Optimizing Dosing Regimens
Therapeutic Concentration Strategy

Target concentration strategy: Application of pharmacokinetics and pharmacodynamics for individualizing dose.

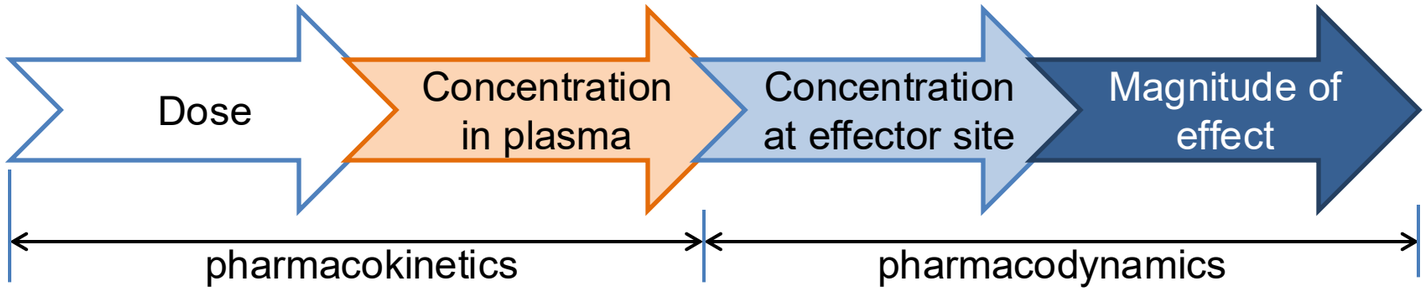
NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

Basis: The assumption that the target concentration will produce the therapeutic effect.

Therapeutic Goal: To maintain steady state drug levels within the therapeutic range to provide therapeutic efficacy and minimum toxicity

Target concentration strategy: Desired steady state concentration (C_{ss}) is selected and a dose is calculated that is predicted to achieve this value.

Dosage adjustments: The standard dose based on heathy individuals is not suitable for all patients. Physiologic and pathologic processes may be applied for dose adjustment in the individual patient. Drug concentrations may guide dose changes. Information is in the drug monographs.



Therapeutic Window:

The range associated with therapeutic efficacy and a minimum of toxicity for a given agent

Peak concentration:

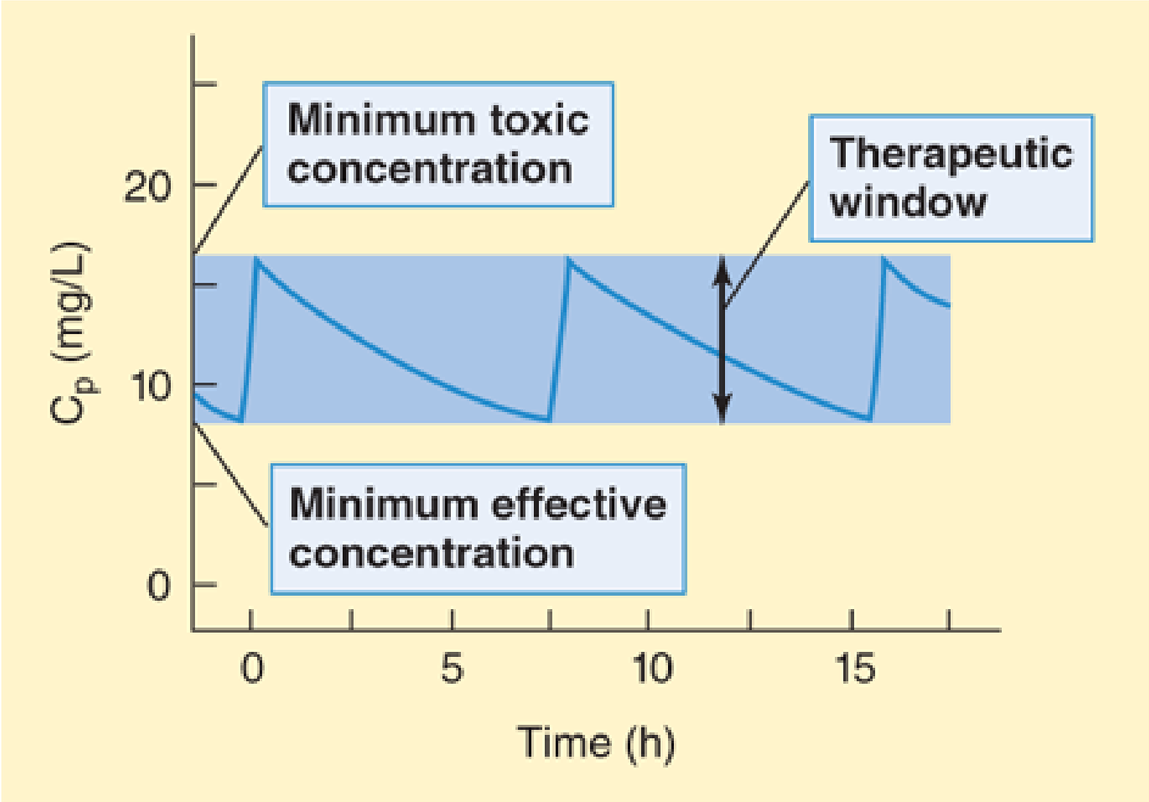
The maximum concentration (C_{max}) achieved during repeated dosing cycles.

