■ *Pharmacokinetcs*

Def'n: branch of pharmacology dedicated to the determination of the fate of substances administered externally to a living organism (after Dost, 1953)

"*What the body does to the drug ...*"

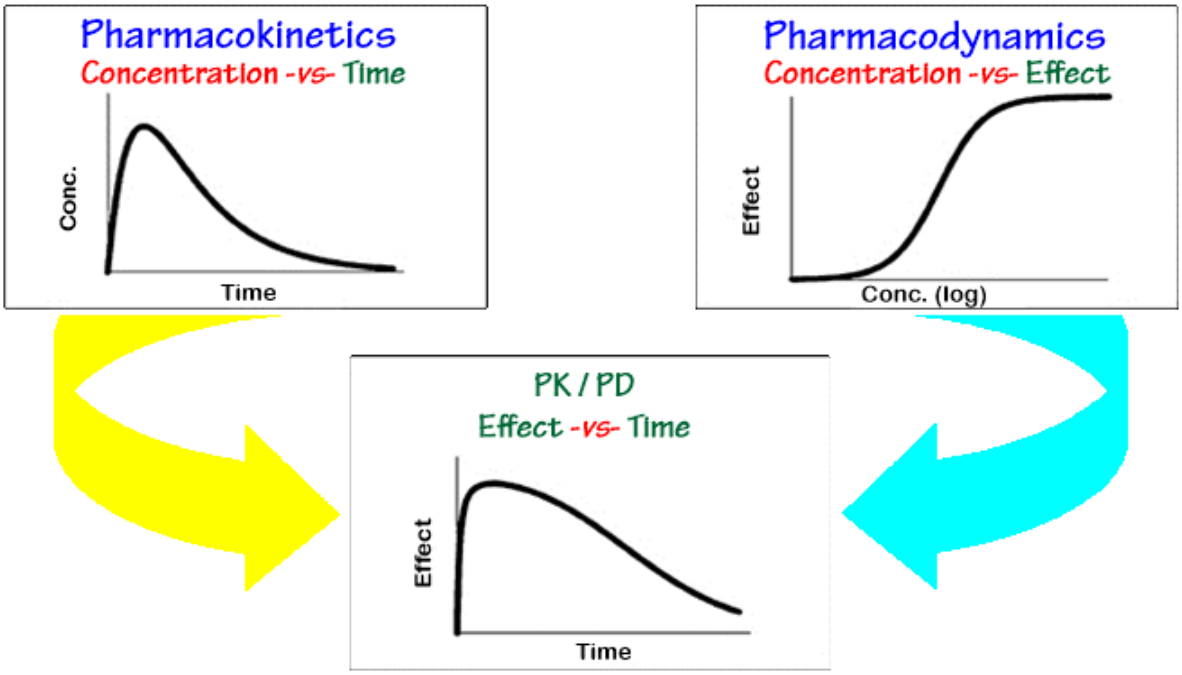
→ plasma concentration -*vs*- time

■ *Pharmacodynamics*

Def'n: branch of pharmacology dedicated to the study of the actions of drugs within the body

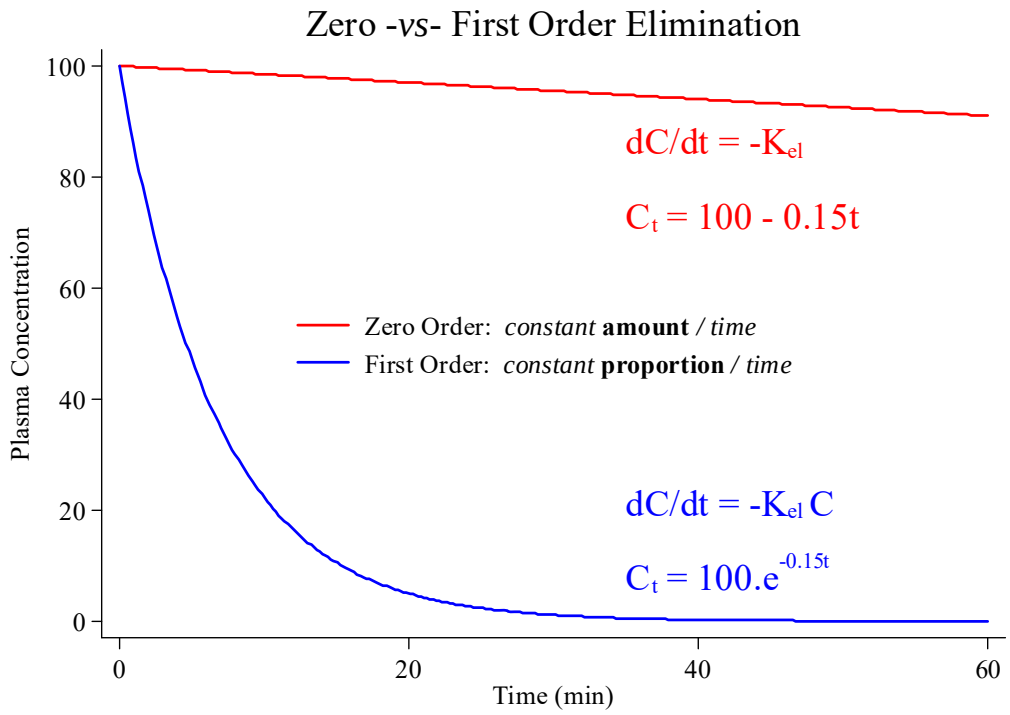
"*What the drug does to the body ...*"

→ effect -*vs*- plasma concentration (log)



Mathematics

Order	Rate Law	Concentration-Time	Half-life
0	$\frac{dC}{dt} = k.C^0$	$C_t = C_0 - kt$	$t_{½} = \frac{C_0}{2k}$
1	$\frac{dC}{dt} = k.C^1$	$C_t = C_0.e^{-kt}$	$t_{½} = \frac{\ln(2)}{k}$
2	$\frac{dC}{dt} = k.C^2$	$C_t^{-1} = C_0^{-1} + kt$	$t_{½} = \frac{1}{kC_0}$



NB: Zero Order:

- Saturable kinetics → zero-order at high [plasma]
- e.g. ethanol, phenytoin, salicylates, omeprazol

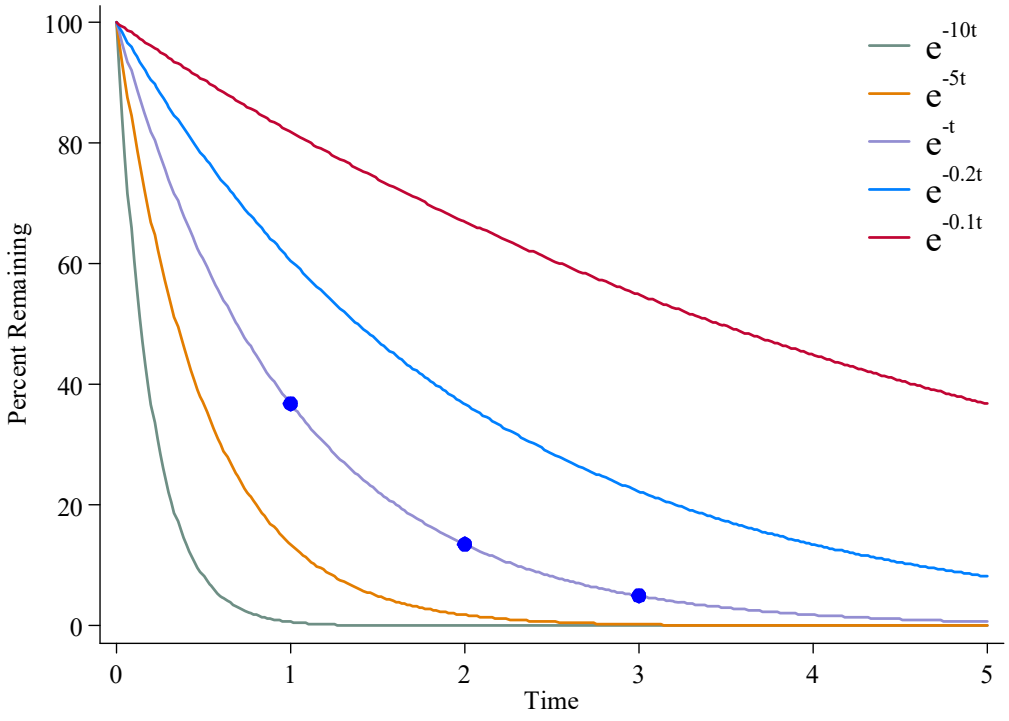
■ *First Order Process - Exponential Decay*

