TEXAS A&M UNIVERSITY
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NAPLEX Review
Pharmacokinetics and Pharmacodynamics

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NAPLEX Review: Pharmacokinetics and Pharmacodynamics

Pharmacokinetics

- Pharmacokinetics is the science of what the body does to the drug

Pharmacodynamics

- Pharmacodynamics is the science of what the drug does to the body

Absorption – Distribution – Metabolism – Excretion (ADME)

Absorption

- Process that brings a drug from the administration, e.g., tablet, capsule, into the systemic circulation
- The process of absorption includes **liberation**, or the process by which the drug is **released from its pharmaceutical dosage form**
- **Bioavailability** is the **fraction** of the originally administered drug that arrives in **systemic circulation** and depends on the properties of the substance and the mode of administration
  - Bioavailability of medication administered intravenously is 100%
  - Bioavailability of oral medications is typically < 100% but may achieve 100% in certain cases
    - Factors that affect oral bioavailability include digestive enzymes, and first-pass metabolism
  - Absolute bioavailability

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Absolute Bioavailability

- Measuring bioavailability (absolute bioavailability) of an oral formulation
- Administer IV drug to a group of volunteers
- Administer oral formulation on separate occasions
- Determine the respective area under the plasma concentration–time curves

$$\text{Absolute bioavailability} = F = \frac{\text{AUC}_{\text{oral}} / \text{dose}_{\text{oral}}}{\text{AUC}_{\text{i.v.}} / \text{dose}_{\text{i.v.}}}$$

$$F_{abs} = 100 \cdot \frac{AUC_{tablet} \cdot Dose_{IV}}{AUC_{IV} \cdot Dose_{tablet}}$$

Review Questions #23 and 24 Uworld – Absolute Bioavailability

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Absorption

- First Pass Effect
  - Drug metabolism at a specific location in the body resulting in a reduced concentration at site of action or the systemic circulation
  - Frequently associated with the liver, as this is a major site of drug metabolism
  - May occur in the lungs, vasculature, gastrointestinal tract, and other metabolically active tissues
- Area Under the Curve (AUC)
  - The AUC is a method of calculating the drug bioavailability of substances with different dissemination characteristics, and this observes the plasma concentration over a given time

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Case 1

BJ is a 55-year-old female patient with a history of acute myelogenous leukemia (AML). BJ weights 90 kg, and is 67 inches tall, and is scheduled to receive pre-hematopoietic stem cell transplant (HSCT). Her conditioning regimen included busulfan, administered as 0.8 mg/kg body weight IV over 2 hours every 6 hours for 16 doses followed by cyclophosphamide 60 mg/kg IV over 1 hour for 2 doses on 2 consecutive days. Serial blood samples were collected with the busulfan dose first dose for determination of the busulfan AUC. After a day of rest, the HSCT was performed. Your team asks you to calculate the starting busulfan dose for BJ.

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Case 1 Continued

Ideal Body Weight (IBW) - Devine equation

- 1. IBW, kg (male) = 50 + [2.3 × (height, inches – 60)]
- 2. IBW, kg (female) = 45.5 + [2.3 × (height, inches – 60)]

Busulfan Dosing

- 3. Adjusted body weight (ABW25), kg = IBW, kg + 0.25 × (actual body weight, kg – IBW, kg)
- 4. ABW25 = 61.6 kg (IBW) + 0.25 (90-61.6 kg)
  68.7 kg

Busulfan Dose = 0.8 mg x 68.7
= 54.96 or 55 mg

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Case 1 continued

The following are results of the busulfan blood sample analysis reported:

Time (min)	Time (hr)	Busulfan (μM/L)	Busulfan (mcg/L)	Busulfan (ng/ml)
0	0	0	0	0
118	1.96	3.15	775	775
135	2.25	2.95	726	726
165	2.75	2.53	622	622
180	3	2.23	549	549
300	5	1.33	327	327
360	6	1.05	258	258

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Case 1 continued

Converting busulfan concentration of 3.15 µM to mcg/L and ng/mL

Molecular weight of busulfan = 246 g/mol
Busulfan 246 mcg/L = 1 x 10^{-6} M or 1 µM

