Pharmacokinetics and Pharmacodynamics 101

M. Daniel Gordin, Ph.D.
Pharmaceutical Executive

Background and Career

Education

- BS Biology, BS Laboratory Science
- Ph.D. Pharmaceutical Sciences (Pharmacokinetics)

Career

- Pharmacokinetic Reviewer, Division of Biopharmaceutics, CDER, Food and Drug Administration
- Mid 90's departed FDA, transitioned to Regulatory Affairs, Made several stops along the way small, medium, big-pharma and start-up companies
- Big Pharma Novartis 14 years
- Retired after 35+ years in Pharma

Agenda

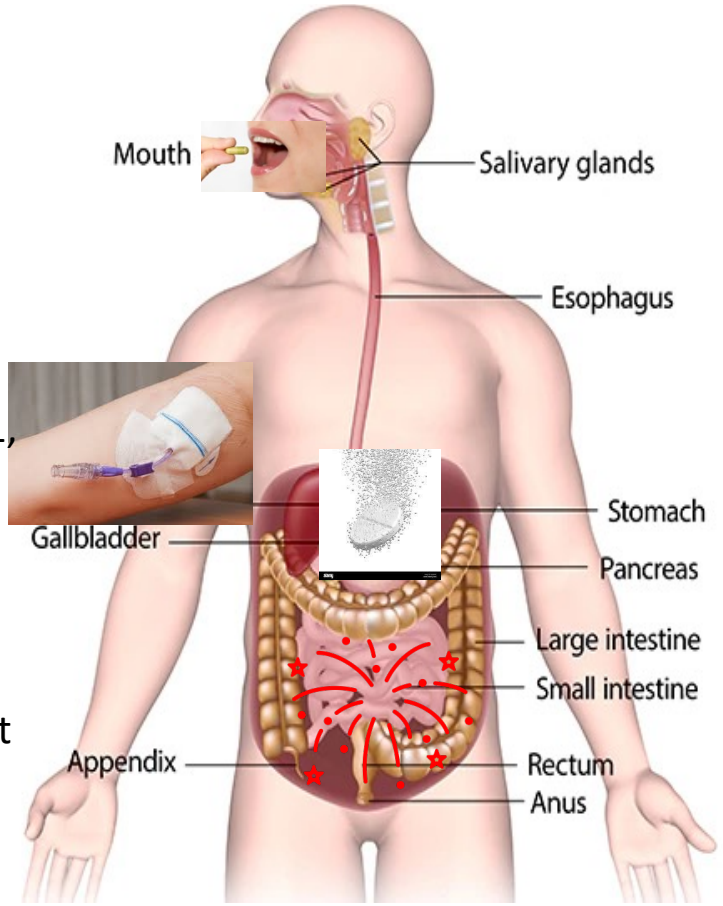
- Pharmacokinetics
  - Concept
  - Key PK parameters
- PK Studies and Objectives Conducted for a New Oral Drug
- In vitro dissolution
- Pharmacodynamics

Kinetics

- Kinetics
  - Definition – Rate of Change (d/dT)
- Pharmacokinetics
  - Determination rate of change of drug concentration (C) over time (T) after administration as to its
    - Rate of absorption
    - Rate of distribution
    - Rate of elimination
- Toxicokinetics
  - Determination of pharmacokinetic of a drug in animals during toxicity studies to determine concentrations at which toxicities occur

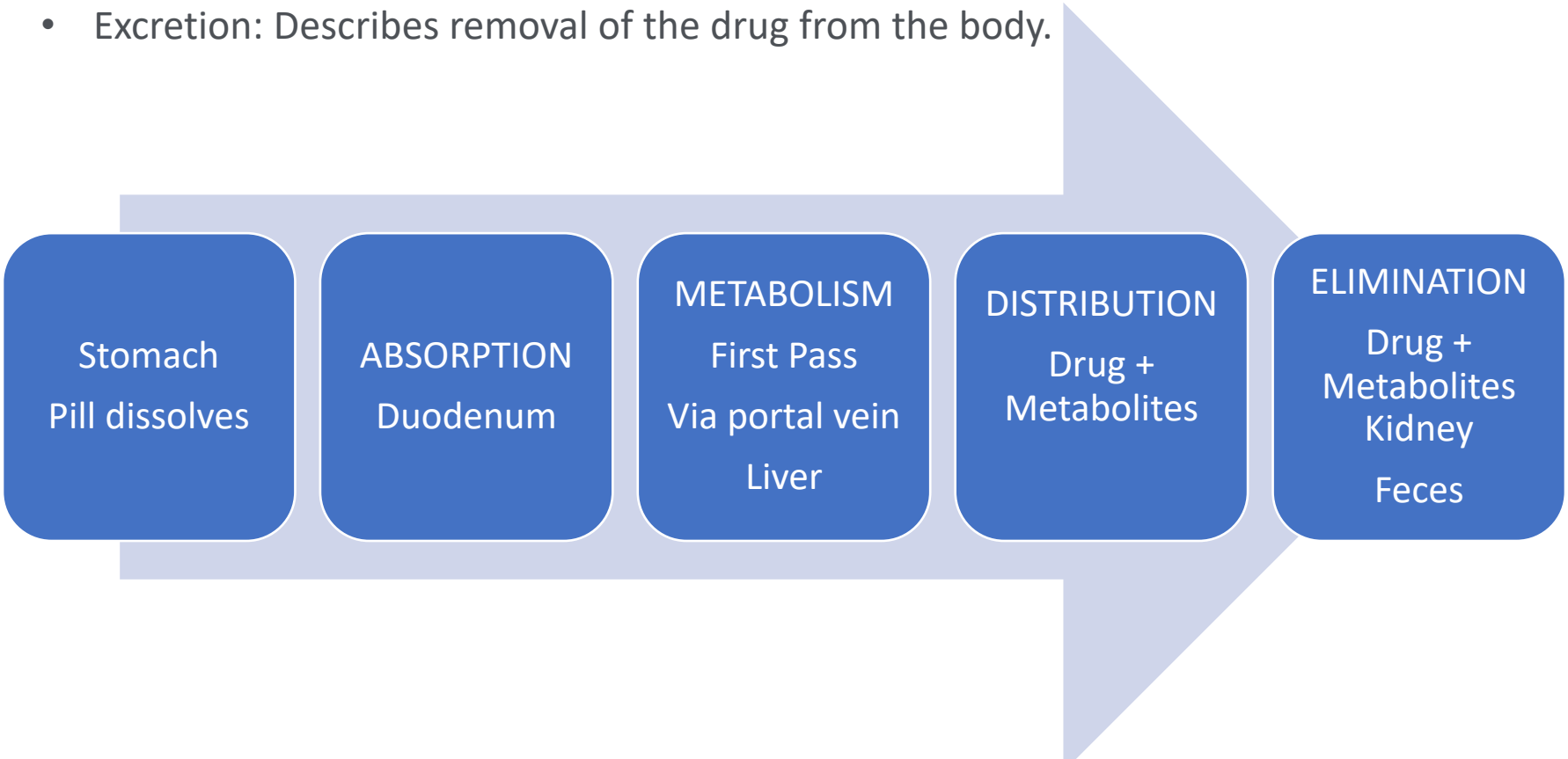
How to determine PK of a drug? Single Dose Drug Study

