Pharmacokinetics II
Drug Elimination & Multiple Dosing

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LEARNING OBJECTIVES
1. Explain the difference between first-order, zero-order and dose-dependent kinetics of drug elimination.
2. List examples of commonly prescribed drugs that follow zero-order, first-order and dose-dependent kinetics.
3. Recognize the importance of steady-state plasma drug concentrations for maintenance therapy and describe the time course for achieving steady state with intermittent dosing or continuous infusion.
4. List the primary pharmacokinetic parameters and describe how they are used to determine appropriate loading dose and maintenance dose.
5. Interpret the effects of altered distribution or clearance of drugs on plasma drug concentrations and formulate an appropriately adjusted dosing strategy.
6. Discuss the roles of the kidney and liver in the elimination of drugs from the body.

TWO-COMPARTMENT DRUG DISTRIBUTION
VOLUME OF DISTRIBUTION (Vd)

• A measure of how evenly distributed a drug is in the body.
• Vd is the theoretical volume of fluid into which the total drug administered would have to be diluted to produce the concentration in plasma.

\[
V_d = \frac{\text{Dose}}{C_0} \quad \text{mg/kg/mg/L}
\]

C₀ = Initial concentration

VOLUME OF DISTRIBUTION

Relates dose (amount) to plasma concentration of drug:

\[
L/kg = \frac{\text{Dose}}{C_0} \quad \text{mg/kg/mg/L}
\]

Duration

Minimum Effective Concentration

Onset

Therapeutic Range

Maximum Tolerated Concentration

Time Course of Plasma Drug Concentration: Area Under the Curve (AUC)
REPETITIVE DOSING: IT TAKES ~4-6 HALF-LIVES TO REACH STEADY-STATE

LOADING DOSE

- If a drug takes a long time to reach therapeutic levels, then a higher dose (the loading dose) may be given initially before dropping down to a lower maintenance dose.

- Three variables are used to calculate loading dose:
  - $C_p$ (peak desired concentration of drug)
  - $V_d$ (volume of distribution of drug in body)
  - $F$ (bioavailability)

  
  - \[ \text{Loading dose} = \frac{C_p \cdot V_d}{F} \]

A LOADING DOSE MORE RAPIDLY ACHIEVES A THERAPEUTIC DRUG LEVEL
TIME TO REACH STEADY STATE IS NOT REDUCED BY THE LOADING DOSE

LOADING DOSE = TC x Vd/F

TIME (multiples of elimination half-life)

CONCENTRATION IN Plasma

MAINTENANCE DOSE

LOADING DOSE = TC x Vd/F

EXAMPLE: DIGOXIN

DIGOXIN 0.75 mg

Target concentration in plasma

Vd = 536 L

Loading dose = TC x Vd / F

= 1.4 µg/L x 536 L

= 750 µg

MAINTENANCE DOSING

- Dosing strategy to maintain a steady state of drug in the body.
- Dose is based on replacing the amount of drug cleared from the body since the previous drug administration.
- Clearance is the primary determinant for calculating the maintenance dose.

Maintenance Dose = CL x TC x T/F
AT STEADY-STATE, MAINTENANCE DOSE REPLACES DRUG LOST SINCE PREVIOUS DOSE

LOADING DOSE (depends on $V_d$)

Target Concentration (TC)

MAINTENANCE DOSE (depends on $CL_e$)

TIME (multiples of elimination half-life)

$MD = CL_e \times TC \times T$

CLEARANCE

- **Elimination Clearance ($CL_e$):** Irreversible drug removal from the plasma through an eliminating organ(s).

- **Intercompartmental Clearance ($CL_{int}$):** Drug distribution between plasma and tissues, a bidirectional process.

TWO-COMPARTMENT MODEL

Dose

$V_P$ $CL_e$ $V_T$

$CL_e$
Maintenance Dosing Rate
(e.g., mg/day or mg/min)
selected in relation
to expected clearance.