- a process where a constant ***fraction*** of substance/drug is removed per unit time
- represented by the following ***differential equation***, viz:

$$\frac{dC}{dT} = -kC$$

- applying implicit ***integration***, giving the equation:

$$C_t = C_0.e^{-kt}$$



■ *Half Life*

Def'n: time taken for plasma concentration to fall to half the current level

$$C_{t_{1/2}} = C_0 . \frac{1}{2}$$

$$C_0 . \frac{1}{2} = C_0 . e^{-kt_{1/2}}$$

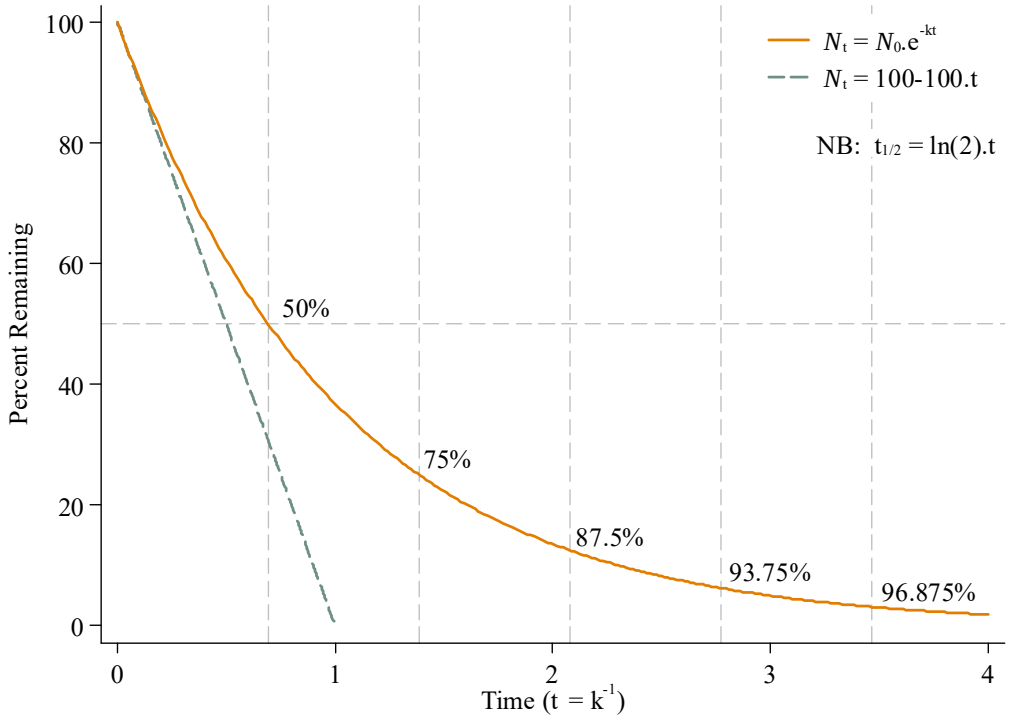
$$\frac{1}{2} = e^{-kt_{1/2}}$$

$$\ln(\tfrac{1}{2}) = -kt_{½}$$

$$kt_{½} = -\ln(\tfrac{1}{2}) = \ln(2)$$

$$t_{½} = \ln(2)/k$$

$$t_{½} = 0.693 \cdot \tau$$

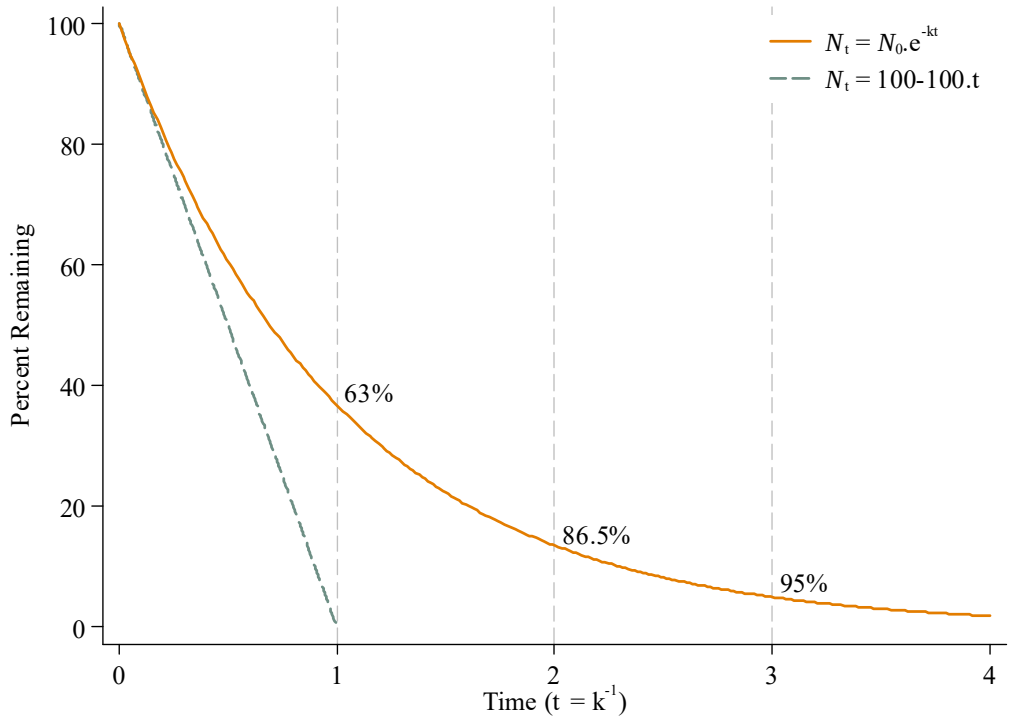


■ *Time Constant*

Def'n: the time taken for a process to run to completion if the initial rate of change continued unabated, *or*
the time it takes the system's step response to reach approximately 63% of its final (asymptotic) value

- τ (tau) is related to the exponential decay constant by

$$\tau = 1/k$$

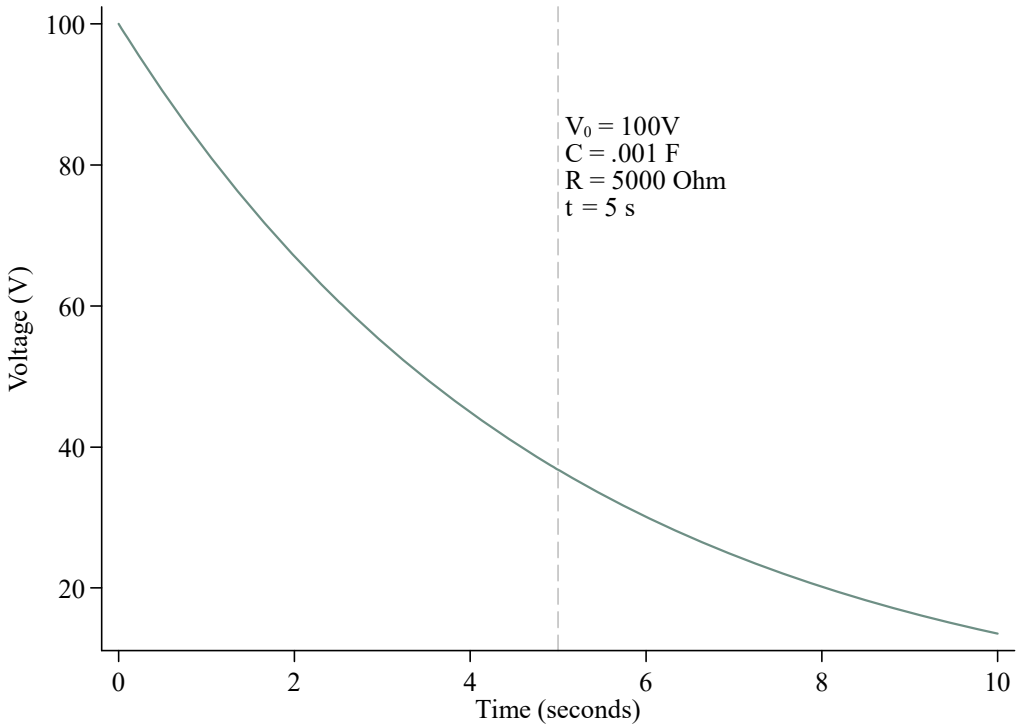


- in physics and engineering, it characterizes the frequency response of a first-order, linear time-invariant (LTI) systems (RxL and RxC)
- classic physiology example is the time-constant of the lung,

$$\tau = R_L.C_L$$

- however, this is only approximate for the lung as both C & R vary with lung volume

- taken from electrical theory for voltage decay for a capacitor (Farads) discharging through a fixed resistance (Ohms):



■ *First Order Exponential Decay*

- percent remaining after 'x' period intervals:

Half-lives	Time Constants
1. 50%	1. 37%
2. 25%	2. 13.5%
3. 12.5%	3. 5%
4. 6.25%	
5. 3.125%	

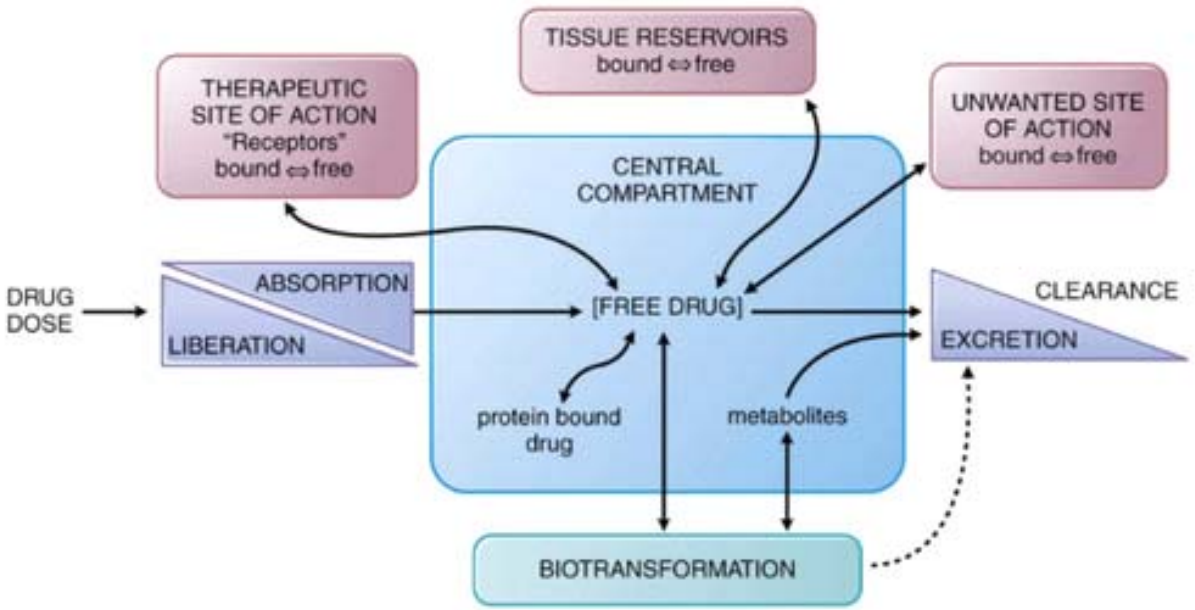
LADME

- divided into several areas which includes the extent and rate of absorption, distribution, metabolism and excretion
- commonly referred to as the ADME scheme:

1.	**L**iberation	- delivery formulation
2.	**A**bsorption	- the process of a substance entering the body - lipid solubility, ionization, bioavailability
3.	**D**istribution	- the dissemination of substances throughout the body - V_{dss}, loading dose, compartment models
4.	**M**etabolism	- transformation of parent compounds into daughter metabolites - hepatic, plasma, lung, renal
5.	**E**xcretion	- the elimination of the substances from the body - clearance, half-life

*in rare cases, some drugs irreversibly ***accumulate*** in a tissue in the body.