- Study objective
  - To determine the PK of a drug
- Study procedure
  1. Recruit, Screen, Informed Consent
  2. Study subjects: HV (N=24)
  3. After overnight fast, swallow pill (time 0)
  4. Withdraw serial blood samples at 0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, and 24 hours
  5. Analyze serum by validated HPLC/MS
  6. Determine drug concentrations (ug/mL)
  7. Plot drug concentrations (ug/mL) against Time (Hr) at which samples were withdrawn



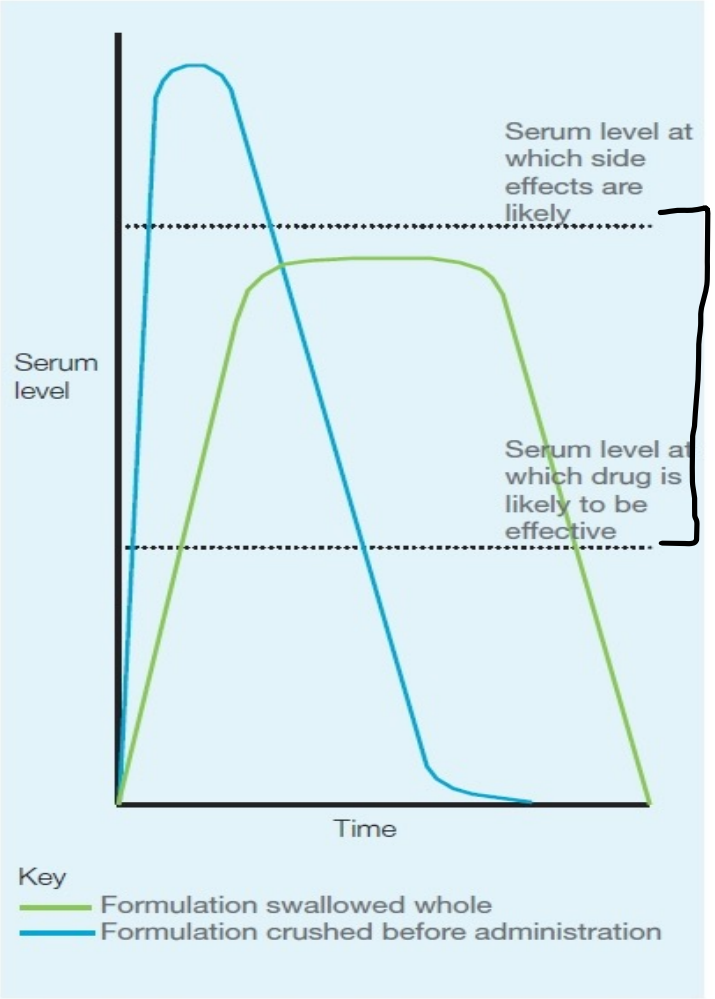
Fate of Drug After being Swallowed

- Absorption: Describes how drug moves from site of administration to site of action.
- Distribution: Describes journey of drug through the bloodstream to various tissues of the body.
- Metabolism: Describes the process that breaks down the drug.
- Excretion: Describes removal of the drug from the body.



Why is the Drug concentration Important

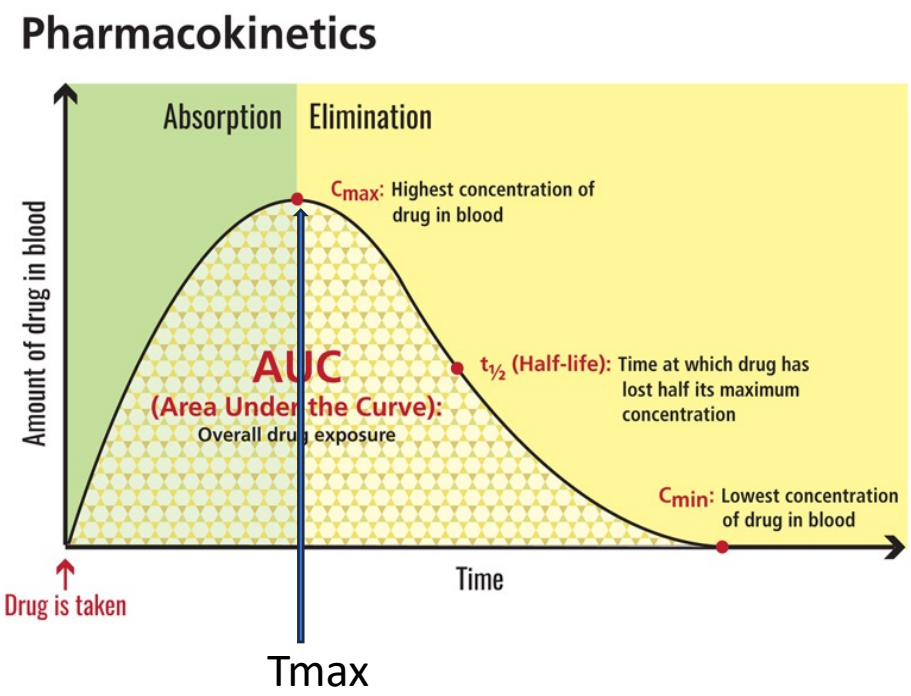
- Too high concentration
  - Efficacy: Great
  - Safety: Intolerable
- Too low concentration
  - Efficacy: Ineffective
  - Safety: Tolerable
- Effective concentration
  - Efficacy: Effective
  - Safety: Tolerable



Theoretical release of active from a modified release formulation which is swallowed whole and crushed

PK Parameters Derived from SD Conc vs Time Curve

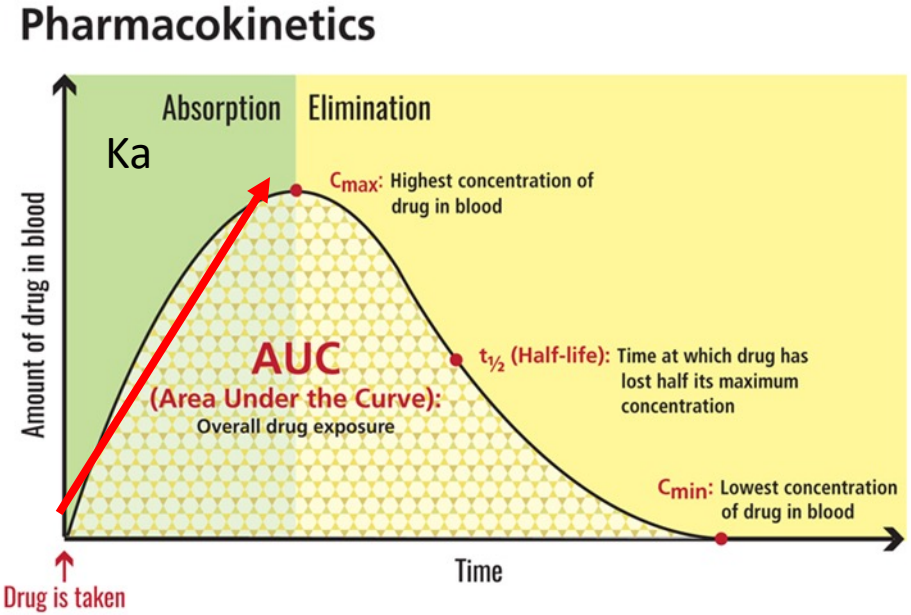
- Area Under the Curve (AUC)
  - Unit: ug*h/L
  - Represents total drug exposure across time
- Maximum Concentration (Cmax)
  - Unit: ug/mL
- Tmax
  - Unit: Hr
  - Time of maximum drug concentration
- Elimination rate (Ke)
  - Unit: ug/hr
  - Rate of drug elimination from body
- Elimination half-life ($T_{1/2}$)
  - Unit: Time
  - Time drug concentration decreases from 50% of Cmax
- Minimum Concentration (Cmin)
  - Unit: ug/mL
  - Lowest concentration of drug