At steady state:
Dosing Rate = Rate of elimination
= CL_x Target concentration

MAINTENANCE DOSE
EXAMPLE: DIGOXIN

DIGOXIN 0.25 MG

1.4 ng/ml

DIGOXIN 0.25 MG

DAILY ELIMINATION: one third (0.25 mg) of total body stores
(0.75 mg) if renal function is normal (first-order kinetics)

STEADY-STATE CONCENTRATION
A function of dosing rate
and elimination clearance

\[ C_{ss} = \frac{\text{Dosing Rate} \cdot F}{\text{Clearance}} \]
STEADY STATE
RATE OF DRUG ADMINISTRATION = RATE OF DRUG ELIMINATION

- **STEADY STATE**
  - attained after approximately four half-lives
  - time to steady-state independent of dosage

- **FLUCTUATIONS**
  - proportional to dosage interval/half-life
  - blunted by slow absorption

- **STEADY STATE CONCENTRATION**
  - proportional to dosage interval
  - inversely related to CL/F

- **CONCENTRATION IN PLASMA**
  - RATE OF DRUG ADMINISTRATION = RATE OF DRUG ELIMINATION
  - \( C_{ss} = \text{Dosing rate} \times \frac{F}{CL} \)

CONTINUOUS I-V INFUSION

- **STEADY STATE**
  - attained after approximately four half-lives
  - time to steady-state independent of dosage

- **STEADY STATE CONCENTRATION**
  - proportional to infusion rate
  - inversely related to CL

- **CONCENTRATION IN PLASMA**
  - Infusion rate = CL \( \times \) \( C_{ss} \)

DRUG ADMINISTRATION BY CONTINUOUS INFUSION

- Clearance can be estimated from the infusion rate and the steady-state plasma concentration achieved:
  \[ CL = \frac{I}{C_{ss}} \]
KINETICS OF DRUG ELIMINATION

- 1st-order elimination (or kinetics): the elimination rate of the drug is a constant fraction of the drug remaining in the body per unit time (rather than a constant amount of drug per unit time).

FIRST-ORDER KINETICS

ELIMINATION RATE

\[ \frac{dC}{dt} = -kC \]

MOST DRUGS USED CLINICALLY

\[ C = C_0 e^{-kt} \]

\[ t_{1/2} = \frac{0.69}{k} \]

FIRST-ORDER ELIMINATION OF LIDOCAINE

Log scale Y-axis

- Elimination phase

\[ C = C_0 e^{-kt} \]
Drugs that are eliminated primarily by metabolism may display zero-order kinetics of elimination.

- When metabolic pathways are saturated, metabolism occurs at a fixed rate, i.e. it does not change in proportion to drug concentration.
- A fixed amount of drug is metabolized per unit time (zero-order kinetics).

\[
\frac{dC}{dt} = -k
\]

PHENYTOIN, ETHANOL

\[C = C_0 - kt\]
Drugs that may exhibit zero-order kinetics of elimination:

- Aspirin
- Ethanol
- Heparin
- Phenylbutazone
- Phenytoin
- Salicylates
- Theophylline
- Tolbutamide
- Warfarin

DOSE-DEPENDENT KINETICS

- When a drug’s elimination is mediated predominantly by metabolism, its elimination will tend to follow first-order kinetics when concentrations are well below the $K_M$ of the metabolic enzymes, but will follow zero-order kinetics at doses that greatly exceed the $K_M$ of the metabolic enzymes.

DOSE-DEPENDENT KINETICS

If $C << K_M$

\[
\frac{dC}{dt} = -\frac{V_{MAX} \cdot C}{K_M + C}
\]

First-order
DOSE-DEPENDENT KINETICS

If $C \gg K_M$

ELIMINATION RATE

\[
\frac{dC}{dt} = -\frac{V_{\text{MAX}}}{K_M + C}$

Zero-order ASPIRIN

A patient with grand mal seizures is receiving phenytoin 300 mg po per day. The phenytoin plasma level is 9.5 µg/ml (therapeutic range 10-20 µg/ml). The dose of phenytoin is increased to 500 mg po per day and one week later the patient presents with lethargy and ataxia. A repeat phenytoin plasma level is now 30 µg/ml. Which of the following best explains this clinical picture?