- analysis is performed by ***noncompartmental*** (model independent) or ***compartmental*** methods
  1. Non-compartmental methods estimate the exposure to a drug by estimating the area under the curve of a concentration-time graph.
  2. Compartmental methods estimate the concentration-time graph using kinetic models



■ *Parameter Equations*

Bioavailability:

$$F_{Route} = \frac{[AUC]_{Route}}{[AUC]_{IV}} \cdot \left(\frac{Dose_{IV}}{Dose_{Route}} \right)$$

Volume of Distribution:

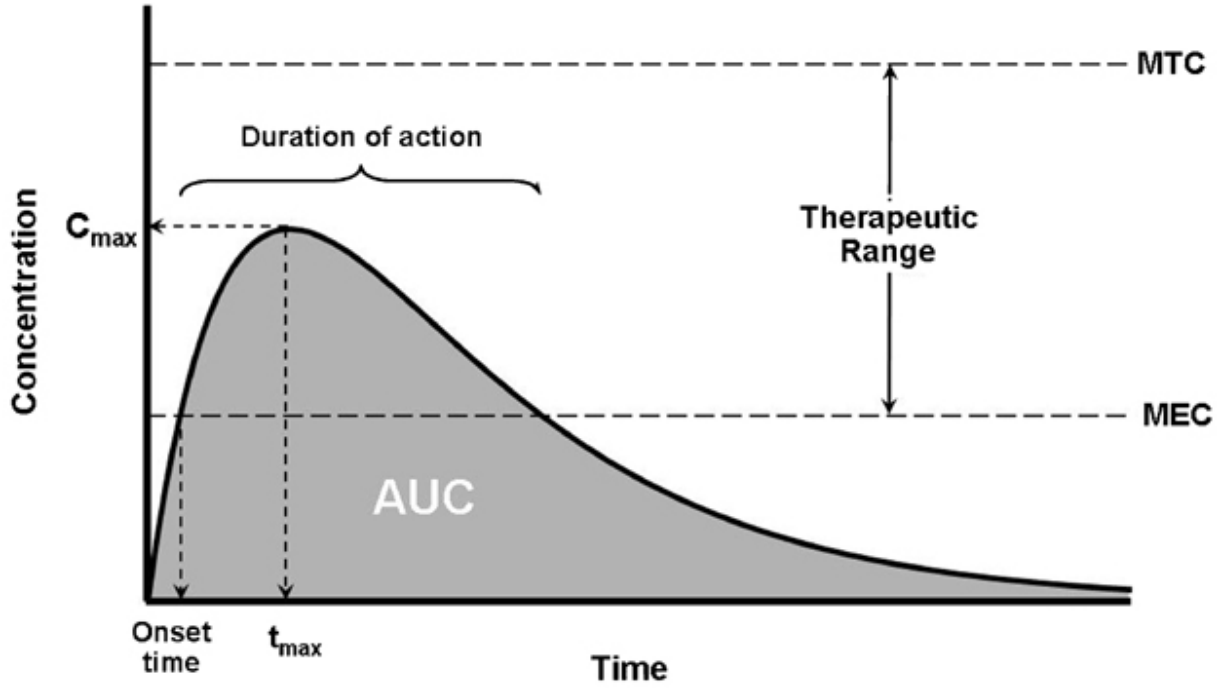
$$V_d = \frac{Dose}{C_0}$$

Plasma Clearance:

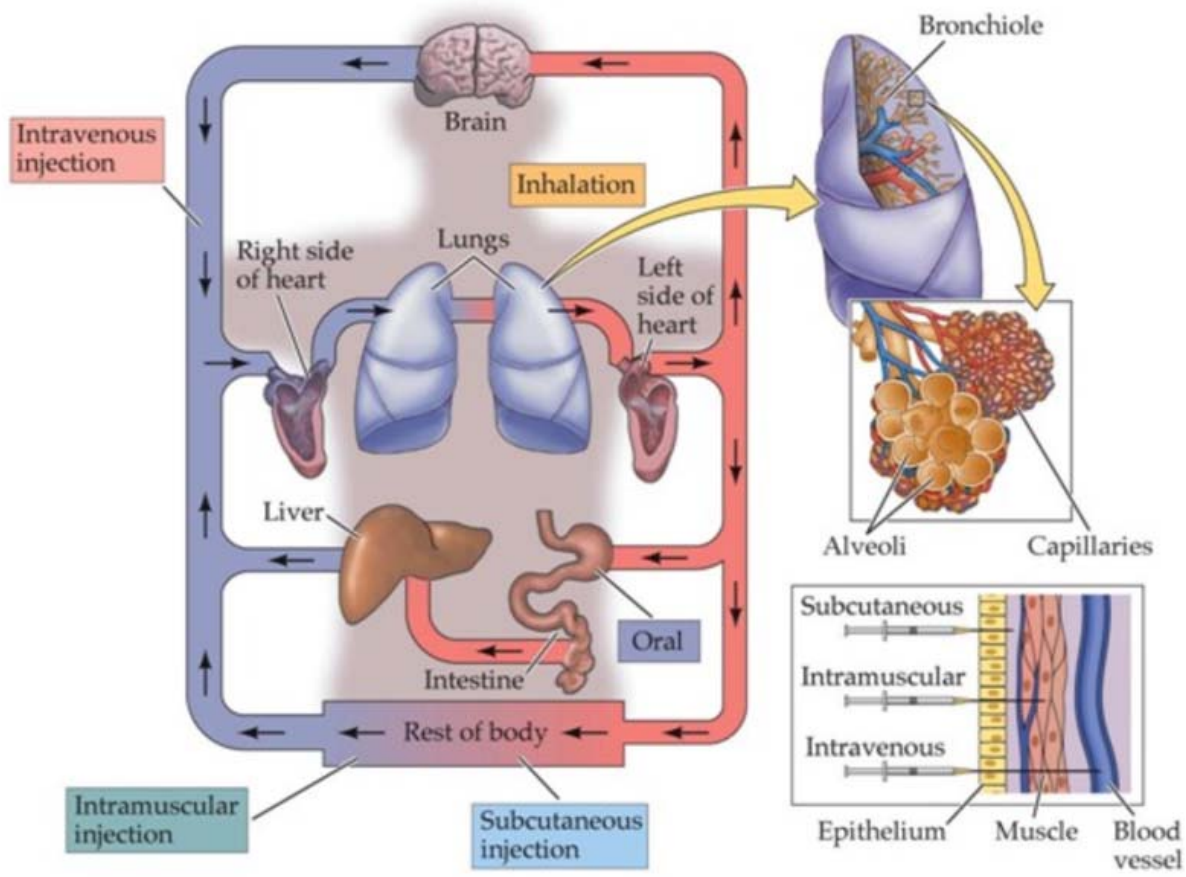
$$Cl = k_{el} \cdot V_d = \frac{Dose}{AUC}$$

Plasma half-life:

$$t_{½} = \tau \cdot \ln(2) = \frac{\ln(2)}{k_{el}} = \frac{0.693 \times V_{dSS}}{Cl}$$

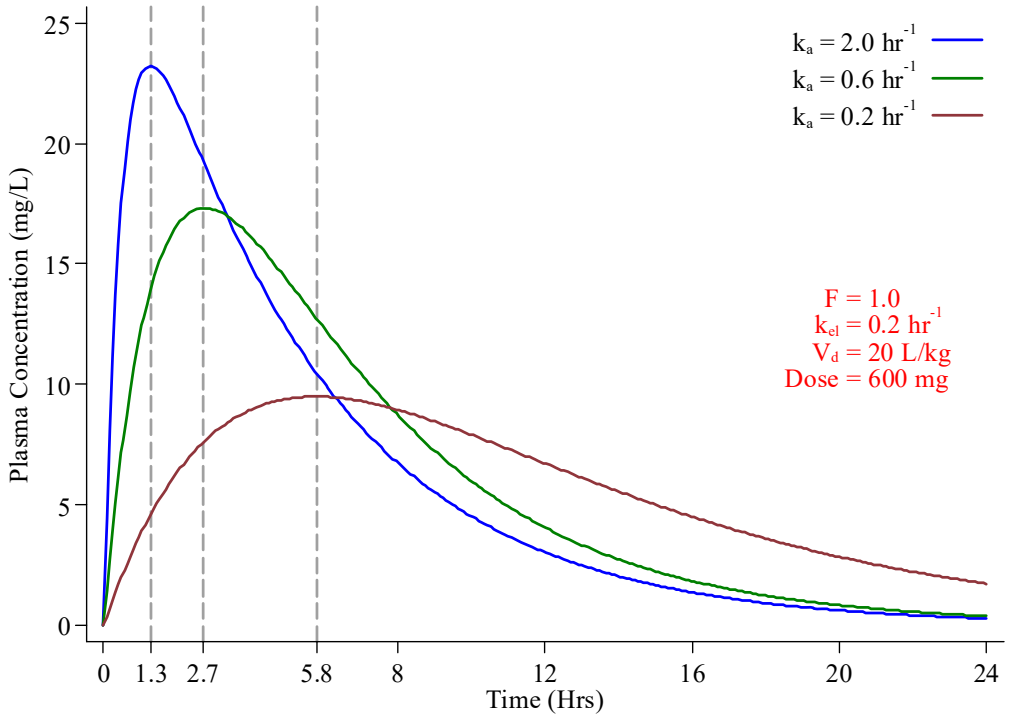


Absorption



▪ *In general:*

- Time to peak plasma level: Lungs > IV > IM > SC > GIT
- AUC IV and SC/IM will be equal.
- AUC PO/PR may approach but will likely be less depending upon ***bioavailability***.