X axis = Time (h)
Y axis = Plasma Drug Concentration

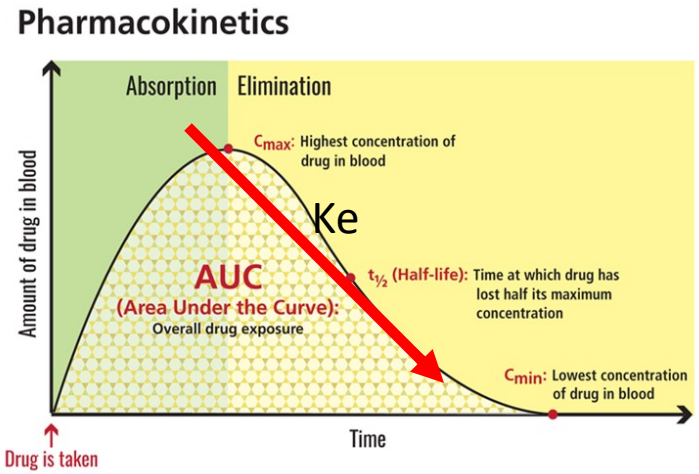
Drug Absorption

- Drug dissolves in stomach (pH2)
- Dumped into duodenum which has extensive surface area for absorption
- Absorption rate = rate at which a drug enters the system
- Factors that affect absorption dissolution, solubility, permeability and gastric emptying



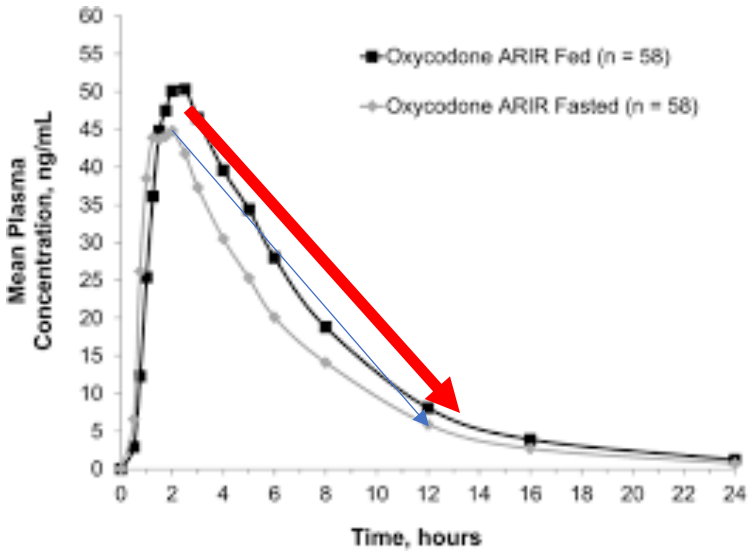
Drug Elimination: Two Primary Routes of Drug Elimination

- Hepatic
  - Lipid soluble drugs/metabolites
  - Hepatic cytochrome P-450 enzymes eg CYP3A4, CYP2D6
  - Dumped into bile and eliminated fecally
  - First pass determines extent of metabolism of parent to metabolites
    - X% parent drug (active drug); X% metabolites (inactive drug)
    - Pro-Drugs are 100% metabolized to active drug
    - Significance is Potential for Drug-Drug Interaction of Comeds
      - induction liver enzymes (decreases half-life)
      - inhibition liver enzymes (increases half-life)
- Renal
  - Water soluble drugs/metabolites
  - Eliminated via kidneys



Half-live ($T_{1/2}$)

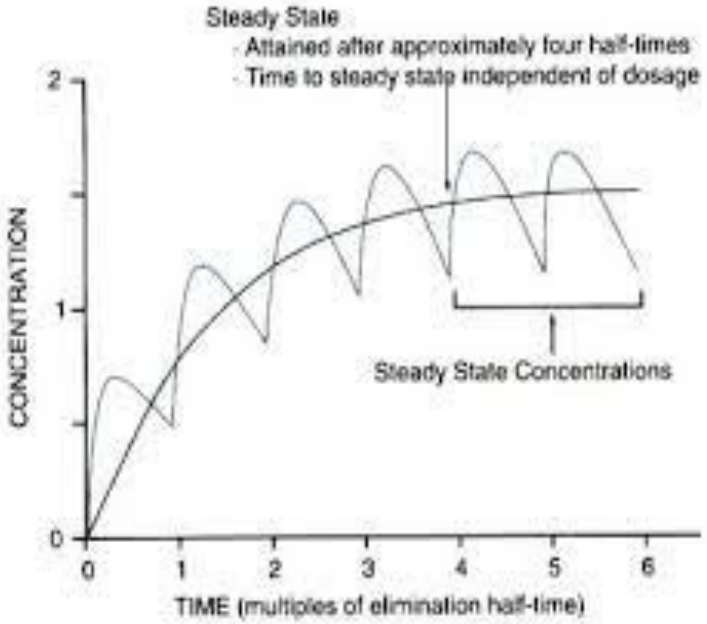
- Determined from slope of line post Cmax
- Different drugs have different half-lives; however, they all follow this rule: after one half-life has passed, 50% of the initial drug amount is removed from the body
- $T_{1/2} = 0.693/K$
  - Ke = elimination rate
- T½ = 0.693 × Vd /CL
  - Vd = volume of distribution
  - Cl = drug clearance



Time (h)	Conc (mg/L)
0	160
8	80
16	40
24	20
32	10
40	5
48	2.5
56	1.25
64	0.625

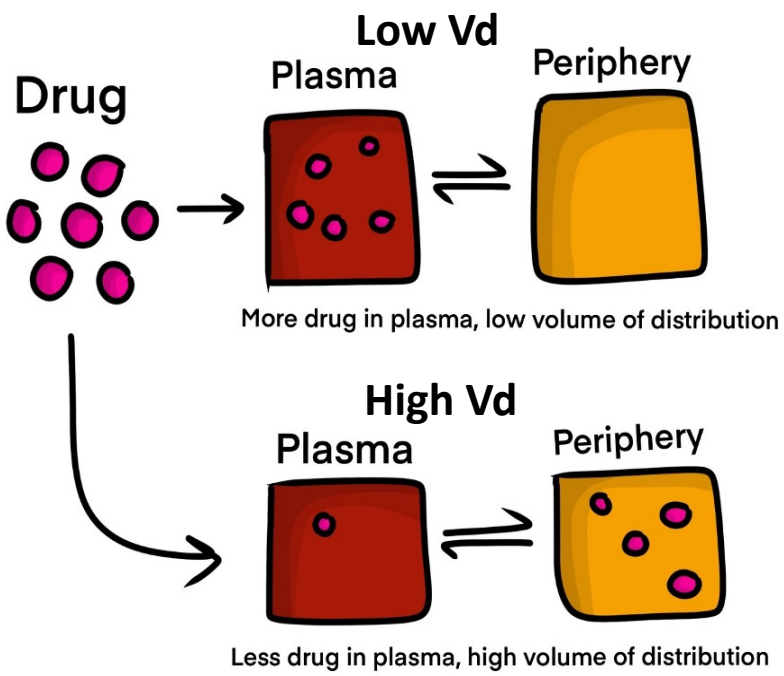
Steady-State

- $T_{1/2}$ used to determine
  - Steady-state
    - Rate of administration = rate of elimination
    - Plateau (Css) reached after 5 half-lives of dosing
  - Total elimination of drug from body
    - After stopping drug administration, 5 half-lives
- Example Drug X has a 6-hour half-life
  - Steady state reached with every 6 hr dosing x 5 $T_{1/2}$ = 30 hrs
  - After stopping drug administration, total drug eliminated after 30 hrs