*** Busulfan Conc (µM/L) = $\frac{\text{Busulfan Conc (mcg/L)}}{\text{246 mcg/µmol}}$

*** Busulfan Conc (mcg/L) = Busulfan Conc (µM) x 246 mcg/µmol
e.g. = 3.15 x 246
= 775 mcg/L or x 1000 = 775000 ng/L
or 775000 ng/1000 ml = 775 ng/mL

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AUC Calculation (Linear (Trapezoid) and Logarithmic) Methods

- The linear method slightly overestimates the AUC
- The logarithmic method is only effective when concentrations are decreasing
- Linear – Logarithmic Method
  - The linear method is recommended for use used from point zero to the peak
  - The logarithmic method is employed for declining concentrations

$$AUC_{trapezoid} = \frac{(C1 + C2)}{2} \Delta t \quad \text{(Linear)}$$

$$AUC_{log} = \frac{(C1 - C2)}{(\ln C1 - \ln C2)} \Delta t \quad \text{(Logarithmic)}$$

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AUC - Linear Method

Time (min)	Busulfan (μM)	C1+C2	C1+C2/2	Δt (t2-t1)	AUC-linear = (C1+C2)/2 X Δt	AUC total
0	0	0	0	0	0	0
118	3.15	3.15	1.575	118	185.85	185.85
135	2.95	6.1	3.05	17	51.85	237.7
165	2.53	5.48	2.74	30	82.2	320.0
180	2.23	4.76	2.38	15	35.7	355.7
300	1.33	3.56	1.78	120	213.6	569.3
360	1.05	2.38	1.19	60	71.4	640.7
					AUC Per Interval	AUC total = Added interval values of previous Column

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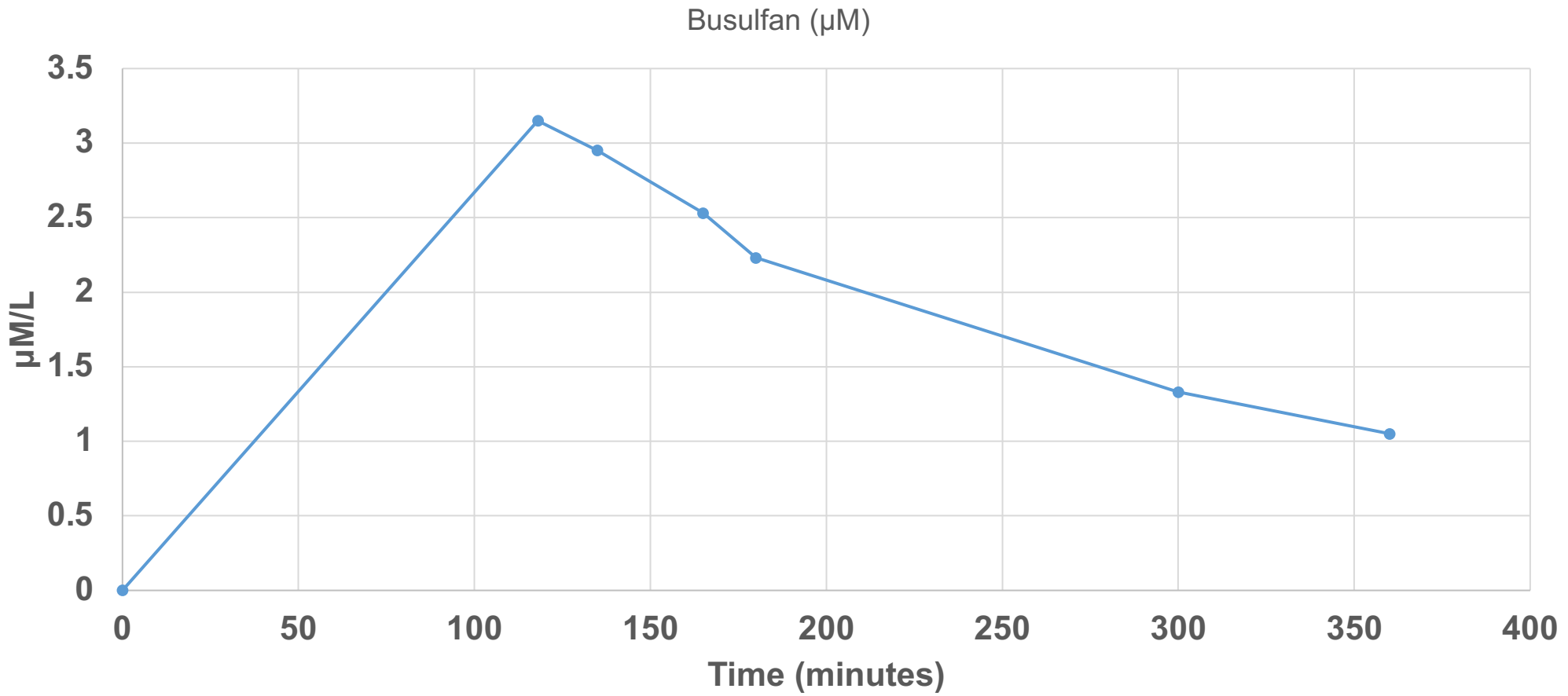
Linear Trapezoid Method of AUC Calculation

