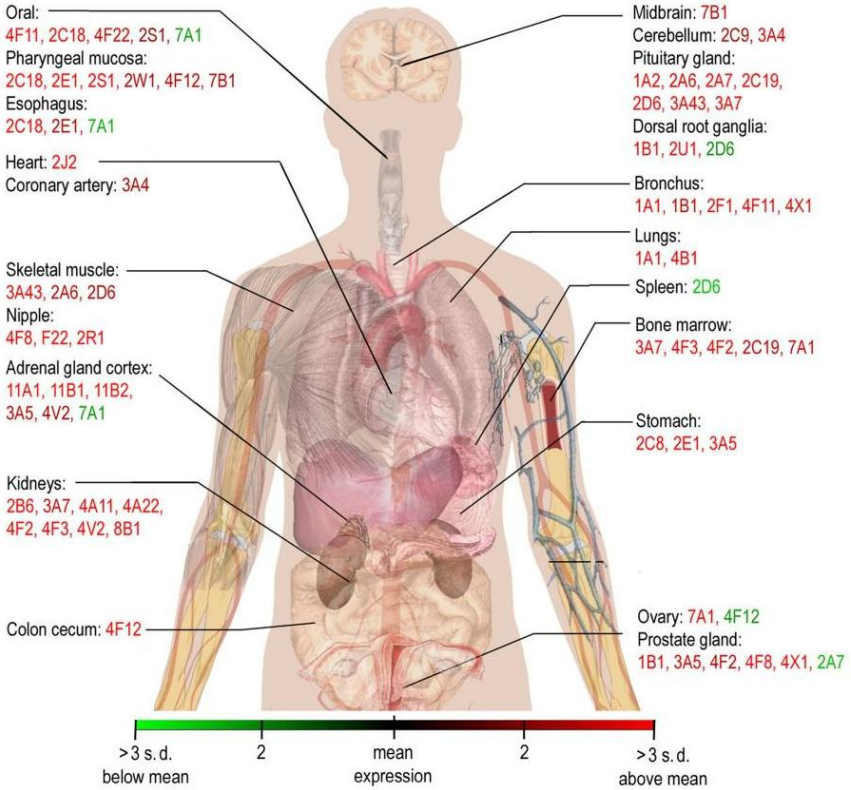
Drug Metab Rev. 2005;37(4):575-80.

Phase I metabolism: CYP enzymes

- Cytochrome P450: superfamily of microsomal monooxygenases found in endoplasmic reticulum of myriad tissues, principally liver
  - P450 refers to peak spectrophotometric absorbance band at 450nm
  - Some other expression locales include gut wall, lung, brain, kidneys
- Catalyze substrate-specific oxidation, typically through electron transfer from NADPH to activate molecular oxygen
- Isozymes categorized by family and subfamily sequence homology
  - Most hepatic metabolism is mediated by CYP1, 2, and 3 families
  - Five isozymes participate in metabolism of approximately 90% of drugs: CYPs 3A4, 2D6, 2C9, 2C19, and 1A2
- Drug-, food/lifestyle-, disease-, and polymorphism-mediated effects on CYP function are crucial considerations for clinical research

Genome Biol. 2000;1(6):REVIEWS3003.
Curr Drug Metab. 2002;3(6):561-97.
Drug Des Devel Ther. 2018;12:1147-56.
Curr Drug Metab. 2011;12(5):487-97.

CYP mRNA expression across various tissues



Derivative of: PLoS One. 2013;8(12):e82562.
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Phase I metabolism: Non-CYP450 enzymes

- Various other enzymes participate in hepatic and extra-hepatic drug metabolism via biotransformation
  - Aldehyde dehydrogenase (eg, cyclophosphamide)
  - Carbonyl reductase (eg, doxorubicin)
  - Cytidine deaminase (eg, cytarabine)
  - Dihydropyrimidine dehydrogenase (eg, 5-fluorouracil)
  - Esterases (eg, capecitabine)
  - Flavin-containing monooxygenases (FMOs) (eg, tamoxifen)
  - Myeloperoxidase (eg, etoposide)
  - Thiopurine methyltransferase (eg, 6-mercaptopurine)
  - Xanthine oxidase (eg, 6-mercaptopurine)
- Participation of non-CYP enzymes in biotransformation of a given drug is often poorly-understood

Figg WD, McLeod HL, Editors. Handbook of Anticancer Pharmacokinetics and Pharmacodynamics, 2e. New York, NY, United States: Springer Science+Business Media; 2014.