A) Phenytoin follows first-order kinetics of elimination.
B) The bioavailability of phenytoin has decreased.
C) Saturation of metabolic pathways resulted in toxic levels.
D) The $V_{\text{MAX}}$ for phenytoin metabolism has increased.
E) The renal clearance of phenytoin has decreased.
Which of the following is true when a drug exhibits zero-order kinetics of elimination?

A) A constant fraction of the drug is eliminated per unit time.
B) A constant fraction of the volume of distribution is cleared of drug.
C) A constant amount of drug is eliminated per unit time.
D) A constant half-life of elimination is observed.
E) A constant oral bioavailability is seen regardless of the dose.

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ELIMINATION CLEARANCE

Volume of plasma cleared of drug per unit time.
Units are ml/min or L/hr (“flow”)

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CLEARANCE

- Elimination Clearance: Drug elimination may occur through the kidneys, the liver, the lung, and other organs.
- Total Clearance is equal to the sum of all these individual and simultaneously occurring organ clearances:
  \[ CL_{total} = CL_{renal} + CL_{hepatic} + CL_{other} \]

ELIMINATION HALF-LIFE

Time to eliminate 50% of the body content of the drug

\[ t_{1/2} = \frac{0.69 V_d}{CL} \]

Which of the following is considered a “primary” pharmacokinetic parameter?

A) The loading dose
B) The elimination half-life
C) The elimination clearance
D) The \( V_{max} \) and the \( K_m \)
E) The infusion rate
Which of the following is considered a “primary” pharmacokinetic parameter?

A) The loading dose  
B) The elimination half-life  
C) The elimination clearance  
D) The $V_{\text{max}}$ and the $K_m$  
E) The infusion rate

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**TIME TO REACH STEADY-STATE**

A function of the elimination $t_{1/2}$

**EXAMPLE:** $t_{0.90} = 3.3 \cdot t_{1/2}$

Lidocaine $t_{1/2} = 1.5 \text{ hr}$, so $t_{0.90} = 4.95 \text{ hr}$

Digoxin $t_{1/2} = 1.6 \text{ days}$, so $t_{0.90} = 5.28 \text{ d}$

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Propranolol has a half-life of elimination ($t_{1/2}$) of 4 hours and is prescribed to a patient at a dose of 20 mg orally every 6 hours. How long will it take to reach 90% of the steady-state plasma level with continuous therapy?

A. 6 hours  
B. 9 hours  
C. 13 hours  
D. 18 hours  
E. 26 hours
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DOSE ADJUSTMENT FOR BIOAVAILABILITY

- Dosing by different routes of administration must take into account any differences in bioavailabilities for those routes.

$$D_1 \times F_1 = D_2 \times F_2$$

D = dose  
F = bioavailability

SALT FACTOR

- In rare cases a drug may be prepared in a formulation that provides a fraction of the total weight of drug as active drug and the remainder as an inactive salt.
- The fraction of total drug that will be delivered as active drug to the systemic circulation is called the “salt factor” (S).
AMINOPHYLLINE

• 1 gram of aminophylline contains 0.8g of the active drug (theophylline) and 0.2g of salt.
• The salt factor for aminophylline is therefore 0.8.
• The dose of aminophylline (loading dose or maintenance dose) must be adjusted by the salt factor to achieve a specific target concentration of the active drug (theophylline).

\[
\text{Loading dose} = \frac{V_d \times TC}{F \times S} \\
\text{Maintenance Dose} = \frac{CL \times TC \times T}{F \times S}
\]

DOSE ADJUSTMENT IN RENAL INSUFFICIENCY

Impaired renal function often results in reduced clearance of drugs that are eliminated primarily by the kidneys. Daily drug dose must be reduced by the ratio of measured clearance in renal failure (CL\(_{RF}\)) over expected normal, average clearance (CL\(_N\)).

\[
\text{Dosing Rate}_{RF} = \text{Dosing Rate}_{normal} \times \frac{\text{CL}_{RF}}{\text{CL}_N}
\]