NB: Effect of varying ***absorption*** (k_a) with constant bioavailability (F=1.0)

- Absoption depends predominantly on ***passive diffusion***
- Aqueous or lipid diffusion → ***Fick's Law:***

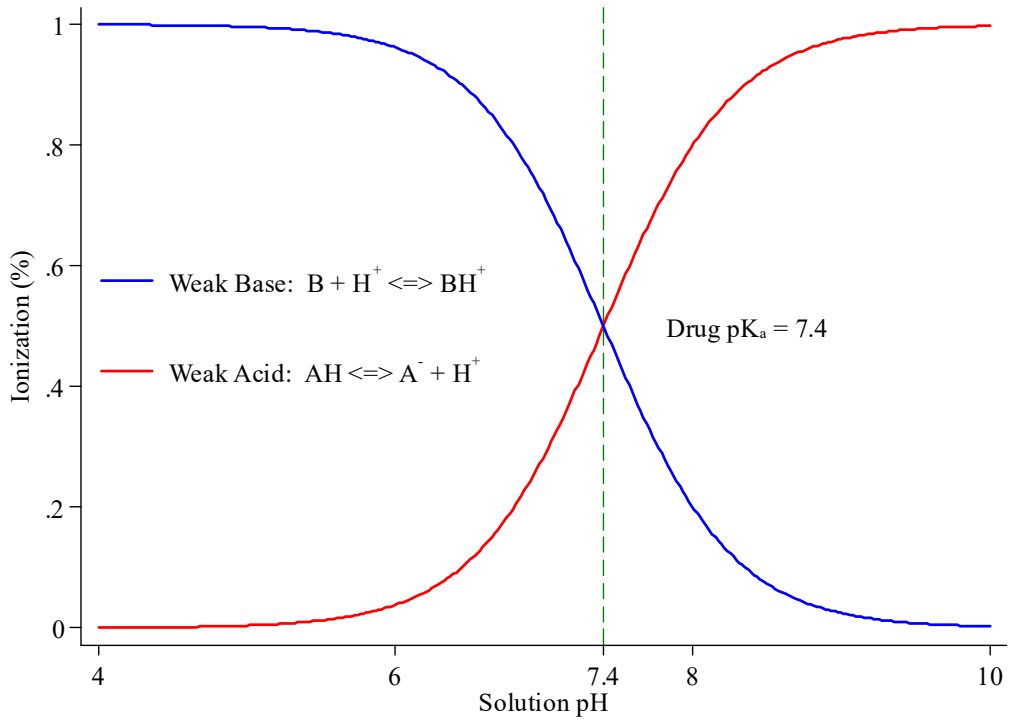
$$J \simeq \Delta C \cdot D \cdot \left(\frac{SA}{t}\right)$$

  - **C**oncentration gradient
  - **D**iffusion coefficient
  - **S**urface **A**rea
  - **T**hickness

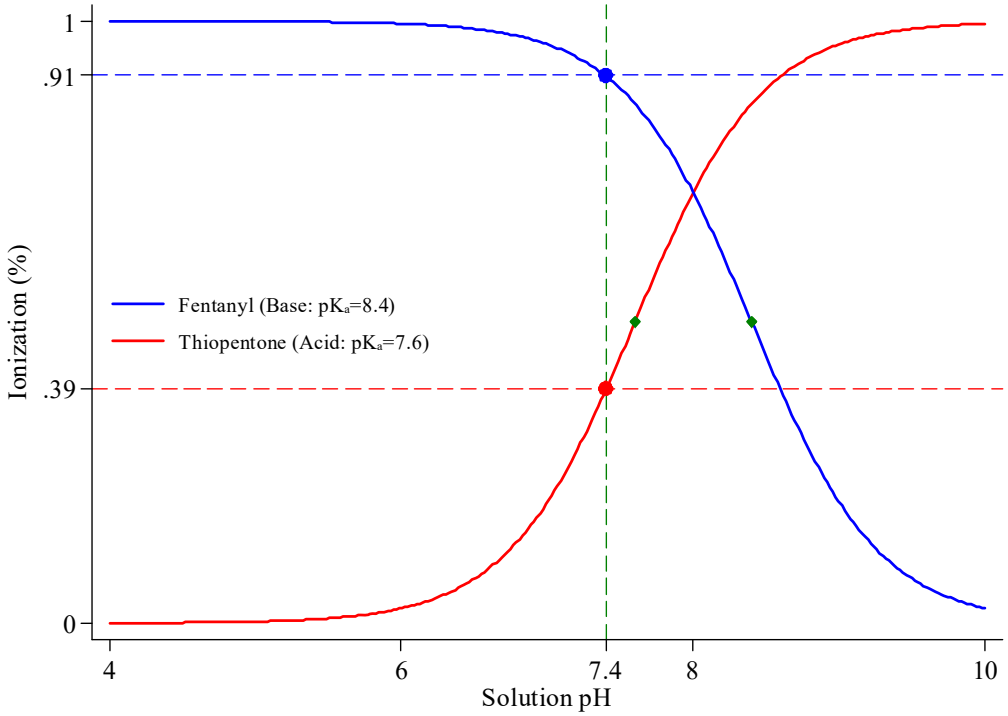
- Rarely by specialized transport systems

- Diffusion coefficient determined by:
  a. Particle size $\propto 1/\sqrt{MW}$
  b. Lipid solubility
  c. Ionisation
     - Most drugs are either weak acids or bases
     - Effects of pH and "ion-trapping" (below)
  d. Others
     - Formulation, e.g. slow release
     - Membrane characteristics - lipid nature, carrier mechnisms

■ *Ionization - Weak Acids/Bases*



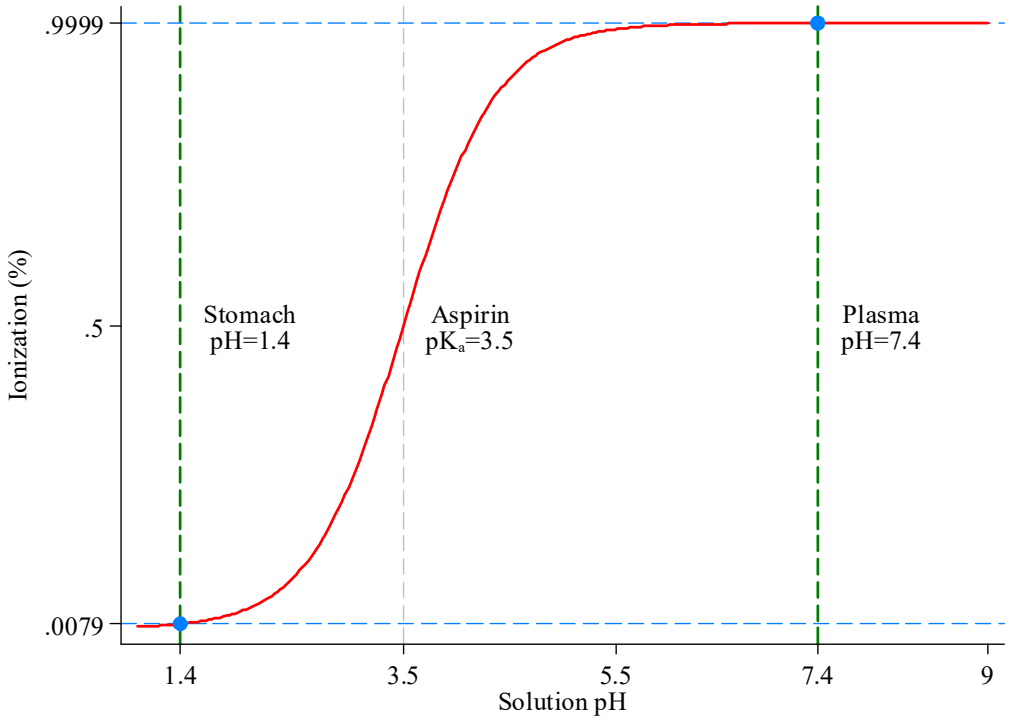
- So, at pH=7.4, the ionization (%) for
    - Fentanyl (base) ≈ 91%
    - Thiopentone (acid) ≈ 39%



- This can result in ***ion-trapping*** for certain drugs
- e.g. for aspirin ($pK_a \approx 3.5$) across the gastric mucosal barrier:
    - Gastric lumen: pH ≈ 1.4 Ion% < 0.01%
    - Plasma: pH ≈ 7.4 Ion% > 99.9%

*$\approx 10^{pH-pKa}/(1+10^{pH-pKa})$

- Where, for an acidic drug, the Plasma:Gastric ratio ≈ $\mathbf{10^{(7.4-1.4)}:1}$