Phase II metabolism

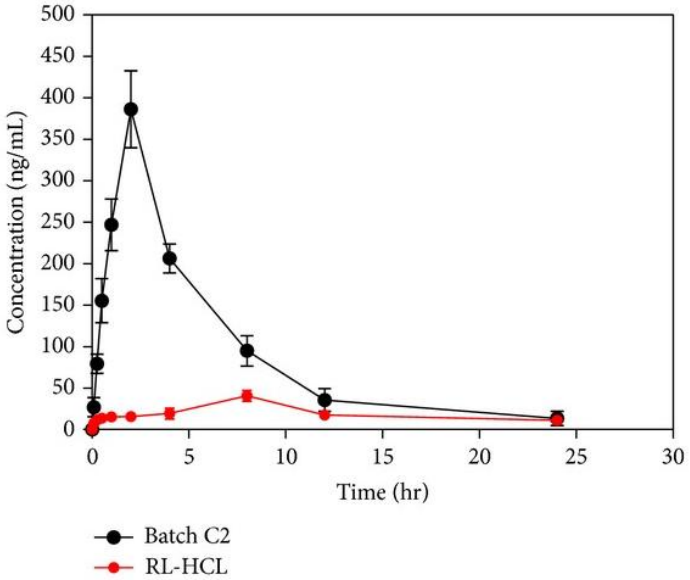
- Major reaction pathways include glucuronidation, sulfation, and acetylation, significantly increasing water solubility
  - Glucuronidation by UDP-glucuronosyltransferase (UGT) superfamily
    - Substrate specificity, similar to CYPs, with numerous drug substrates and high enzymatic capacity
    - Also prone to polymorphism-mediated variability in function
  - Sulfation by sulfotransferases (limited substrates, lower capacity)
  - Acetylation by N-acetyltransferases 1 and 2 (variable capacity due to polymorphism potential)
- Other pathways include methylation, amino acid conjugation (eg, glutathione S-transferases)

Figg WD, McLeod HL, Editors. Handbook of Anticancer Pharmacokinetics and Pharmacodynamics, 2e. New York, NY, United States: Springer Science+Business Media; 2014.

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First-pass metabolism

- Drugs administered orally have potential to undergo significant metabolism before reaching systemic distribution due to:
  - Intestinal enterocyte CYP3A4 expression
  - Absorption into portal vein circulation with potential for hepatic metabolism and/or biliary excretion
- Drugs known to undergo first-pass metabolism may have altered kinetics in patients with liver disease or injury



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Biochem Pharmacol. 2014;87(1): 93-120.

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Metabolism-related questions to consider in study design

- Does the drug undergo significant CYP-mediated metabolism? If so, is it mediated by a single isozyme or multiple isozymes?
- Does the drug undergo significant non-CYP-mediated metabolism? If so, is/are the metabolic pathway(s) well-characterized? Saturable?
- In either case above, how sensitive is the drug to changes in enzyme function? Do polymorphisms need to be considered? Should an interaction study be done?
- Is the administered drug a prodrug?
- Does the drug undergo first-pass metabolism? How does this affect bioavailability?
- Are metabolites formed? Have they been characterized as active (if so, how active?), inactive, and/or toxic (if so, what toxicities?)

Case #2

Compound Y is being studied *in vivo*. A 10 mg dose is administered both IV and PO, and respective blood draws occur to form a concentration/time curve. The AUC of the PO drug was lower than the IV drug, and the bioavailability (F) was determined to be 0.25. It's determined the compound Y undergoes extensive first metabolism. How much of the PO 10 mg dose is absorbed and reaches systemic circulation?