Volume of Distribution (Vd)

- Represents drug's propensity to remain in
  - plasma (1st compartment) or
  - distribute to other tissue compartments (2nd compartment)
- Drugs with a low Vd
  - more hydrophilic
  - remains in blood (1st compartment)
  - short T½
- Drugs with a high Vd
  - more lipophilic
  - able to diffuse more into surrounding tissues (2nd compartment)
  - can only be eliminated when in blood so drug can be slow to diffuse out of tissues and back into blood
  - takes longer to eliminate, longer T½)



Clearance (Cl)

- Defined as the hypothetical volume of body fluid eg blood, containing the drug from which the drug is removed in a specific period of time

- Clearance (Cl) = $\frac{\text{Elimination Rate (Ke)}}{\text{Plasma drug concentration (C)}}$

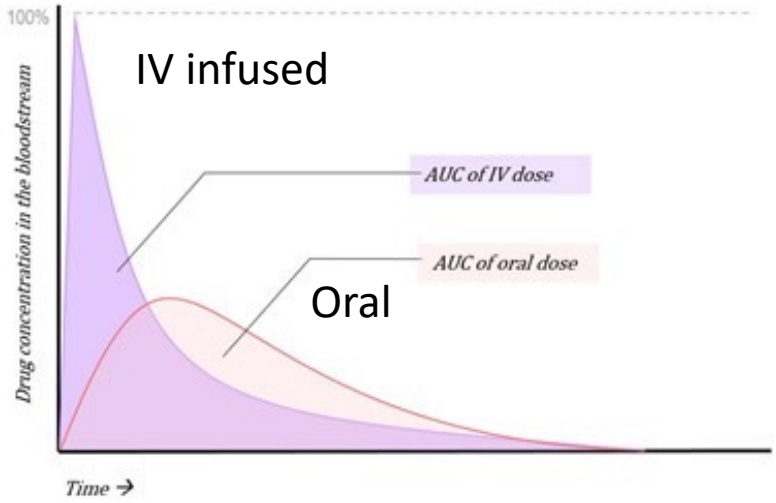
- Cl = mL/min

- Total body clearance = sum of individual clearance by all eliminating organs, renal, liver, lung

- Cl_T -= $Cl_r + Cl_h + Cl_L$

Oral PK versus Intravenous PK

	Intravenous	Oral
Dosage form	Solution	Solid
Route of administration	Bolus/infusion directly into vein	Mouth
Cmax	At time of injection	When absorption is completed
Elimination	Rapid onset once bolus/infusion stops	After Cmax is reached



Types of PK Studies and Objectives Conducted for a New Oral Drug

PK Studies and Objectives Conducted for New Oral Drug

1. Single ascending dose study in HV
   - Objectives
     - To determine maximum tolerated dose (MTD)
     - To dose proportionality (linear) and safety
   - Design
     - N=6 subjects (4 active + 2 placebo)
     - After overnight fast, First dose is lowest safe dose, then increase doses to the dose that is intolerable
2. Multiple dose study Objectives
   - Objective
     - To determine dose linearity, optimum frequency of dosing based on $T_{1/2}$ and safety
   - Design
     - N=12 (10 active + 2 placebo)
     - After overnight fast start dosing BID for 7 days
     - Blood samples on Day 1 at 0-24 hrs, Days 2-6 at Cmin, Day 7 at 0-24 hrs
3. Food effect study
   - Objective: To determine if dosing with high fat food affects drug absorption and safety
   - Design
     - Two-way cross over study
     - N=12 (10 active + 2 placebo), after overnight fast, randomize to fast or high fast meal
     - Blood samples on Day 1 at 0-24 hrs

PK Studies and Objectives Conducted for New Oral Drug

4. Absolute Bioavailability study
   - Objective: To determine percent of drug absorbed from oral dosage form compared to drug administered in solution
   - Design
     4. N=12 (10 active + 2 placebo)
     5. Single-dose, Two-way cross-over study
     6. After overnight fast start dose Group 1 oral and Group 2 IV/oral solution
     7. Blood samples on Day 1 at 0-24 hrs
5. Hepatic impaired study
   - Objective: To determine hepatic impairment effect on drug PK and safety
   - Design
     4. Normal (N=6), Mild (N=6), Moderate (N=6) and Severe (N=3)
     5. Single-dose
     6. Blood samples on Day 1 at 0-24 hrs
6. In Vitro Hepatic Enzyme study
   - Test drug against panel of hepatic enzymes in vitro
   - Objective: To identify primary hepatic enzyme involved in the metabolism of the drug

PK Studies and Objectives Conducted for New Oral Drug

7. Renal impaired study
    - Objective: To determine renal impairment effect on drug PK and safety
    - Design
        - Single-dose
        - Stage 2: Mild reduction in GFR (60-89 mL/min/1.73 m 2)
        - Stage 3: Moderate reduction in GFR (30-59 mL/min/1.73 m 2)
        - Stage 4: Severe reduction in GFR (15-29 mL/min/1.73 m 2)
    - Blood samples on Day 1 at 0-24 hrs

8. Population PK modelling
    - Objective: used to investigate sources of variability in patient exposure and factors ie covariates, that may impact drug clearance
    - Design: All Pk data collected from all sources used for modelling (Mix Effect Model)
    - Covariates: Subject characteristics Gender, Age, disease severity, impairments,

Pharmacometrics Syst Pharmacol. 2013 Apr; 2(4): e38.
Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development—Part 2: Introduction to Pharmacokinetic Modeling Methods
D R Mould1,* and R N Upton1,2

Output of a PK study

Table 1. PK parameters of Drug X after 10, 20, and 50 mg single doses

	Cmax +/- SD (ug/mL)	Tmax +/- SD (Hr)	AUC +/- SD mg*h/L	T1/2 (Hr)
10 mg	20 +/- 5	2	120 +/- 50	6
20 mg	40+/- 5	2	240 +/- 50	6
50 mg	80+/- 5	2	480 +/- 55	6

PK Drug-Drug Interaction (DDI) Studies

- Objective: To determine if PK of Drug A is impacted if administered with Drug B
- Source of DDI
  - inducing metabolism
  - inhibiting metabolism/renal excretion
- Two-arm, single-dose cross-over studies
  - Arm one: Drug A
  - Arm two: Drug A administered with Drug B
  - N=12 HV
- Serial blood samples withdrawn at 0, 0.5, 1, 2, 4, 8, 16, and 24 hours
- Analyze blood and plot
- Statistical analysis is 90% CI 80-125%
  - If outside CI, then dose adjustment may be warranted or contraindicated

Why is DDI Study Critical?