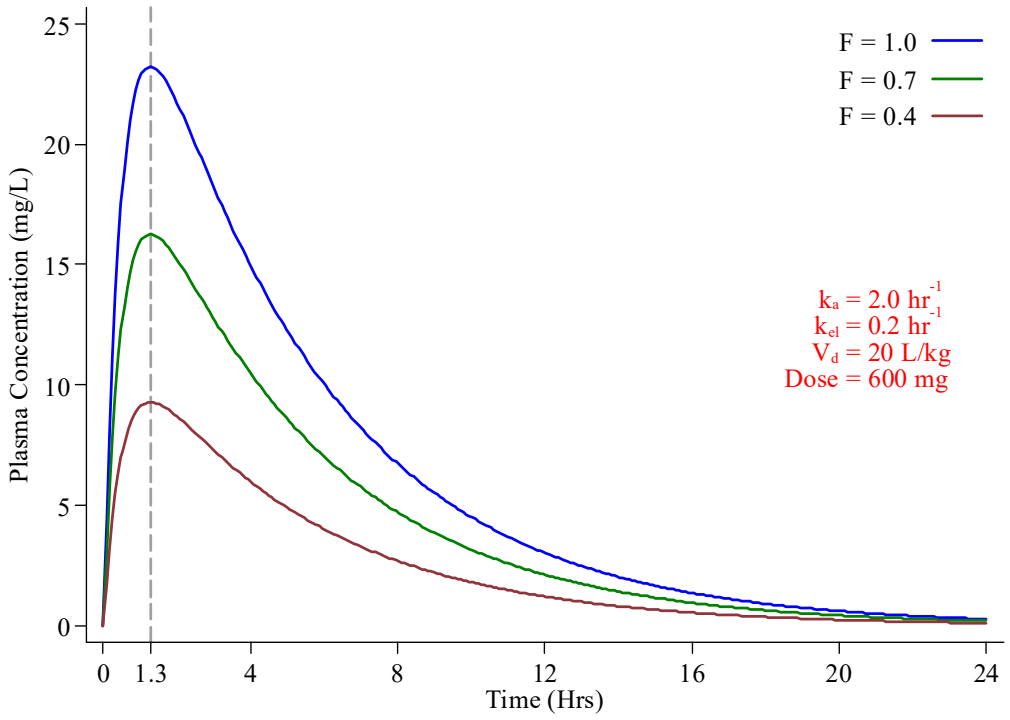


- However, overall absorption is also affected by ***surface area***:
  - Stomach: pH ≈ 1.0-4.0
    - Almost all unionized ↑ absorption
    - Small SA ↓ absorption
  - Small intestine: pH ≈ 7.4
    - Almost all ionized ↓ absorption
    - Large SA ↑ absorption

Bioavailability

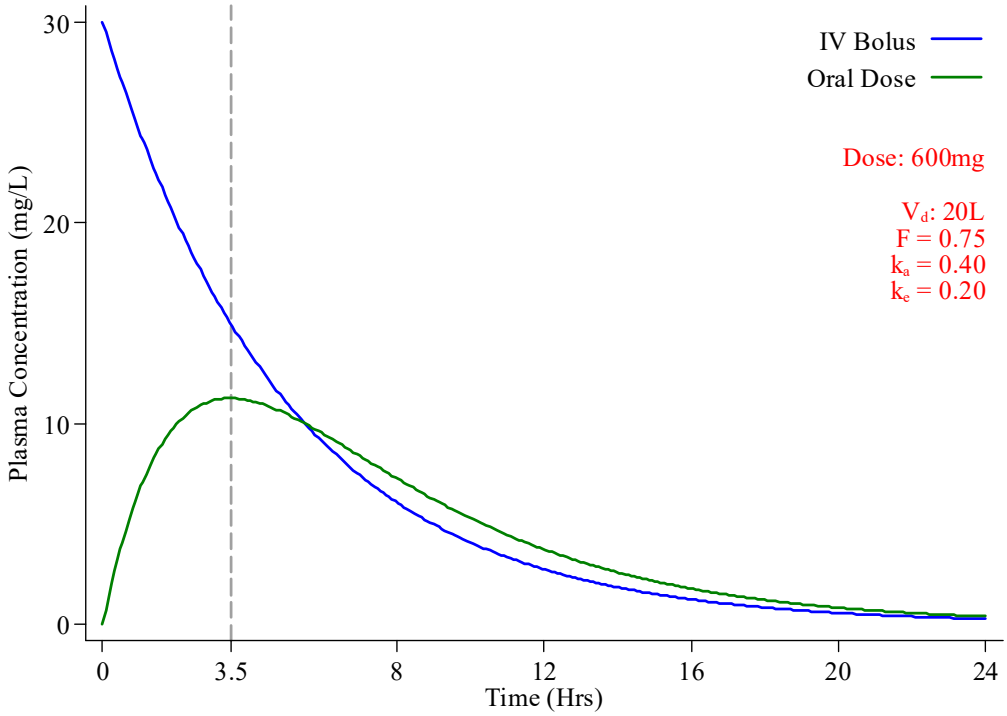
Def'n: the fraction of an administered dose of unchanged drug that reaches the systemic circulation

• If absorption and elimination were held constant, the effect of ***bioavailability*** (F) is simply the AUC:



• ***Absolute bioavailability*** is the dose-corrected area under curve (AUC) non-intravenous divided by AUC intravenous, e.g. for oral administration:

$$F_{PO} = 100 \cdot \left(\frac{AUC_{PO} \cdot Dose_{IV}}{AUC_{IV} \cdot Dose_{PO}} \right)\%$$



NB: In reality, for oral dosing, both absorption and bioavailability vary c.f. IV

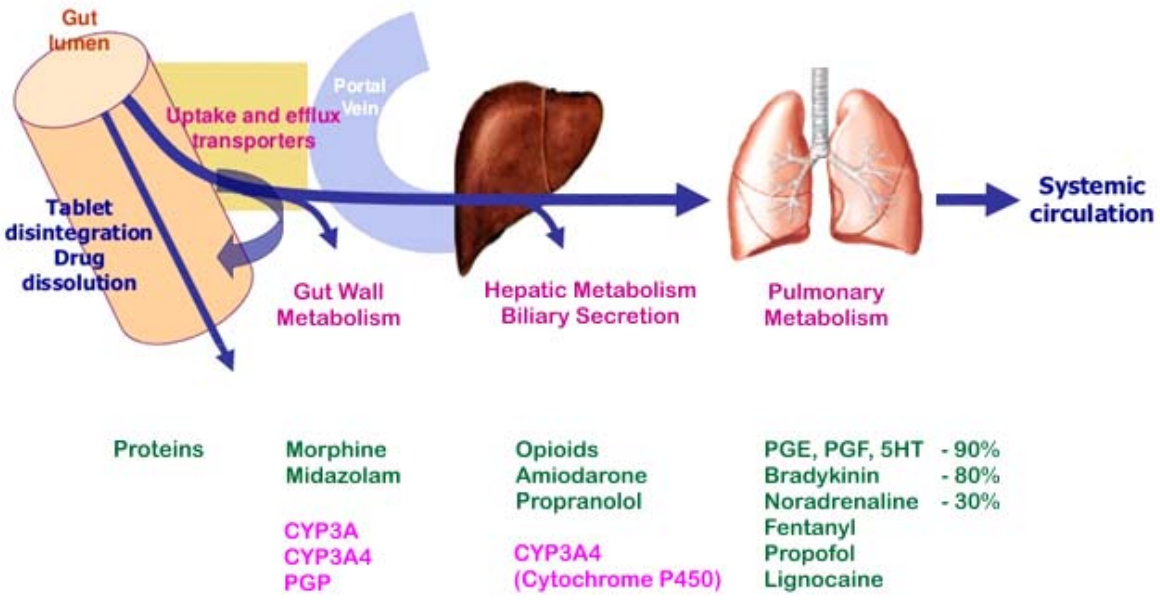
■ *Bioavailability Factors*

- absolute bioavailability, non-IV, is usually less than one, i.e. F<1
- various physiological factors reduce the availability of drugs prior to their entry into the systemic circulation:

1. Physical properties of the drug (hydrophobicity, pKa, solubility)
2. The drug formulation
   i. immediate release, excipients used, manufacturing methods
   ii. modified/delayed release, extended/sustained release, etc.
3. If the drug is administered in a fed or fasted state
4. Gastric emptying rate
5. pH or bacterial-mediated metabolism of the drug within the GI tract
6. Circadean differences
7. Enzyme induction/inhibition by other drugs/foods:
   i. Interactions with other drugs (e.g. antacids, alcohol, nicotine)
   ii. Interactions with other foods (e.g. grapefruit juice, pomello, cranberry juice)

8. Enzyme induction/inhibition by other drugs/foods:
   i. Enzyme induction
      - e.g. phenytoin induces CYP1A2, CYP2C9, CYP2C19 and CYP3A4
   ii. Enzyme inhibition
      - e.g. grapefruit juice inhibits CYP3A → higher nifedipine concentrations
9. Excretion back into the GI tract:
   i. Transporters: Substrate of an efflux transporter? (e.g. P-glycoprotein)
   ii. Hepatic metabolism or biliary excretion back into the GI tract
10. Individual Variation in Metabolic Differences
   i. Age
      - drugs metabolized more slowly in fetal, neonatal, and geriatric populations
   ii. Phenotypic differences, enterohepatic circulation, diet, gender.
11. Disease states
   i. GI tract disorders
   ii. hepatic insufficiency
   iii. renal function

NB: The reduction in total drug delivered to the systemic circulation is referred to as the **"First Pass Effect"** - reflecting the loss of drug via its first pass thru the GI tissues & liver before it reaches the systemic circulation.