1. 3.5 mg
2. 10 mg
3. 7 mg
4. 2.5 mg

Case #3

Compound Y is being evaluated in a phase I/II study. The investigational brochure describes a CYP450 phenotyping study performed in human liver microsomes and human recombinant CYP enzyme assays. The results show that compound Y is a strong CYP3A4 substrate, with minor/potential contributions from CYP2C8 and CYP2C9. Which of the of the following statements is true?

1. Compound Y should not be administered with any strong CYP3A4 inhibitors to prevent toxicity
2. Compound Y should be administered with strong CYP3A4 inducers to improve efficacy
3. Compound Y should be administered with strong CYP2C8 inhibitors to improve efficacy
4. Compound Y should be administered with strong CYP2C9 inducers to improve efficacy

Drug excretion mediated by the kidneys

- Overall renal drug clearance is determined according to rates of:
  - Glomerular filtration: relatively small, unbound compounds
  - Active tubular secretion: transporter-mediated, saturable
  - Tubular reabsorption: passive diffusion, primarily lipophilic compounds
- Renal clearance can be estimated using urine and plasma drug levels over a given time period
- Physiologic clearance mechanism can be further estimated using renal clearance, unbound drug fraction in plasma, and GFR
  - Renal clearance < (unbound fraction • GFR): net reabsorption
  - Renal clearance > (unbound fraction • GFR): net secretion
  - Renal clearance ≈ (unbound fraction • GFR): neither

Biochem Pharmacol. 2014;87(1):93-120.

Drug excretion mediated by the hepatobiliary system

- Larger drug molecules (and some drugs with large conjugates, eg, glucuronide) may be excreted from hepatocytes into bile
- Some drugs are also actively transported into bile
- As drug-containing bile is excreted into intestines, drug/metabolite may undergo:
  - Excretion in feces
  - Enterohepatic recirculation:
    - Reabsorption into circulation unchanged (usually lipophilic compounds)
    - Deconjugation via colonic bacteria and subsequent reabsorption as intact drug
- Biliary excretion is usually not a major elimination pathway due to slow biliary flow

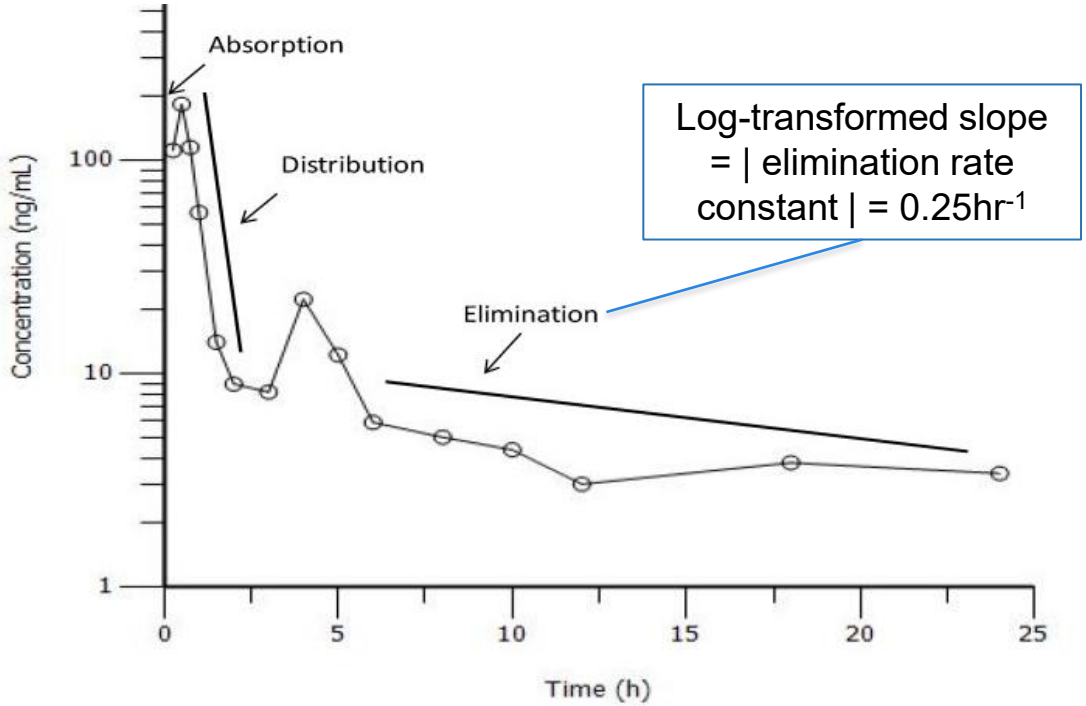
Biochem Pharmacol. 2014;87(1):93-120.
Mol Pharm. 2006;3(3):198-211.