- Case Study
  - Young healthy female administered ketoconazole for toenail fungus by dermatologist and administered Seldane (terfenadine) by Allergist for Seasonal Allergic Reaction
  - After 3 days of dosing with both terfenadine and ketoconazole, patient died suddenly
  - Investigation determined
    - Terfenadine parent drug metabolized by CYP3A4 to active, carboxy- lated metabolite (fexofenadine)
    - CYP3A4 enzyme inhibited by ketoconazole
    - Terfenadine cardiotoxic
    - With 3 days of being administered with ketoconazole, metabolism inhibited, terfenadine concentration exceeded toxic concentration leading to sudden death by QTc prolongation
    - Significant and deadly drug-drug interaction

PK Studies conducted for Generic drug and TBM to CSF Bridge

Generic Drug Bioequivalence Study

- Innovator drug goes off patent, generic drugs can come to market
- Clinical study: Two-arm, cross-over, single dose study comparing PK of generic drug to innovator drug N=24 HV
- Statistical analysis: Two-One Sided T-Test (90% Confidence Interval)
- Acceptance for bioequivalence within 80-125%
- Sampling: Serial blood samples withdrawn at 0, 0.5, 1, 2, 4, 8, 16, and 24 hours

Table 1. PK parameters of Generic compared with Innovator and 90% CI (Two One-Sided T-test)

	Innovator Drug	Generic Formulation	90% Confidence Interval
Cmax +/- SD (ug/mL)	20 +/- 5	24 +/- 5	90-115
AUC +/- SD mg*h/L	180 +/- 5	176 +/- 5	89-110
Tmax +/- SD (Hr)	40+/- 5	38 +/- 5	
T1/2 (Hr)	6 +/- 5	6 +/- 5	

PK Study to Bridge Clinical Service Form (CSF) to To-be-Marketed Formulation (TBM)

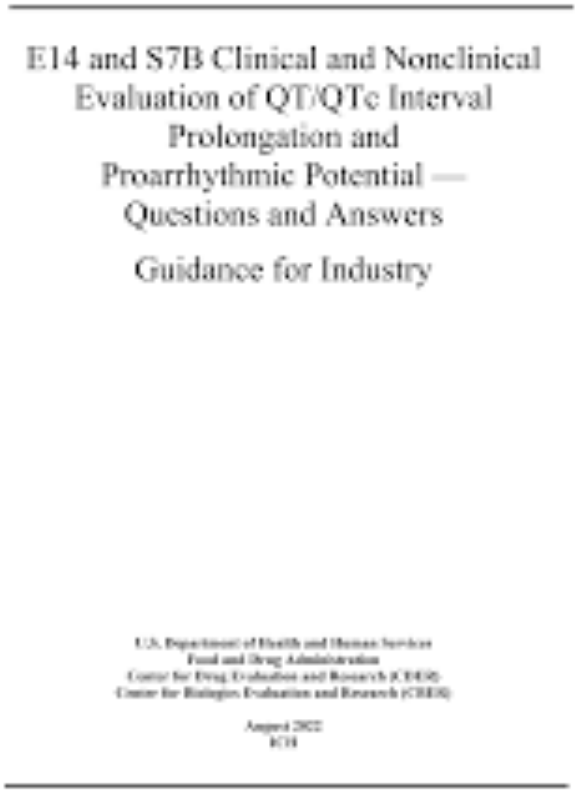
- Two-arm, cross-over single dose study
- Compare CSF to TBM formulation
- N=24 HV
- Statistical analysis: Two-One Sided T-Test 90% Confidence Interval (80-125%)
- Sampling: Serial blood samples withdrawn at 0, 0.5, 1, 2, 4, 8, 16, and 24 hours

Table 1. PK parameters of Innovator Drug compared with Generic Formulation and 90% Confidence Interval (Two One-Sided T-test)

	CSF Drug	TBF	90% Confidence Interval	Equivalent
Cmax +/- SD (ug/mL)	20 +/- 5	24 +/- 5	90-115	✓
AUC +/- SD mg*h/L	180 +/- 5	176 +/- 5	89-110	✓
Tmax +/- SD (Hr)	40+/- 5	38 +/- 5		
T1/2 (Hr)	6 +/- 5	6 +/- 5		

PK Study ICH E14 Evaluation of QT/QTc prolongation

- Objective: To clinically assess a new drug's liability to prolong QT interval (adopted May 2005
- Design: Conducted in HV; blood sampling 0 – 24 hrs, Holter monitoring to match concentration with QT
- Arms: 4-arm study
  - Therapeutic dose, supratherapeutic dose, placebo, positive control to validate the study
- N: Robust enough to detect a 5 msec prolongation of QT interval
- Analysis: Concentration effect
- Significance: If negative, drug can proceed normally in development. However, if positive, all subsequent studies will need extra ECG monitoring and drug may be required to include specific instructions on its label, ranging from special dosing instructions to black box warnings.


E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential — Questions and Answers

Guidance for Industry

https://www.appliedclinicaltrialsonline.com/view/abcs-thorough-qts

In Vitro Dissolution

In Vitro Dissolution

IN-VITRO DISSOLUTION TESTING

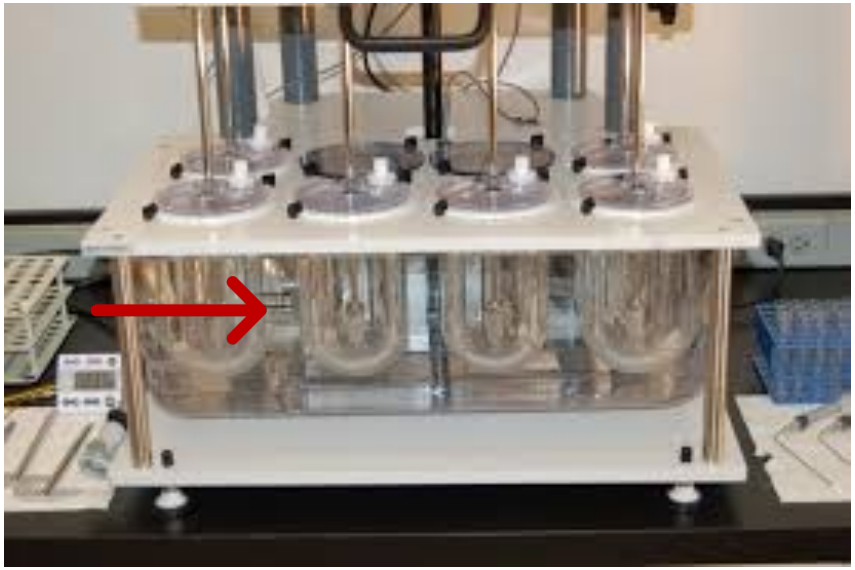
- Dissolution and drug release tests are in-vitro tests that measure the rate and extent of dissolution or release of the drug substance from a drug product, usually aq.medium under specified conditions.
- It is an important QC procedure for the drug product and linked to product performance in-vivo.

❖ **NEED FOR DISSOLUTION TESTING:**

- Evaluation of bioavailability.
- Batch to batch drug release uniformity.
- Development of more efficacious and therapeutically optical dosage forms.
- Ensures quality and stability of the product.
- Product development, quality control, research and application.