The dosing rate can be reduced by:

a) reducing the dose,

b) increasing the dosing interval,

c) both.
DOSE ADJUSTMENT IN RENAL INSUFFICIENCY

CREATININE CLEARANCE

- Creatinine clearance rate (CrCL) is the volume of blood plasma that is cleared of creatinine per unit time and is the most commonly used measure for approximating the glomerular filtration rate (GFR).
- CrCL is not the same as clearance of a drug—it only provides a relative measure of how well the kidneys are functioning. It can be used to adjust drug dosing in a patient with renal failure.
DOSE ADJUSTMENT IN RENAL FAILURE
Cockcroft and Gault formula to estimate creatinine clearance:

\[
\text{CrCL (ml/min)} = \frac{(140 - \text{age}) \times (\text{body wt. in kg})}{72 \times (\text{serum [Cr] in mg/dl})}
\]

(reduce estimates by 15% in females)

Dosing Rate\text{RF} = \text{Dosing Rate}_{\text{Normal}} \times \frac{\text{CrCL}_{\text{RF}}}{\text{CrCL}_{\text{Normal}}}

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DETERMINANTS OF HEPATIC DRUG CLEARANCE

1. Hepatic Blood Flow
   (Rate of drug delivery to the eliminating organ)

2. Plasma Protein Binding
   (Fraction of drug available for clearance)

3. Intrinsic Clearance
   (Hepatocellular metabolism and/or biliary excretion)

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HEPATIC DRUG CLEARANCE
Dependence on Protein Binding, Liver Blood Flow, & Intrinsic Clearance

The Rowland’s Equation:

\[
\text{CL_H} = Q \left[\frac{f \times \text{CL}_{\text{int}}}{Q + (f \times \text{CL}_{\text{int}})}\right]
\]

Q = Liver blood flow
f = Free Fraction (unbound)
CL_{int} = Intrinsic Clearance

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1. RESTRICTIVE HEPATIC CLEARANCE

Drugs with low hepatic extraction ($Q >> f \cdot CL_{int}$)

$$CL_H = f \cdot CL_{int}$$

Little "first pass metabolism" when given orally. A change in binding or drug metabolism/excretion activity will have a greater effect on hepatic clearance than changes in liver blood flow. Capacity-limited clearance.

Examples: warfarin, phenytoin

2. NON-RESTRICTIVE HEPATIC CLEARANCE

Drugs with high hepatic extraction ($Q << f \cdot CL_{int}$)

$$CL_H = Q$$

Hepatic clearance is sensitive to changes in liver blood flow and less sensitive to alterations in binding or intrinsic clearance. Flow-dependent clearance: conditions that reduce hepatic blood flow (CHF, hypotension) will reduce hepatic clearance.

Examples: lidocaine, propranolol

FACTORS AFFECTING THE PHARMACOKINETIC PROFILE

- Individual variability
- Patient compliance
- Disease states
- Pharmacogenetics
- Age and gender
- Medication interactions
PK variations - Neonates

- Immature skin, ↑skin hydration = ↑ absorption of topical products
- ↑ extracellular fluid = ↑ V_d of H_2O soluble drugs
- Metabolic pathways mature at different times
- Immature GFR, tubular secretion & reabsorption

PK variations - Elderly

- Skin thinning = ↑ absorption of topical products
- ↑ adipose tissue = ↑ V_d of fat soluble drugs
- ↓ extracellular fluid = ↓ V_d of H_2O soluble drugs
- Age related changes in renal function = ↓ GFR

Drug Interactions

- 3-5% of preventable inpatient adverse events
- Leading cause of ER visits and hospital admissions
- Can occur before, during, or after administration
Drug interactions

- Drug incompatibility
  - Physico-chemical
  - Therapeutic
- Pharmacokinetic interactions
  - Absorption
  - Distribution
  - Metabolism
  - Elimination
- Pharmacodynamic interactions

SMALL GROUP EXERCISES

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Read the small group exercises before each session!