First-order versus zero-order elimination

- Characteristics of route(s) of elimination culminate in the concentration-time curve to display elimination that is:
  - Concentration-dependent (first-order): A constant **proportion** of plasma is cleared of drug per unit time, with an associated elimination rate constant
  - Time-dependent (zero-order): A constant **amount** of drug is cleared per unit time
- First-order kinetics indicate elimination pathway(s) have high capacity and/or are unsaturated; additional doses/change in dose should produce proportional changes in concentration
- Zero-order (Michaelis-Menten) kinetics indicate elimination pathway(s) are saturated; additional doses/change in dose will produce disproportionate changes in concentration

Figg WD, McLeod HL, Editors. Handbook of Anticancer Pharmacokinetics and Pharmacodynamics, 2e. New York, NY, United States: Springer Science+Business Media; 2014.

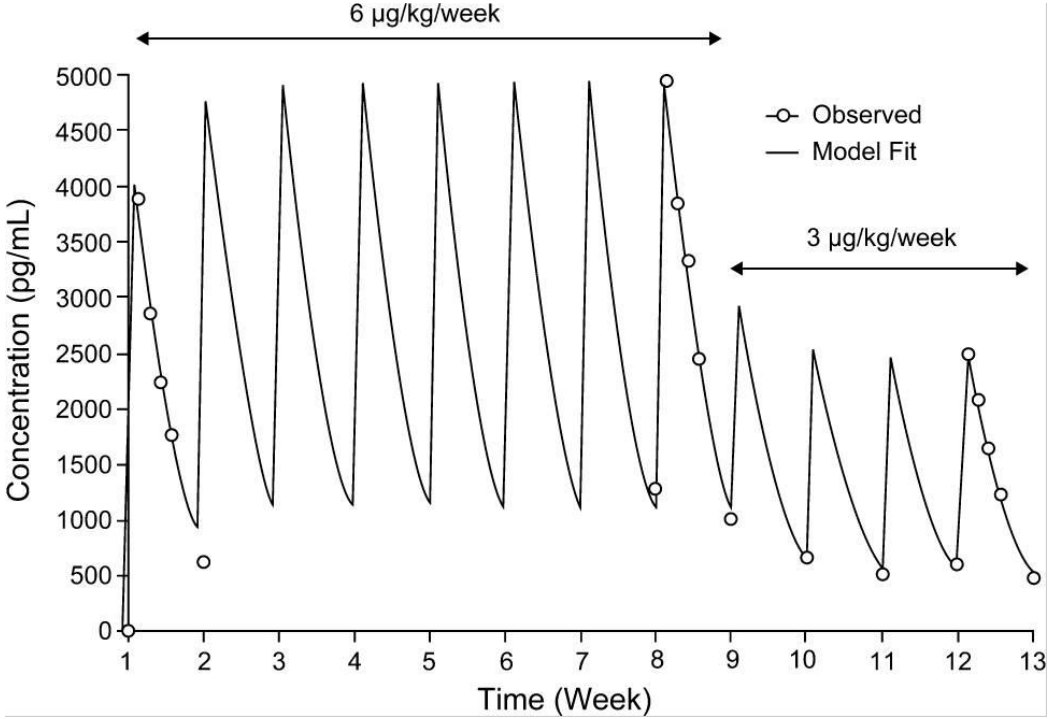
First order kinetics example: Elimination rate constant