In Vitro Dissolution Procedure

- Seven types of dissolution apparatus defined in United States Pharmacopeia (USP)
  - basket type
  - paddle type
  - reciprocating cylinder
  - flow through cell
  - paddle over disc
  - rotating cylinder
  - reciprocating disc.



https://www.fda.gov/media/70936/download#:~:text=In%20vitro%20dissolution%20specifications%20are,problems%20with%20in%20vivo%20bioavailability.

In Vitro Dissolution Procedure

- Basket method Dissolution testing
  - N = 8 tablets, one placed in bottom of each container
  - Basket method rotate at 50/100 rpm
  - Sampling at 15-minute intervals to generate dissolution profile
- For immediate release formulations
  - Sampling @ every 5- or 10-minute intervals
  - For highly soluble formulations (BCS classes 1 and 3),
  - Single-point dissolution test specification of NLT 85% (Q=80%) in 60 minutes or less is sufficient as a routine QC test for batch-to-batch uniformity.
- For slowly dissolving or poorly water-soluble drugs (BCS class 2),
  - Two-point dissolution specification, one at 15 minutes to include a dissolution range (a dissolution window) and the other at a later point (30, 45, or 60 minutes) to ensure 85% dissolution

https://www.fda.gov/media/70936/download#:~:text=In%20vitro%20dissolution%20specifications%20are,problems%20with%20in%20vivo%20bioavailability.

Pharmacodynamics

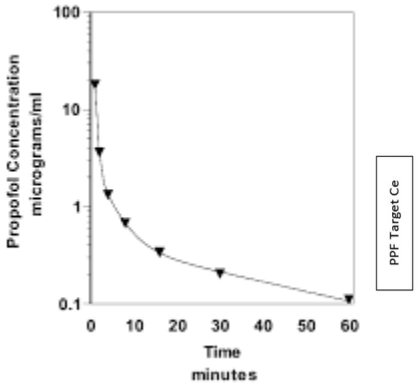
Pharmacodynamics

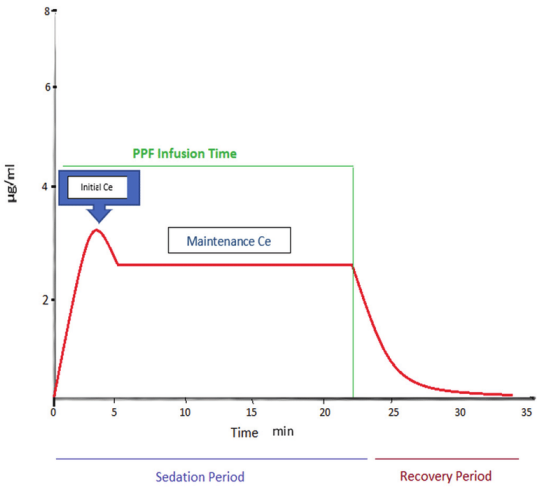
- Science linking concentration (C) and effect (E)
- Two main PD properties of a drug are maximum effect (Emax) and concentration producing 50% of maximum effect (C50)
- Multitude of Receptors in body, sites of actions
  - Neurons in CNS - opiate *Mu-1,* serotonin 5HTs, NMDA, D2, GABA receptors
  - Cardiac muscle – alpha-1, beta-1, M2-muscarinic
  - T-cells – IL-17A (cytokines involved in inflammatory and immune responses
- Effect size of a drug at site of action determined by drug's binding affinity (Ki)
- Ki represents drug concentration (nM) required to occupy 50% of receptors
  - Lower Ki for a drug
    - stronger binding affinity for receptor, low Ki drug is potent, doesn't take much to be effective
  - Higher Ki drug
    - weaker binding, less potent, requires more drug to be effective

- https://www.ashp.org/-/media/store%20files/p2418-sample-chapter-1.pdf

Diprivan (propofol) “The Milk”

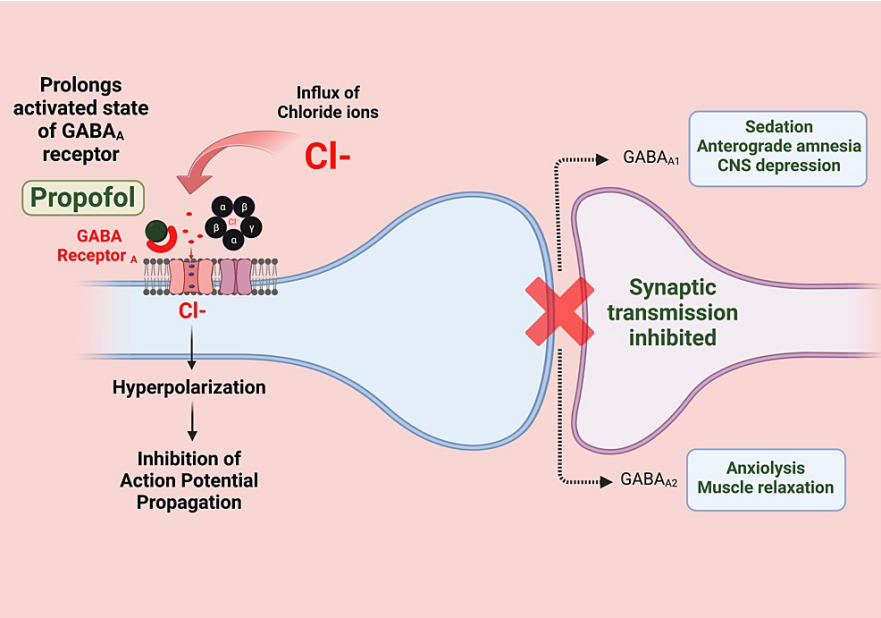
- Intravenous (IV) sedative-hypnotic agent
- FDA Approved October 1989.
- Drug characteristics
  - High lipid-solubility drug
  - Distribution from blood through Blood Brain Barrier to Brain: FAST
- Indication: very short acting sedation
- Administration:
  - Bolus for initiation
  - Infusion for maintenance
- Rate: 10 to 150 ug/kg/min
- Effective Concentration: 1.00 ug/mL
- Site of action: Brain
- Once injected
  - Rapid distribution from plasma to CNS
  - PD effect: Unconsciousness
  - Time to onset: 15-30 sec
- Elimination $T_{1/2}$: 4 min
  - Once infusion stops, rapid elimination
  - Recovery within 20 min