$$AUC_{trapezoid} = \frac{(C1 + C2)}{2} \Delta t$$



Ke = ln(C1/C2)/ Δt = ln(2.23/1.33)/120 = 0.0046

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AUC Trapezoid Calculation Method

- $AUC_{0-\infty} = AUC_{0-360} + Ct(last)/Ke$ = 868.7 µM/LxMin (Initial-trapezoid)
- AUC_{0-360} = 640.7 µM/LxMin
- C(last)/Ke =228 µM/LxMin
- 1.33µM/L/0.0046Min^{-1} = 228 µM/LxMin
- 640.7 µM/LxMin+ 228 µM/LxMin = 868.7 µM/LxMin

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Alternate $AUC_{0-\infty}$ Calculation

- $AUC_{0-\infty} = \frac{(F)Dose}{Cl}$
- $Cl = KeVd$

- $AUC_{0-\infty} = \frac{Dose}{KeVd}$
- To be consistent with the $AUC_{trapezoid}$ approach, Covert dose of 55 mg to micromoles = 55/246 mg x 1000 mcg/mg

  = 223 µmol
- Use two concentration – time points from the linear portion of the graph to calculate Ke (2.23 µM/L, 180 mins) and (1.33 µM/L, 300 mins)
- Use population Vd of 0.8 L/Kg

- $AUC_{0-\infty} = \frac{223\ \mu mol}{0.0046 Min^{-1} \times 0.8\ L/Kg \times 68.7\ Kg}$

  = 884 µM/LxMin

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Review Questions #30 and 31 Uworld - Bioavailability

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Distribution

- Distribution describes how a drug is spread throughout the body
  - When a molecule is **very large, charged, or primarily protein-bound in circulation, such as warfarin** (Vd = 0.11 L/kg (8L)), it stays intravascular, unable to diffuse, reflected by a low Vd
  - A distribution volume similar to the total volume of body water (approximately 0.6L/Kg (42L)), such as theophylline Vd = 0.42 L/kg (30L), represents distribution in total body water. **Smaller and hydrophilic molecules** would have a larger Vd reflected by its distribution into all extracellular fluid
  - A **small lipophilic molecule**, such as chloroquine (Vd = 140 L/kg (1500L)), would have a very large Vd as it can distribute throughout cells and into adipose tissues
- Protein Binding
  - In the body, a drug may be protein-bound or free
  - Only free drug can act at its pharmacologically active sites
  - Reduction in plasma protein binding increases the amount of drug available at receptor site leading to toxicity

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Metabolism

- Metabolism is the processing of the drug by the body into subsequent compounds
- Converts the drug into more water-soluble substances that progresses to renal clearance
- Prodrug, e.g., codeine, require metabolism to convert the drug into active metabolites
- Metabolism occurs in various areas of the body, e.g., GI tract, skin, plasma, kidney or lungs
- Majority of metabolism is via phase I (CYP450) and phase II (UGT) reactions in the liver
  - UDP-glucuronosyltransferase (UGT)
  - Phase I reactions generally transform substances into polar metabolites by oxidation
    - Allows for conjugation reactions of Phase II to take place

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Excretion

- Excretion is the process by which the drug is eliminated from the body
  - Kidneys predominantly, lungs, skin, or GI tract