Derivative of: Pharmaceutics. 2012;4(4):517-30.
https://creativecommons.org/licenses/by/3.0/

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First order kinetics example: Dose proportionality



Derivative of: Cancer Chemother Pharmacol. 2011;67(3):657-66.
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Half-life estimation

- Time required for 50% of drug present to be eliminated
- Can be calculated for drugs with first-order kinetics using elimination rate constant k_e: $t_{1/2} = 0.693/k_e$
- For drugs with zero-order kinetics, half-life depends on the maximum capacity of elimination pathways – once concentration exceeds elimination capacity, half-life will increase with rising concentrations

Elimination following single dose	
Half-lives elapsed	Drug remaining
1	50%
2	25%
3	12.5%
4	6.25%
5	3.125%

Biochem Pharmacol. 2014;87(1):93-120.

Dosing interval, accumulation, and steady state

- Dosing interval is determined according to target therapeutic concentration, half-life, and/or duration of pharmacologic effect
- When multiple doses are administered (with first-order kinetics), drug will accumulate and mean plasma concentration will rise
- When rate of elimination is equal to rate of drug entry (over time), steady state has been reached
- Steady state is effectively reached after roughly 3 to 5 half-lives
- Loading doses can be used to quickly reach mean concentrations closer to the eventual steady state concentration (useful for drugs with long half lives)

Accumulation following repeated doses	
Half-lives elapsed	Proportion of steady state achieved
1	50%
2	75%
3	87.5%
4	93.8%
5	96.9%
6	98.4%
7	99.2%
8	99.6%

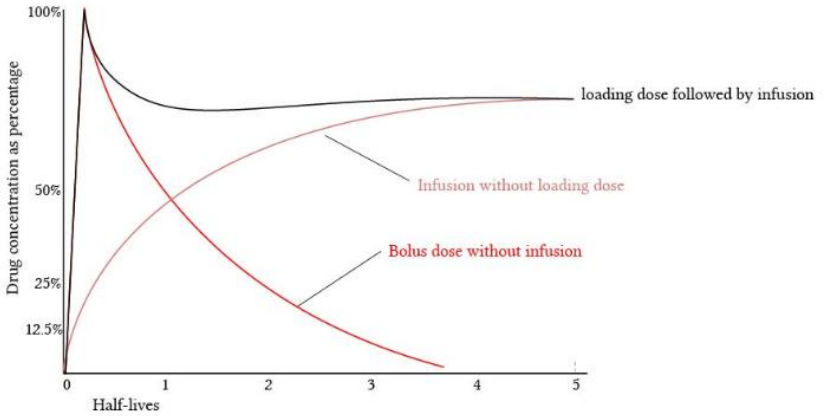
Biochem Pharmacol. 2014;87(1):93-120.

Loading dose and maintenance doses

- Calculating loadings doses and maintenance doses can optimize drug delivery to patients if PK parameters are present
- Loading doses (LD) are dependent on volume of Vd rather than clearance (CL) and rapidly achieve a therapeutic plasma concentration
- Maintenance doses (MD) are administered at a regular interval (or continuous infusion) to achieve steady state plasma concentrations and is dependent on CL

$$LD = \frac{Vd\ X\ TC}{S\ X\ F}$$

$$MD = \frac{CL\ X\ TC\ X\ T}{S\ X\ F}$$



F: Bioavailability
T: Interval (dosing)
TC: Target concentration
S: Salt factor

Miniaci A and Gupta V. Statpearls. 2023

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Example: Calculating LD and targeting specific drug concentrations

What oral LD of drug D tablets (70% bioavailability) will be required to achieve a plasma concentration of 1.5 ug/L in an 80 kg patient if the estimated Vd of drug D in this patient is 7.3 L/kg? The salt factor of drug D is 1.