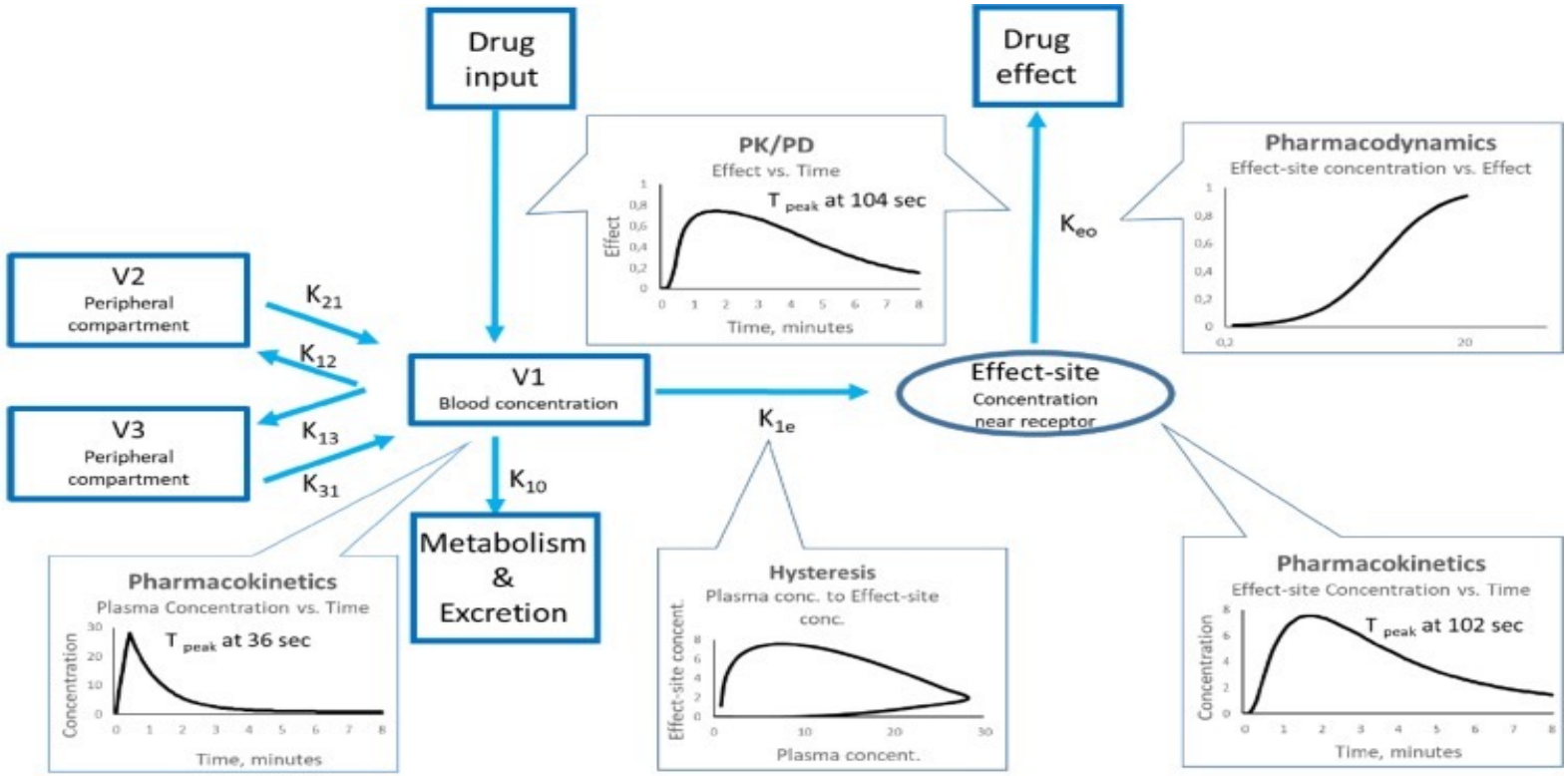
Propofol Pharmacodynamics

- Propofol high binding affinity for GABA receptors in brain
- Propofol exerts its hypnotic effect through potentiation of the effects of the inhibitory neurotransmitter GABA.
- It binds to the β-subunit of the postsynaptic GABAA receptor, where it causes an inward directed chloride current that hyperpolarizes the postsynaptic membrane and inhibits neuronal depolarization.



Paramsothy J et al; Propofol in ICU Settings: Understanding and Managing Anti-Arrhythmic, Pro-Arrhythmic Effects, and Propofol Infusion Syndrome; Cureus 15(6): e40456. doi:10.7759/cureus.40456

Propofol Population PK Modelling



Intercompartmental transfer constants:

$$K_{21}/K_{12} = CL_2$$
$$K_{31}/K_{13} = CL_3$$

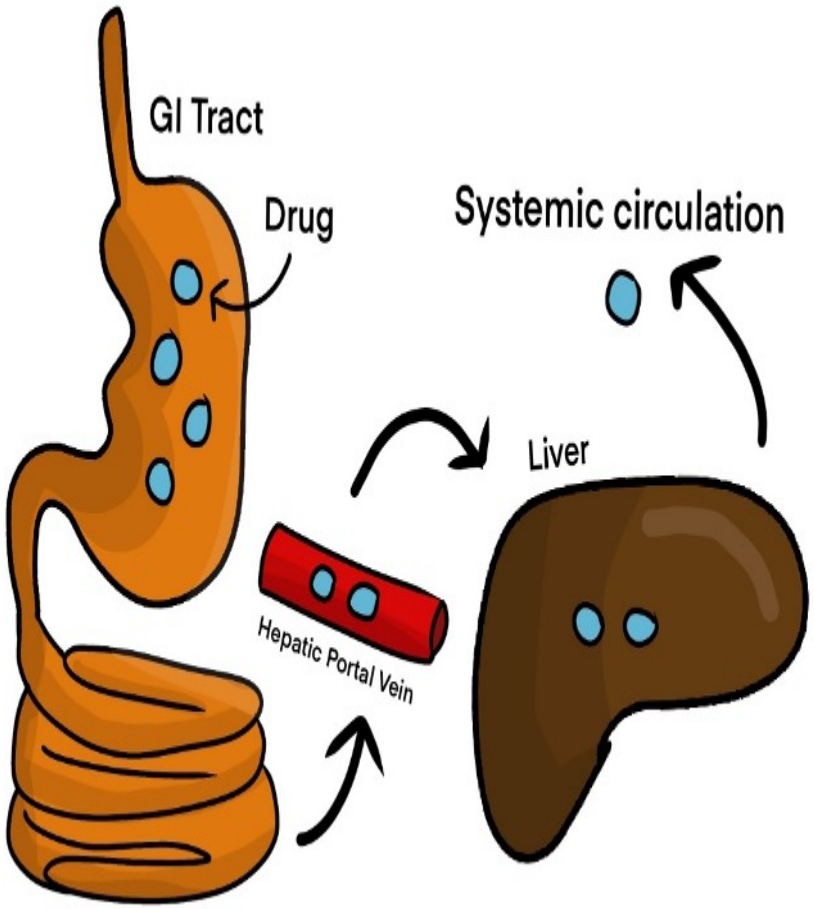
Marko M, Clin Pharmacokinet. Clinical Pharmacokinetics and Pharmacodynamics of Propofol, 2018; 57(12): 1539–1558. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6267518/