Clearance

- Defined as the **ratio drug elimination rate to the plasma concentration**

$$Cl = KeVd$$

$$AUC_{0-\infty} = \frac{(F)Dose}{Cl}$$

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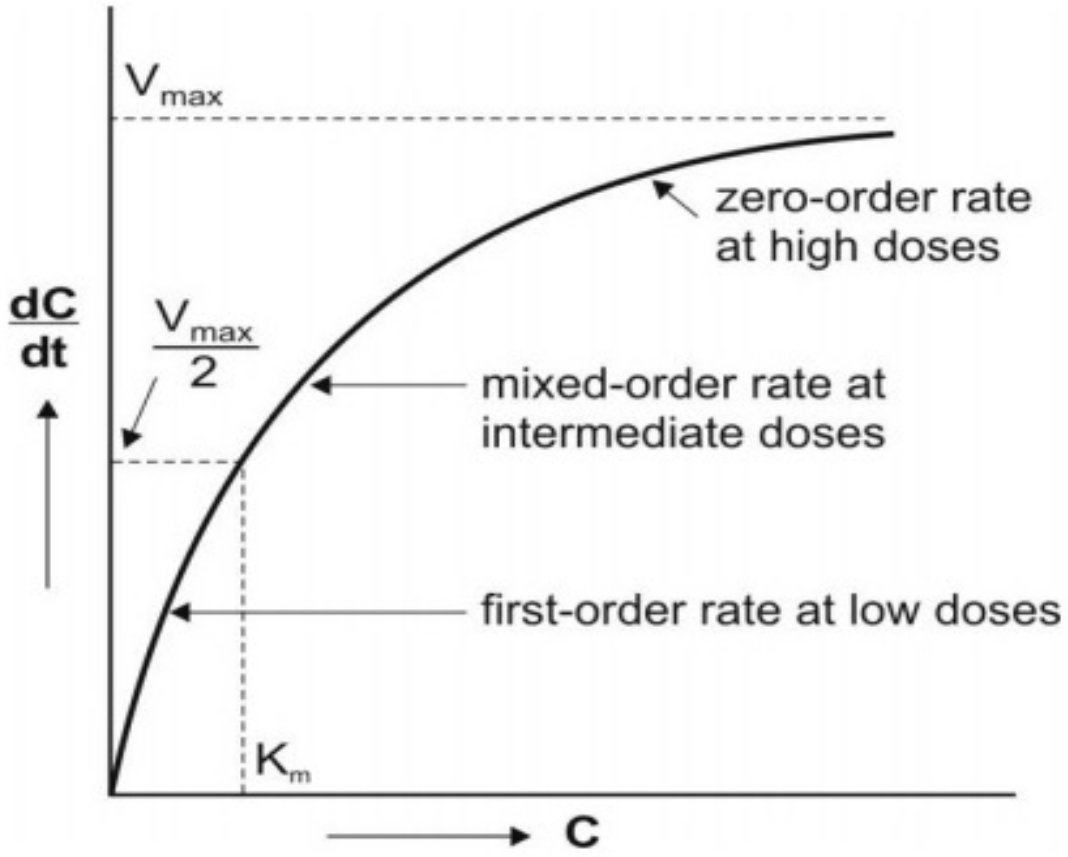
Review Questions #28 and 29 Uworld – Clearance and Elimination Rate Constant

Phenytoin - Pharmacokinetics and Pharmacodynamics

- **Pharmacokinetic Parameters**
  - Clearance
    - Vm = 7 mg/kg/day
    - Km = 4 mg/L
  - Half-life
    - Concentration dependent (Approximately 22 hours)
  - Fu (unbound plasma fraction)
    - 0.1 (Phenytoin is 90% bound to serum proteins, mainly albumin)

Phenytoin - Pharmacokinetics and Pharmacodynamics

Non-linear Pharmacokinetics



- First order kinetics occur when a constant proportion of the drug is eliminated per unit time.
- Zero order: a constant amount of drug is eliminated per unit time

First Order

- Rate of elimination is proportional to the amount of drug in the body.
- The higher the concentration, the greater the amount of drug eliminated per unit time.
- For every half-life, the drug concentration decreased by 50%.
- For example, a drug concentration of 40 mcg/ ml and a half life of 3 hours will fall to 20 mcg/ml in the first 3 hours, 10 in the second 3 hours and 5 in the 3rd 3 hours and so on.
- **Elimination mechanisms are not saturable**