$$LD = \frac{Vd\ X\ TC}{S\ X\ F}$$

$$LD = \frac{7.3\ (L/kg)\ X\ 80\ (kg)\ X\ 1.5\ (ug/L)}{1\ X\ 0.7}$$

$$LD = 1{,}251\ ug\ or\ 1.25\ mg$$

Example: Calculating LD and targeting specific drug concentrations

Drug D achieves therapeutic concentrations with the LD and a MD of 0.25 mg PO daily is given to the patient. After two weeks, the patients steady state plasma concentration (trough level) was found to be 1.0 ug/L and the target therapeutic level for this patient is 1.5 ug/L. What new MD of drug D should be used to ensure he remains therapeutic? Assume drug D follows **first order (linear) kinetics.**

$$\frac{MD1}{Css1} = \frac{MD2}{Css2}$$

$$\frac{0.25\ (mg)}{1.0\ (ug/L)} = \frac{X}{1.5\ (ug/L)}$$

X= 0.375 mg

Css: concentration at steady state

Elimination-related questions to consider in study design

- Is drug principally eliminated hepatically, renally, both, or neither? How does organ dysfunction impact elimination?
- Is elimination saturable (first- vs zero-order kinetics)? Are dose changes expected to have proportional effects on exposure?
- What is/are the route(s) of excretion? How much is present in urine, feces, etc, and in what form (intact drug vs metabolites)?
- What is the half-life of the parent drug? Is the parent drug active? What is/are the half-life/lives of active and/or toxic metabolite(s)?
- Is there a target steady state plasma concentration? Can it be achieved with reasonable dosing intervals? Is a loading dose (or loading phase) warranted?
- How much accumulation occurs with planned dosing intervals? Is there concern this may influence toxicity over time?

Case #3

Compound Z is being evaluated for a phase II trial. PK profiling in healthy human subjects that were administered multiple doses shows concentration time profiling that was indicative of zero order elimination. Which of the following is true based on this information?

1. Compound Z will produce proportionate changes in drug exposure
2. Compound Z is rapidly absorbed with minimal effect from gastric pH
3. Compound Z will produce disproportionate change in drug exposure
4. Compound Z will primarily undergo phase I metabolism via CYP3A4

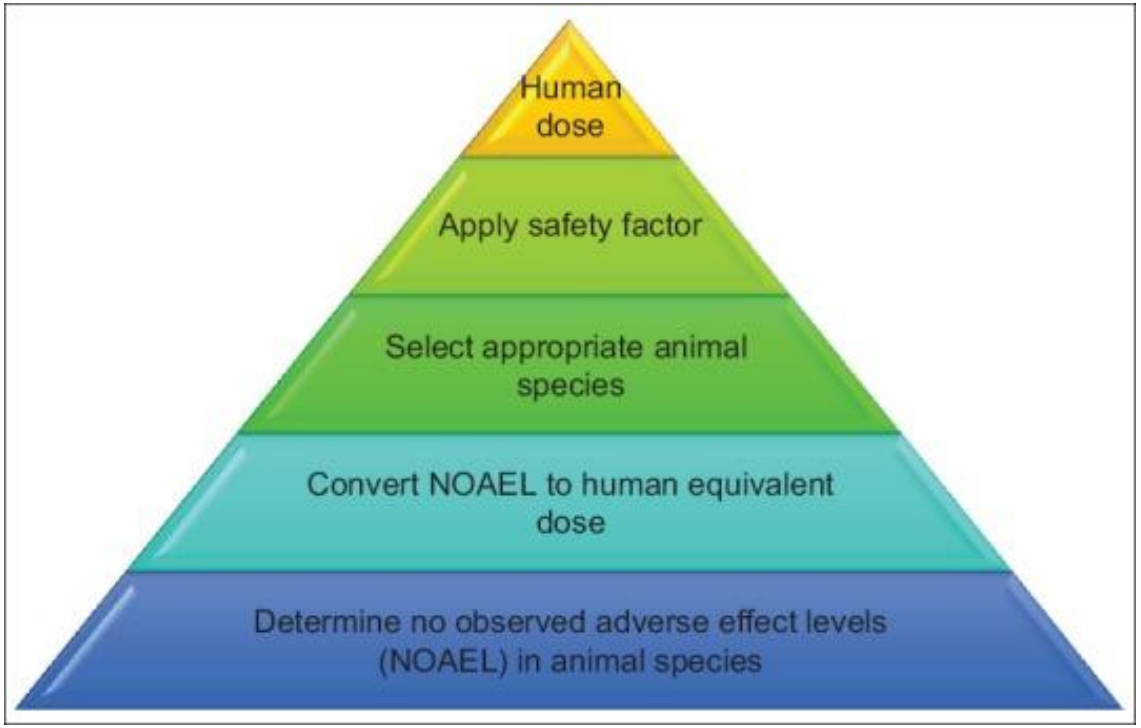
Applying Concepts: How do we use PK principles translationally and clinically?