■ *First Pass Effect*

- Some drugs are ***activated*** on first pass or produce active metabolites
  - Amiodarone → Desethylamiodarone
  - Clopidogrel → CYP2C19 + others!
- Sublingual administration
  - Avoids 1st pass - except for swallowed drug
- Rectal administration variable
  - Proximal → portal circulation
  - Distal → systemic

■ *Example: Fentanyl*

- High lipid solubility
  - pH dependent pKa ≈ 8.4
  - Opioids weak bases: $B + H^+ \leftrightarrow BH^+$
- Oral administration
  - Stomach: pH ≈ 3 → > 99% ionised
  - S-I pH ≈ 7.4 → ≈ 90% ionised
    *some absorption can occur here
  - Large first pass effect – gut mucosa, liver, lung
- Buccal wafers
  - Mouth pH ≈ 7 → > 95% ionised
  - Oral / buccal wafers contain alkalinising agent
- Dermal patches

■ *Suboxone: Buprenorphine + Naloxone (4:1)*

- Sublingual - oral buprenorphine → large first pass effect
  ∴ high dose used in opioid substitution programs
  → risk of abuse / IV use
- Oral naloxone is metabolised in GI wall (bioavailability < 3%)
- Added to prevent end-user IV administration

■ *Targin: SR Oxycodone + Naloxone (2:1)*

- Oxycodone oral bioavailability ≈ 50%
- Constipation primarily local effect at the myenteric plexus
- Naloxone →
  - local competitive antagonism in the gut (myenteric plexus)
  - metabolised in the GI wall

Distribution

Def'n: The ***apparent*** volume of distribution is the theoretical volume that would be necessary to contain the total amount of an administered drug at the same concentration that it is observed in the blood plasma

$$V_d = \frac{Dose}{C_0}$$

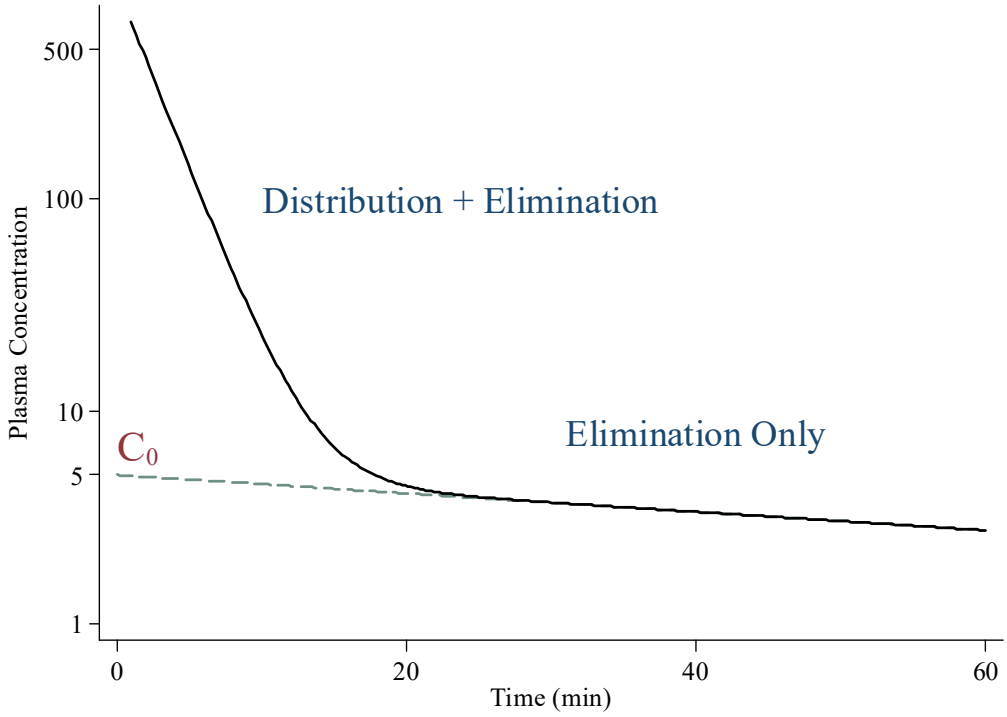
- Does not correspond to any anatomical or physiological tissue compartments
    - Depends upon:
        - Partition coefficient: $\tau_{tissue:plasma}$
        - Plasma protein and tissue drug binding
        - Regional tissue blood flow
    - **V_d < 0.3 l/kg** $\rightarrow$
        - Restricted to plasma or ECF by ionization:
          eg. muscle relaxants, quarternary amines, penicillins
        - Extensively bound by plasma proteins:
          eg. warfarin, phenytoin
    - **V_d > 0.6 l/kg** $\rightarrow$
        - Bound to tissues
        - eg. amiodarone, digoxin, fentanyl
- Used in calculation of a ***loading dose***:

$$D_{Load} = \frac{C_{Pl} \cdot V_d}{F \cdot S}$$

    - C_{Pl} = desired peak concentration of drug (time 0)
    - V_d = volume of distribution of drug in body
    - F = bioavailability
    - S = fraction of drug salt form which is active drug

- Assumes sufficient time for distribution but not elimination
- This is in effect a ***single compartment model***:

$$C_{p0} = \frac{Dose}{V_d}$$



■ *Loading Dose: NMJ Blockers*

- Vd ≈ 0.2 - 0.3 L/kg
- Distribute within plasma water → $\mathbf{D_{load} \approx V_d \times C_{pl}}$
- Predictable & clinically reliable loading doses for NMJ blockade

■ *Loading Dose: Amiodarone*

- Vd ≈ 80 - 150 L/kg
- Distributes extensively to tissues:
  - $\tau_{\text{lipid:plasma}} \approx 300{:}1$
  - $\tau_{\text{heart:plasma}} \approx 20{:}1$
- Therapeutic [plasma] ≈ 0.5 - 2.0 µg/mL
- D_{load} ≈ (100L/kg × 1000)mL × 1.0 µg/mL
  ≈ (7000L × 1000)~~mL~~ × 1.0 µg/~~mL~~
  ≈ 7,000,000 × 1.0 µg
  ≈ 7,000 mg !!!

■ ***Loading Dose:*** ***Propofol***

- Published data: C_{SS} ≈ 8 µg/mL
  V_d ≈ 10 L/kg
  $t_{½}$ ≈ 30-60 min

- Load Dose: $D_{load} \approx C_{SS} \times V_d$
  ≈ 8 µg/~~mL~~ × 10,000 ~~mL~~/kg
  ≈ 80,000 µg/kg
  ≈ **80 mg/kg**

NB: This would be clearly ***fatal***, and like amiodarone, the loading dose needs to accomodate tissue distribution and the loading dose split into phases

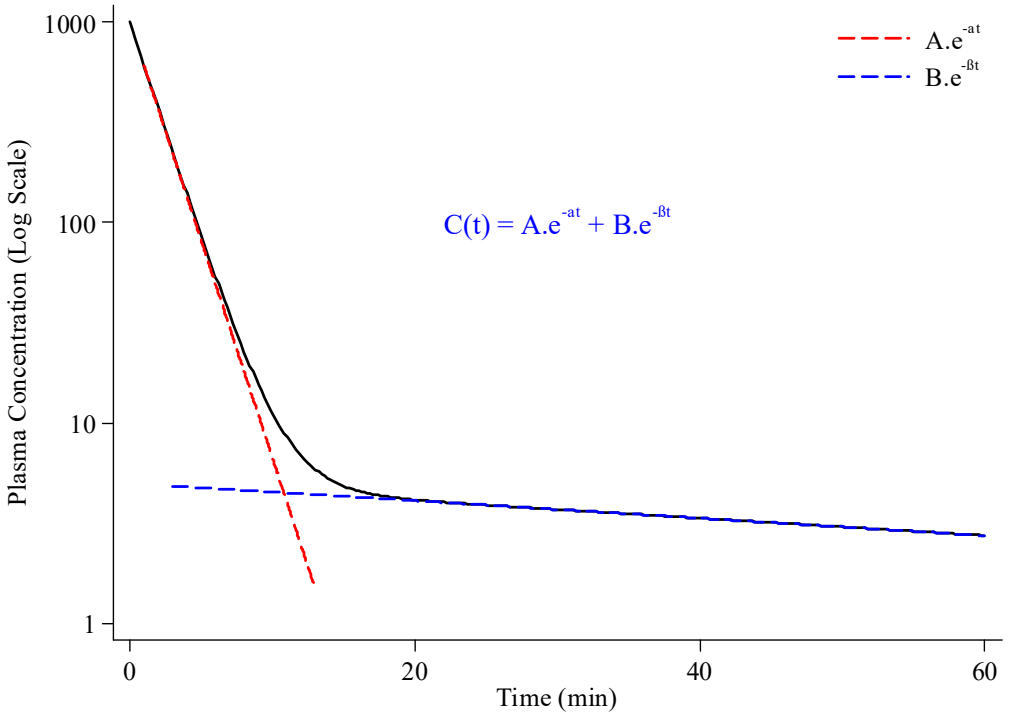
Drug	**Oral Availability (%)**	**Vd (L/kg)**	**Half-Life (h)**
Acetaminophen	88	0.96	2
Aspirin	68	0.16	0.25
Fentanyl	-	0.9 - 6.0	1.5 - 6.0
Morphine	24	3.29	1.9
Ampicillin	62	0.29	1.3
Cephalexin	90	0.26	0.9
Cephalothin	-	0.26	0.57
Gentamicin	-	0.26	2.5
Ciprofloxacin	60	1.86	4.1
Vancomycin	-	0.39	5.6
Diazepam	100	1.1	43
Midazolam	44	1.1	1.9
Phenytoin	90	0.64	**5
Warfarin	93	0.14	37
Amiodarone	30	10-150	60-142 Days
Digoxin	70	7.14	50