BACKUP SLIDES

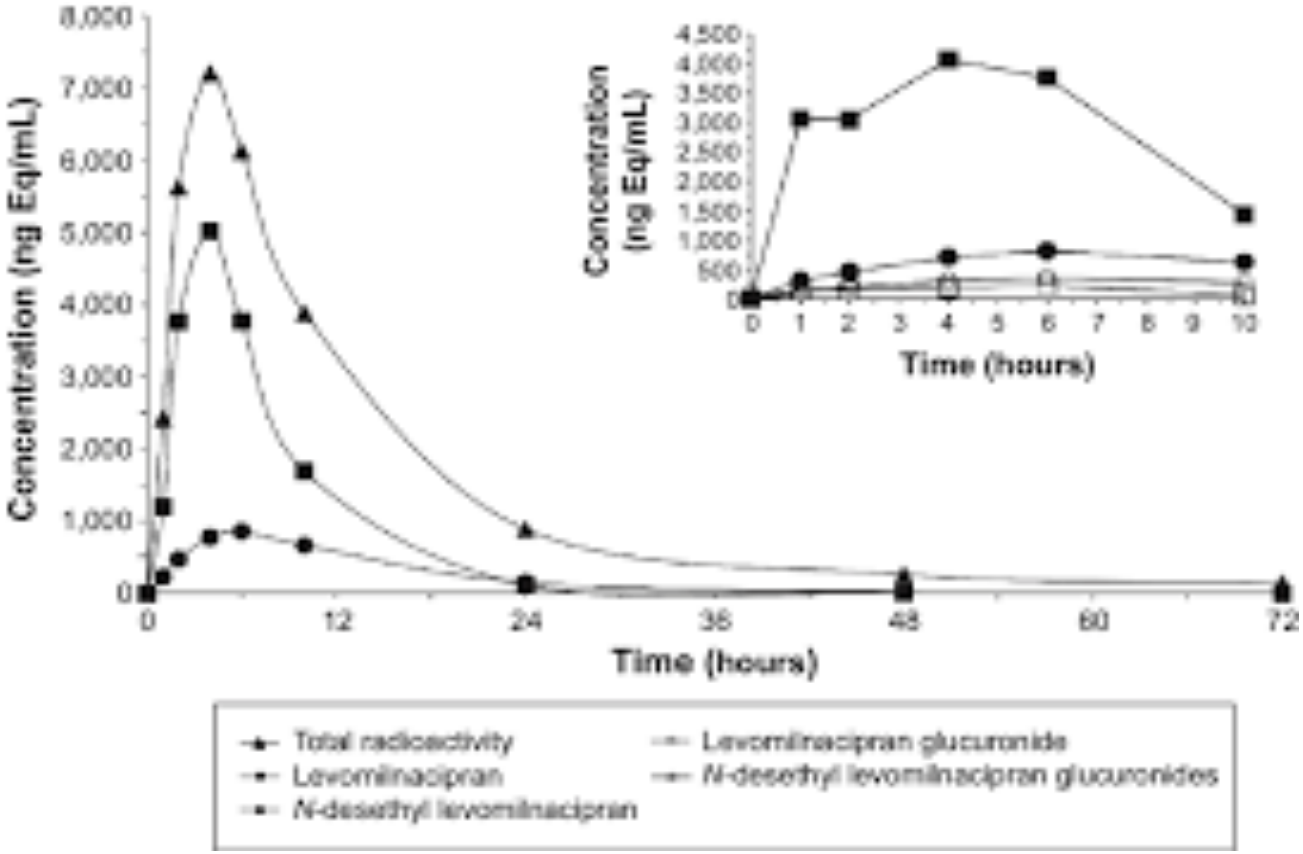
Single Dose Drug Study to determine PK of a drug

- Procedure

1. Recruitment, Screening, Informed Consent
2. Study HV subjects swallow pill
3. Serial blood samples withdrawn at 0, 0.5, 1, 2, 4, 8, 16, and 24 hours
4. Serum analyzed by validated HPLC/MS
5. Drug concentrations (ug/mL) determined
6. Drug Concentrations (ug/mL) plotted against Time (Hr) the samples were withdrawn

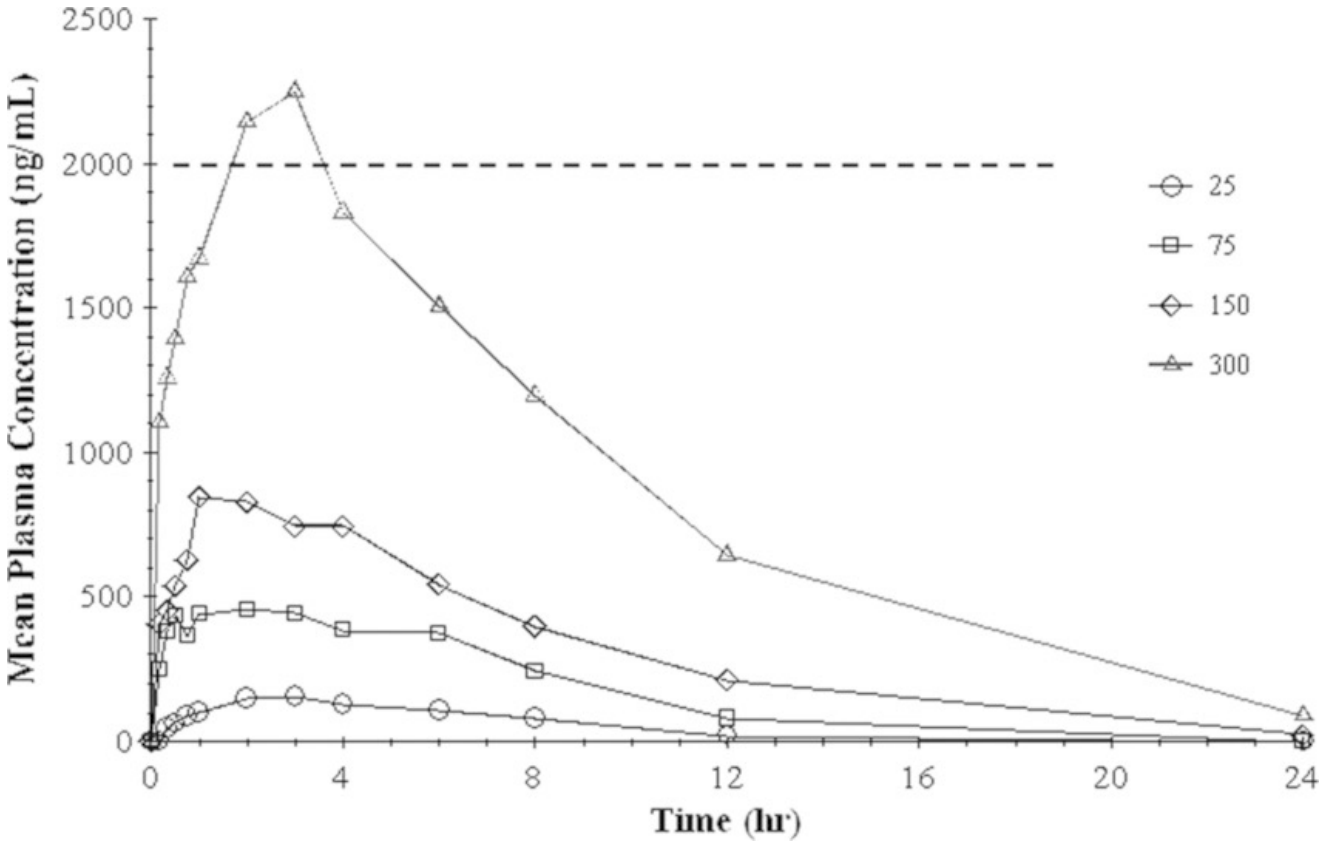


Plasma Drug Concentration versus Time Curve



Time versus Plasma Drug Concentration Curve

X axis = Time (h)
Y axis = Plasma Drug Concentration



Organ groups for central and peripheral compartments

Central Compartment	Peripheral Compartment
Heart	Fat Tissue
Liver	Muscle Tissue
Lung	CSF
Kidneys	Brain
Blood