Maximum Recommended Starting Dose (MRSD)

- Animal PK, PD and toxicity data are used to determine human dosing
- No observed adverse effect levels (NOAEL) is used to estimate the human equivalent dose (HED)
  - NOAEL is the highest dose that does not produce a significant increase in adverse events compared to the control group
- Highest non-severely toxic dose (HNSTD) represents the highest dose that does not produce severe toxicity and is used for oncology drugs
- Allometric scaling: empirical approach to dose drugs based on normalization to BSA
  - Ideal for drugs with lesser hepatic metabolism, lower Vd, and renal excretion
  - Normally applied to oral and intravenous routes
- Drugs can be scaled to mg/kg if certain parameters are met
  - NOAEL occurs at similar mg/kg dose across test species

FDA. Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. https://www.fda.gov/media/162346/download (2005).

Estimating starting dose in human studies



- Safety Factor: Allows for variability in extrapolating from animal toxicity to human toxicity
- Default safety factor is 10 (although this varies pending toxicity and PK data)
  - Safety factor of 6 is often used for oncology drugs with non-rodent species

Nair AB et al. J Basic Clin Pharm. 2016;7(2):27-31.

Example: Using NOAEL to find HED

A new blood pressure medication is being studied, and researchers want to find the HED based on the NOAEL found in rat models. The NOAEL in rats with an average weight of 150 g is 10 mg/kg. What is the HED based off the following equation:

$$HED\ (mg/kg) = Animal\ NOAEL\ (mg/kg) x \left(\frac{Animal\ weight\ (kg)}{Human\ weight (kg)}\right)^{0.33}$$

$$HED\ (mg/kg) = 10\ x(\frac{0.15}{60})^{0.33}$$

$$HED = 1.38\ mg/kg$$

$$HED = 1.38\ mg\ x\ 60\ kg = 83.08\ mg$$

$$Safety\ factor\colon \frac{83.08}{10} = 8.31\ mg$$

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Human equivalent dose calculation based on BSA

Species	Reference body weight (kg)	Working weight range (kg)	Body surface area (m^2)	To convert dose in mg/kg to dose in mg/m^2, multiply by K_m	To convert animal dose in mg/kg to HED in mg/kg, either	
					Divide animal dose by	Multiply animal dose by
Human	60	-	1.62	37	-	-
Mouse	0.02	0.011-0.034	0.007	3	12.3	0.081
Hamster	0.08	0.047-0.157	0.016	5	7.4	0.135
Rat	0.15	0.08-0.27	0.025	6	6.2	0.162
Ferret	0.30	0.16-0.54	0.043	7	5.3	0.189
Guinea pig	0.40	0.208-0.700	0.05	8	4.6	0.216
Rabbit	1.8	0.90-3.0	0.15	12	3.1	0.324
Dog	10	5-17	0.50	20	1.8	0.541
Monkeys (rhesus)	3	1.4-4.9	0.25	12	3.1	0.324
Marmoset	0.35	0.14-0.72	0.06	6	6.2	0.162
Squirrel monkey	0.60	0.29-0.97	0.09	7	5.3	0.189
Baboon	12	7-23	0.60	20	1.8	0.541
Micro pig	20	10-33	0.74	27	1.4	0.730
Mini pig	40	25-64	1.14	35	1.1	0.946