Two Compartment Model

- Plasma concentration follows a biphasic pattern with,
    - Initial rapid ***distribution***
    - Terminal ***elimination***
- With plasma concentration over time estimated via a ***bi-exponential model***:

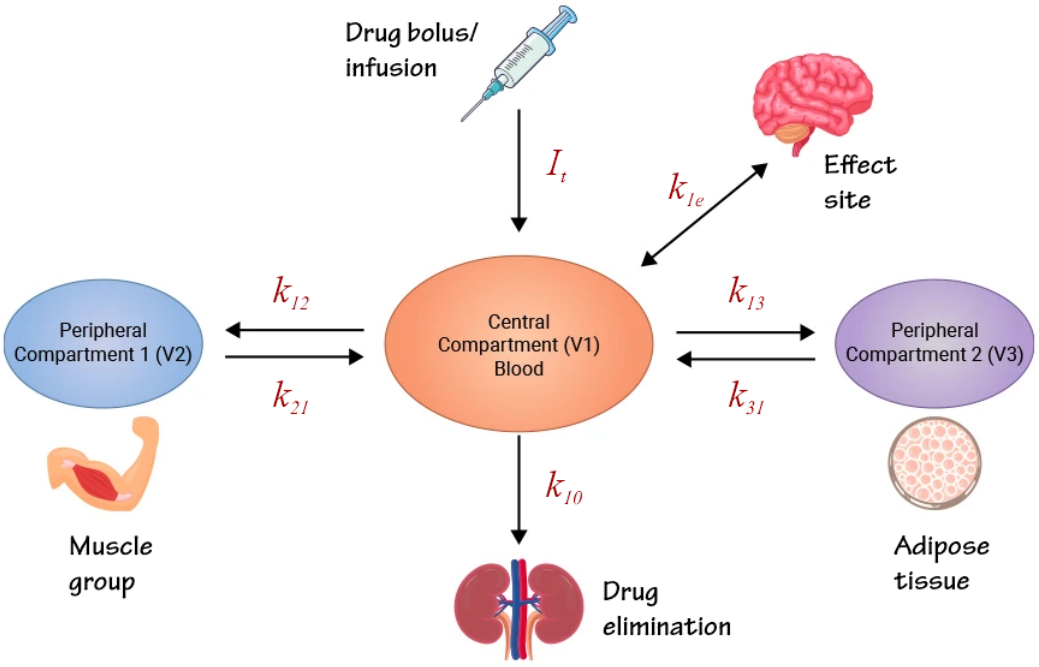
$$C_t = A.e^{-\alpha t} + B.e^{-\beta t}$$

    - where {A, B} are the y-intercepts at t=0
    - assumes:
        - drug enters and is eliminated only from the central compartment
        - the effect site is not included in the model
    - i.e. this is an approximation / model



Three Compartment Model

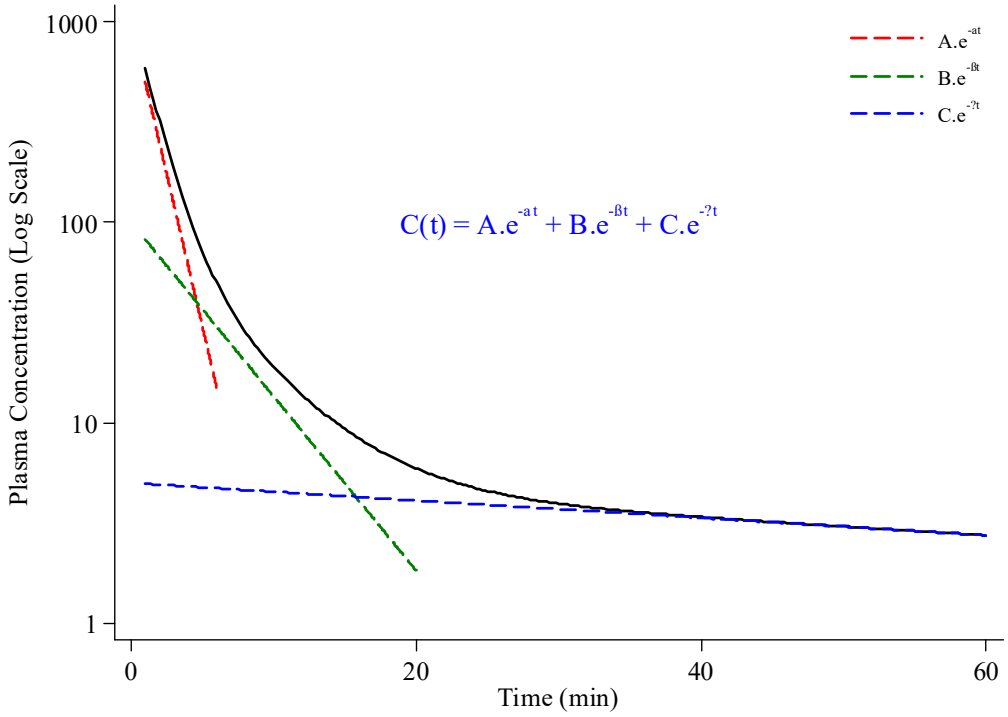
- Many ICU drugs, especially anaesthetics, approximate a 3-compartment model



- Loading dose based upon V_{dss} would result in toxic/lethal plasma levels
- Loading is therefore staggered to accomodate redistribution, e.g.
  a. Loading infusion - dexmedetomidine
  b. Stepped infusion - TCI propofol, amiodarone
  c. Stepped PO regimen - amiodarone

- For many ICU drugs,
  - C_{Pl} declines due to ***redistribution*** >> elimination.
  - Duration of clinical effect $\propto$ C_{Pl}

NB: Incrementing the infusion rate to maintain clinical effect risks accumulation and prolonged effect, e.g. Fentanyl & ***context sensitive half-time***


1000
100
10
1
Plasma Concentration (Log Scale)
0
20
40
60
Time (min)
C(t) = A.e-at + B.e-ßt + C.e-?t
A.e-at
B.e-ßt
C.e-?t

Elimination

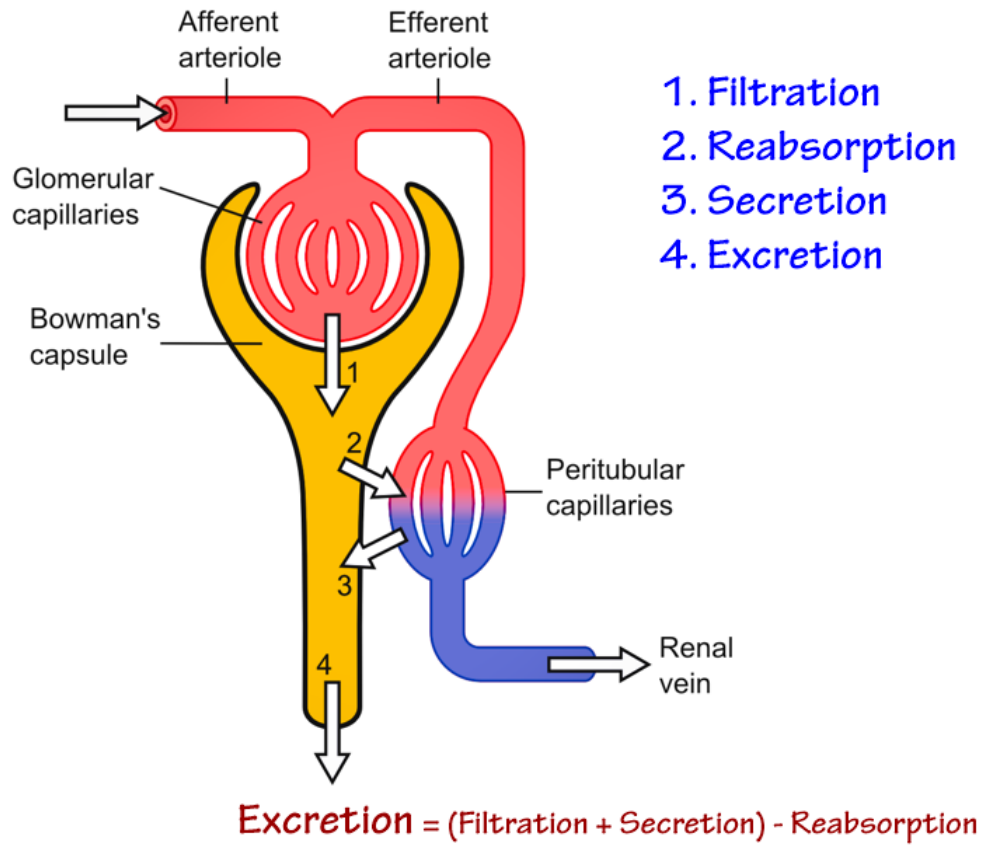
■ *Clearance*

Def'n: The volume of plasma from which the drug is removed per unit time. Usually in mL/min, or L/hr

- Additive, $$Cl_{Tot} = Cl_{Renal} + Cl_{Hepatic} + Cl_{Other}$$
- Determines dosing rate for steady-state,

$$\text{Maintenance Dose} = Cl_{Tot} \times [D]_{SS}$$

■ *Renal Clearance*



1. Filtration → free unbound drug ∝ **GFR**
   - Effects of protein binding
   - Age-related changes in GFR
     - Decreaed in neonate
     - Adult range by 3 years
     - Cockroft-Gault (male):

$$Cl_{Creat} = (140 - Age) \times \frac{Wt.(kg)}{0.814} \times [Creat.]_{Pl}$$

     - Weight in kg
     - $[Creat.]_{Pl}$ in µmol/L
     - Female = Male × 0.85
2. Tubular secretion / reabsorption
   - Alkalinization/acidification → organic acids/bases
   - Active transport - competitive/saturable
   - Protein binding - bound drugs can be secreted
   - Weak acids
     - Anions at physiologic pH *Urine $pH_{Min} \approx 4.4$
     - Actively transported from plasma to tubular lumen
   - Weak bases
     - Can be actively transported, fewer systems
   - Metabolism - minor but does occur