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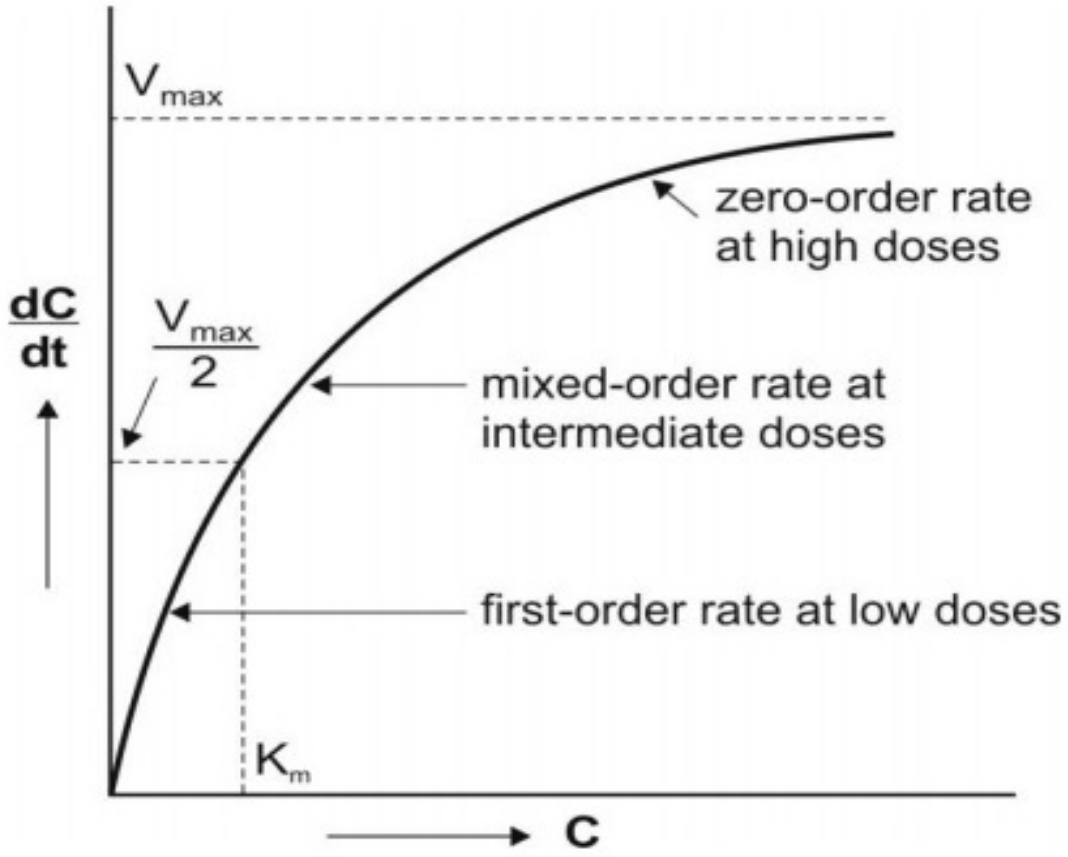
Non-linear Pharmacokinetics