*Data obtained from FDA draft guidelines.[7] FDA: Food and Drug Administration, HED: Human equivalent dose

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Calculating HED based off Km ratio

- The correction factor (K_m) is estimated by dividing the average body weight of species to its BSA and is used to convert mg/kg to mg/m^2
  - Can also use be used to easily convert mg/kg dosing between species (using columns 6 and 7 of table on previous slide)
- Example: Calculate the HED of a new compound that exhibits a NOAEL value of 60 mg/kg in rats with an average weight 0.25 kg (250 g)

$$HED = 60\ (\text{mg/kg}) \times 0.162 = 9.7\ (\text{mg/kg})$$

OR

$$HED = \frac{60\ (\text{mg/kg})}{6.2} = 9.7\ (\text{mg/kg})$$

Species	Reference body weight (kg)	Working weight range (kg)	Body surface area (m^2)	To convert dose in mg/kg to dose in mg/m^2, multiply by K_m	To convert animal dose in mg/kg to HED in mg/kg, either	
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Rat	0.15	0.08-0.27	0.025	6	6.2	0.162

Key Points in Scaling Dose

- Larger animals have lower metabolic rates
- Physiological processes of larger animals is slower
- Allometry accounts the difference in physiological time among species
- Do not apply allometric scaling to convert adult doses to pediatrics

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First in human (FIH) studies

- Once FIH studies have commenced, blood sampling at specific timepoints is essential to determine human PK data
  - Early phase trials will typically follow appropriate dose escalation designs to ensure safety (3+3 design or Bayesian design)
- Blood samples at scheduled times to determine PK parameters (Cmax, Tmax, CL, half-life, AUC etc)
- Several models exist for characterization of drug sampling with associated software for analysis based on population PK
- Data from phase I trials (goal = safety/PK) is used to determine phase II dosing for further efficacy analysis

FDA. Population Pharmacokinetics: Guidance for Industry. https://www.fda.gov/media/162346/download (2022).

Kurzrock et al. J Clin Oncol. Vol 41. 2021.

Resources for drug PK and transporter profiles

Resource	Pearls	Pitfalls
Tertiary databases – LexiComp, Micromedex, Clinical Pharmacology	All available via OneMSK Clinical Pharmacology (occasionally Micromedex) often has detailed PK info	(Very) often lack transporter info
Drugs@FDA accessdata.fda.gov/scripts/cder/daf/	Contains FDA's reviews of NDAs for approved drugs (posted ~30d after approval) Often much more detailed PK info than has been published in literature or package insert	Information may be redacted Older drugs may not have reviews available or may be of lower quality/difficult to navigate
Investigator's brochure	Often much more detailed PK info than will be published in literature/package insert	Confidential, may not have human data
SuperCYPsPred Banerjee P, et al. Nucleic Acids Res. 2020;48(W1):W580-85.	Prediction software for CYP metabolism – search by drug or IUPAC name (via PubChem) Useful for identifying potential metabolism or interactions mediated by key CYPs	Limited to 1A2, 2C19, 2D6, 2C9, 3A4 Do NOT use to guide clinical decisions


Questions



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Pharmacokinetic considerations in clinical and translational cancer research

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- **Safety Margin Calculations for Starting Dose Determination**

Study	STD10	HED	Starting Dose (1/10 STD10)	HNSTD	HED	Starting Dose (1/6 HNSTD)
GLP Rat 28 day	350 mg/kg	2100 mg/m^2 or 3402 mg	340 mg			
GLP NHP 28 day				300 mg/kg	3600 mg/m^2 or 5832 mg	972 mg

Allometric Scaling Factors for Human (multiply by the mg/kg dose): Rat-6; Monkey-12.

Human BSA: 1.62 m^2.