■ ***Hepatic Clearance***

- Metabolism ± biliary excretion:

    1. Metabolism - major
        - Phase I Reactions
        - Microsomal enzymes - P_{450}
        - Inactivate (or activate) metabolites
    2. Phase II Reactions
        - Most are cytosolic (microsomal)
        - Conjugation → glucuronide, glycine, sulphate
        - ↑ water solubility → excretion in urine/bile
    3. Active metabolites may have same or different properties as parent molecule
    4. Biliary Secretion – active transport

- Cytochrome P_{450} mono-oxygenase:

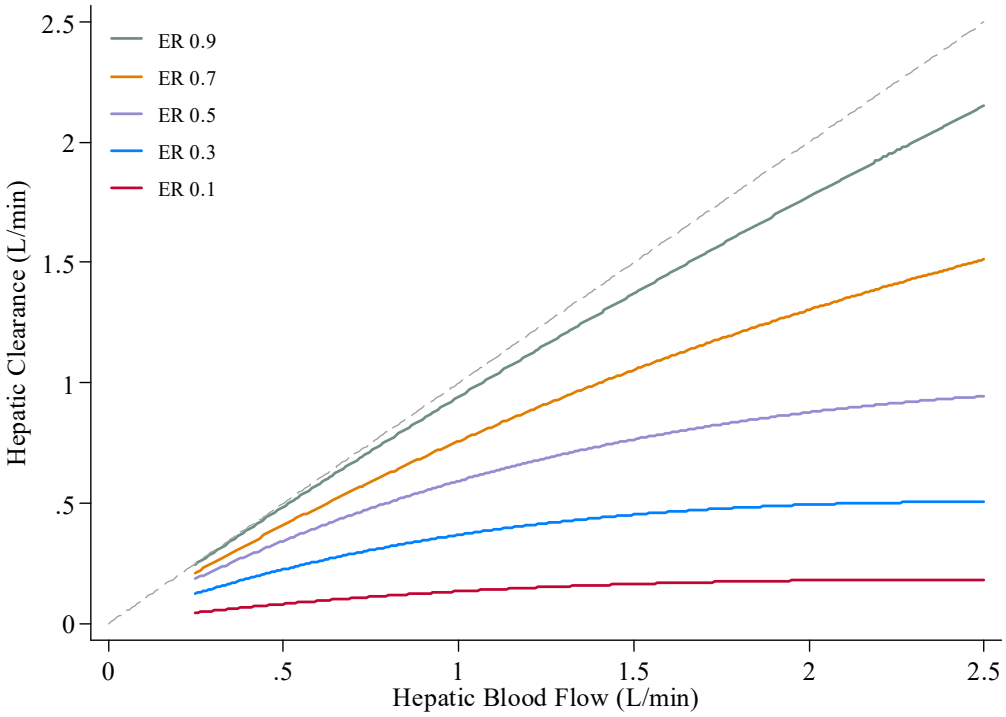
    1. 1000^{+} known cytochrome P_{450} enzymes
        - ≈ 50 functionally active in humans
        - ≈ 17 families / subfamilies
        - CYP for identification of isoforms, e.g. CYP2D6 metabolizes morphine
    2. Found in ER (microsomal fraction)
    3. Reactions are ***oxidation*** or ***reduction*** → change functional group
    4. Enzyme induction / drug interactions

- Hepatic clearance,

$$Cl_{Hep} = Q \times ER_{Hep.}$$

- Hepatic extraction ratio (SS),

$$ER_{Hep.} = \frac{C_a - C_v}{C_a}$$



Effect on $Cl_{Hepatic}$	**Flow Limited**	**Capacity Limited**
Hepatic ER	> 0.7	< 0.3
Hepatic Blood Flow	↑↑↑	±
Enzyme induction	±	↑↑↑
Protein binding	±	↓↓
First-Pass Effect	High	Low
Bioavailability	Low	High
Example	Morphine	Alfentanyl

■ *Measurement of Clearance*

- Single dose:

$$Cl = \frac{Dose}{AUC} \qquad \frac{mg}{\left(\frac{mg}{mL}\right)\cdot \min} = mL/\min$$

- Steady-state infusion:

$$Cl = \frac{Infusion\ rate}{C_{SS}} \qquad \frac{mg}{\min} \cdot \frac{mL}{mg} = mL/\min$$

■ *Elimination Half-Time*

Def'n: Time for ***plasma concentration*** to decline by 50%

■ *Elimination Half-Life*

Def'n: Time for 50% of a drug to be ***eliminated from the body***

- Proportional to V_d
- Inversely proportional to $Cl \quad = k_{el} \times V_{dSS}$
  - $k_{el} = Cl \,/\, V_{dSS}$

$$t_{½} = \tau \cdot \ln(2) = \frac{\ln(2)}{k_{el}} = \frac{0.693 \times V_{dSS}}{Cl}$$

■ *Context-Sensitive Half-Time*

Def'n: Time for the plasma concentration to fall to ½ of its steady state value on cessation of an infusion

- ***Context*** is the duration of the infusion
- Also dependent on plasma SS concentration

- Empirically derived and we invent theories to explain them!!
- Dependent on V_d, tissue binding, k_{eo}, elimination

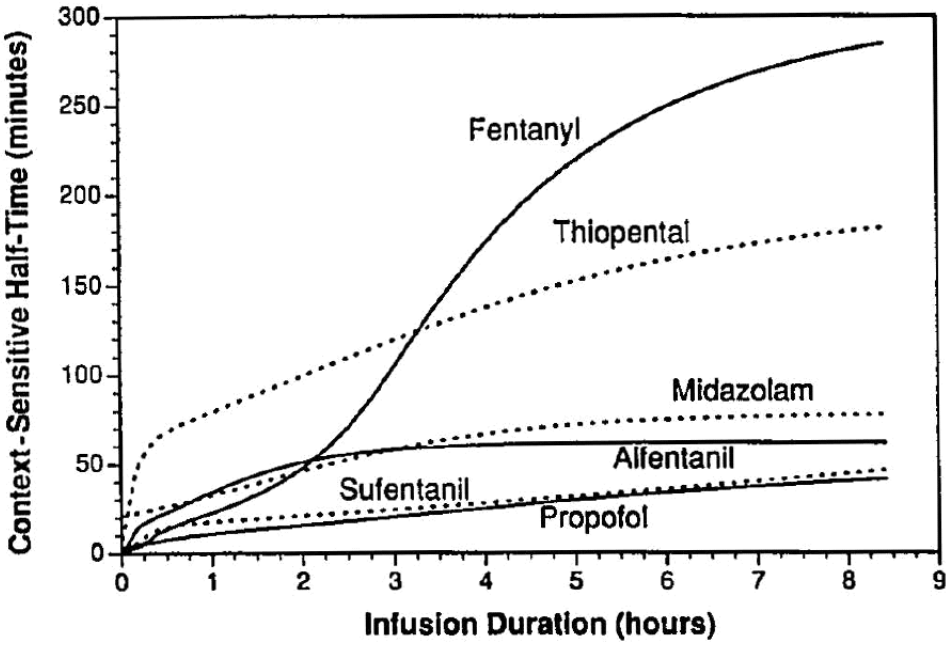


FIG. 1. Context-sensitive half-times as a function of infusion duration for each of the pharmacokinetic models simulated. Solid and dashed line patterns are used only to permit overlapping lines to be distinguished.

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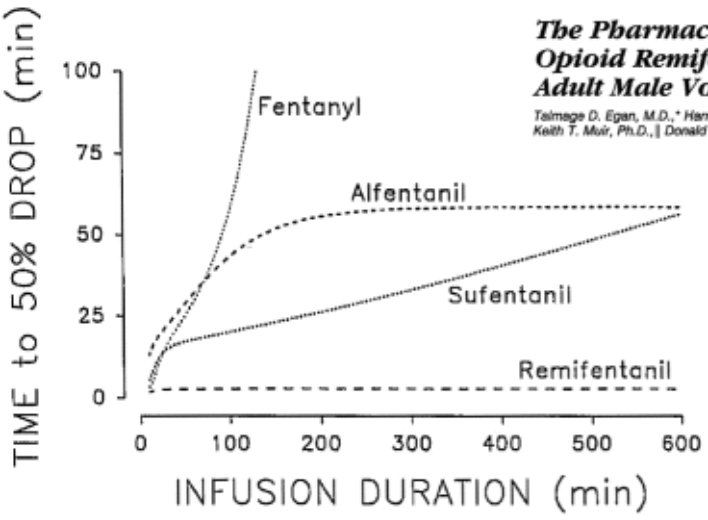

The Pharmacokinetics of the New Short-acting Opioid Remifentanil (GI87084B) in Healthy Adult Male Volunteers

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Fig. 6. A simulation of the time necessary to achieve a 50% decrease in drug concentration in the blood (or plasma) after variable-length intravenous infusions of remifentanil, fentanyl, alfentanil, and sufentanil. The simulation for remifentanil was done using the NONMEM three-compartment model parameters; the curves for the other opioids were simulated using parameters obtained from the literature (see text).

NB: So, these are ***model-based simulations*** to explain what is observed clinically.