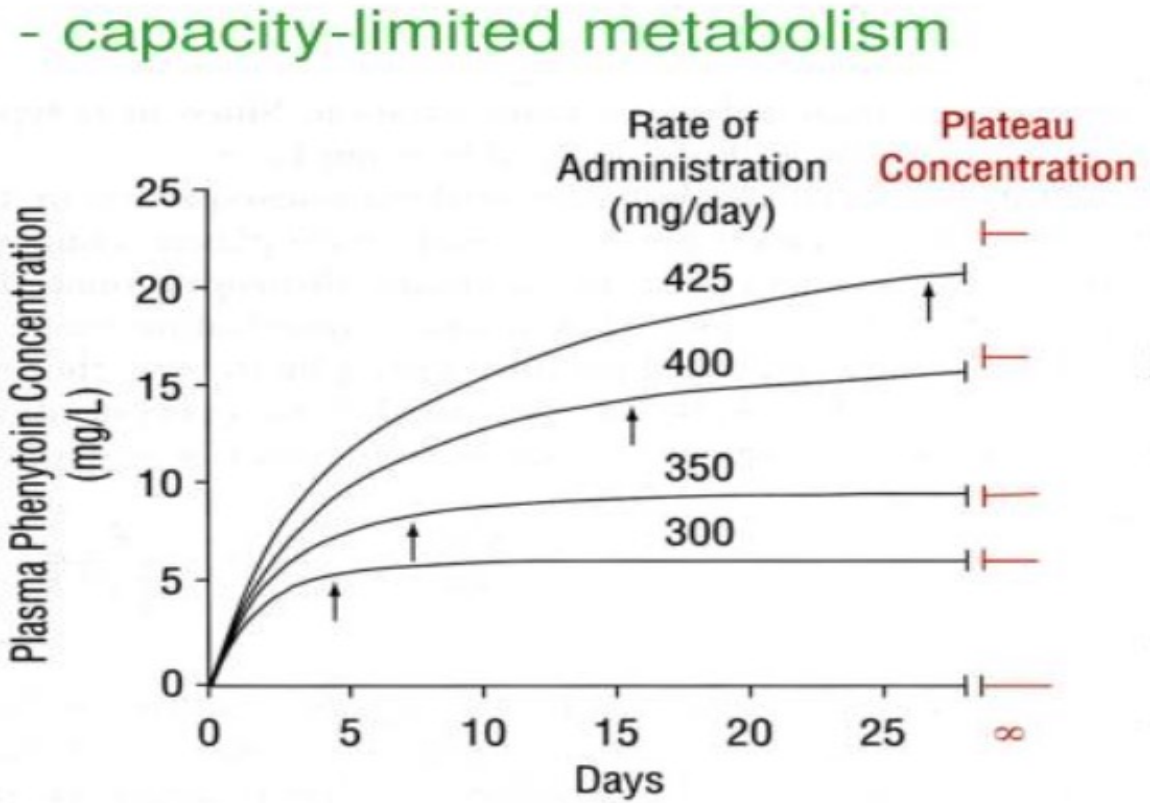
Zero Order

- A constant amount of drug is eliminated per unit time
- For example, 25 mg of a drug maybe eliminated every hour
- The rate of elimination is constant and is independent of the total drug concentration in the plasma
- Zero order kinetics are mechanisms are saturable

Phenytoin - Pharmacokinetics and Pharmacodynamics

Capacity-Limited Metabolism

- At **high drug concentrations**, the **maximal rate of metabolism** is reached and cannot be exceeded
- Under these conditions, **a constant amount of drug is eliminated per unit time (Zero order)** no matter how much drug is in the body
- **Zero order kinetics** apply here rather than the usual **first order kinetics where a constant proportion** of the drug in the body is eliminated per unit time



https://www.slideserve.com/leon/nonlinear-pharmacokinetics

Phenytoin - Pharmacokinetics and Pharmacodynamics

Capacity-Limited Metabolism

- **For first-order drugs clearance**
  - **Rate of drug administration (RA) = (Cl)(Css ave)**
- **Michaelis - Menten model** appears to fit the metabolic pattern for phenytoin elimination
  - The **velocity (V) or rate** at which an enzyme system can metabolize a substrate (S) can be described by the following equation (***rate of drug elimination***):

$$V = \frac{(Vm)(S)}{Km + S}$$

- V is the velocity of reaction
- S is the substrate concentration
- Vmax is the maximum velocity at very high substrate concentrations
- Km is the substrate concentration at half Vmax
- Km is a measure of the affinity of the substrate for the enzyme

$$(S)(F)Dose/\tau = \frac{(Vm)(Css\ ave)}{Km + Css\ ave}$$

Must Commit to Memory Equations

1. Cl = KeVd

2. Ke = $\ln(C1/C2)/\Delta t$

3. $Cpt = Cpo^{e\text{-}ket}$

4. $AUC_{0\text{-}\infty} = \frac{(F)Dose}{Cl}$

5. $$F_{abs} = 100 \cdot \frac{AUC_{tablet} \cdot Dose_{IV}}{AUC_{IV} \cdot Dose_{tablet}}$$

6. LD = Cp x Vd

7. Maintenance Dose $= \frac{(Cl)(Css\ ave)(\tau)}{(1)(F)}$

UWorld

https://lp.uworld.com/app/districtportal/district/1023/library/presentations

Questions?