Trough concentration:

The minimum drug concentrations achieved during repeated dosing cycles.

Minimum effective concentration:

the minimum concentration required to produce a therapeutic effect



B. G. Katzung, M. Kruidering-Hall, R. L. Tuan, T. W. Vanderah, A. J. Trevor
Katzung & Trevor's Pharmacology: Examination & Board Review, 13e

The therapeutic window for theophylline in a typical patient. The minimum effective concentration in this patient was found to be 8 mg/L; the minimum toxic concentration was found to be 16 mg/L. The therapeutic window is indicated by the blue area. To maintain the plasma concentration (C_p) within the window, this drug must be given at least once every half-life (7.5 h in this patient) because the minimum effective concentration is half the minimum toxic concentration and C_p will decay by 50% in 1 half-life. (Note: This concept applies to drugs given in the ordinary, prompt-release form. Slow-release formulations can often be given at longer intervals.)

Citation: Chapter 3 Pharmacokinetics, Katzung BG, Kruidering-Hall M, Tuan R, Vanderah TW, Trevor AJ. *Katzung & Trevor's Pharmacology: Examination & Board Review, 13e;* 2021, Figure 3-6. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=3058&sectionid=255304212 Accessed: August 18, 2021

Target Calculation Approach to Rational Dosing

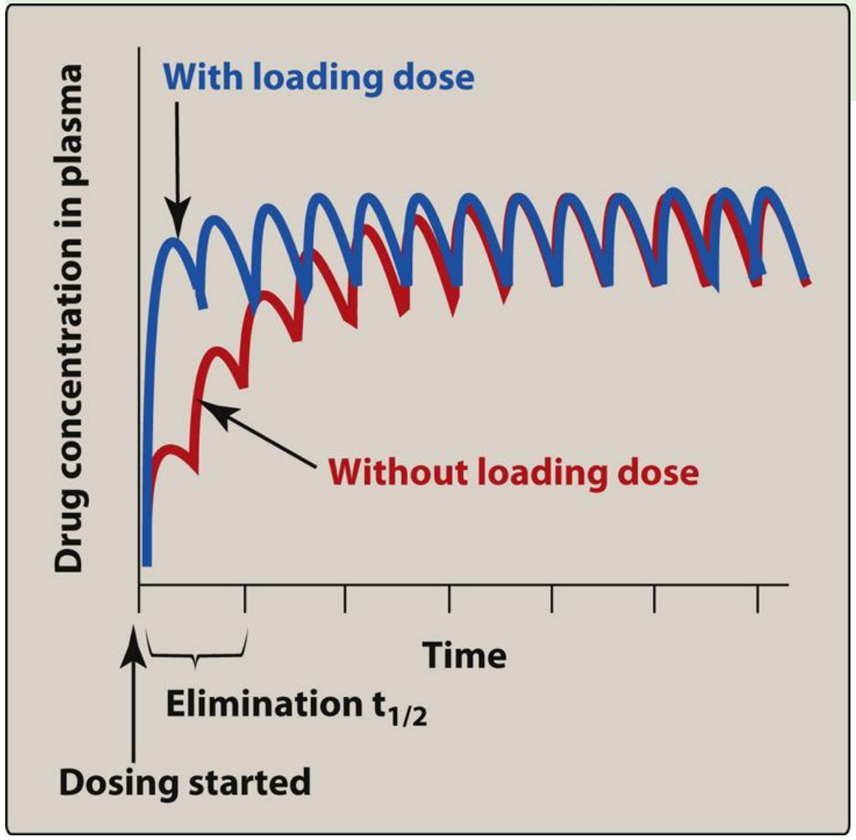
$$\text{Loading Dose} = \frac{V_d \times C_{ss\ \text{desired}}}{F}$$

relates amount of drug in the body to drug concentration in plasma

$$\text{Maintenance dosing rate} = \frac{C_{ss\ \text{desired}}}{F} \times CL$$

relates the dosing rate to the rate of elimination at steady state

From: **1 Pharmacokinetics**
Lippincott® Illustrated Reviews: Pharmacology, 8e, 2023



Legend:

Accumulation of drug administered orally without a loading dose and with a single oral loading dose administered at t = 0.

A loading dose promptly raises the concentration of drug in plasma to the target plasma concentration ($C_{desired}$ or C_{ss})

- V_d is the proportionality factor that relates total amount of drug in the body to the concentration in plasma.
- V_d at steady state V_{ss} is clinically relevant and used to determine the loading dose.

$$V_d = \text{dose} / C_{ss} \rightarrow$$

$$\text{Loading dose} = \frac{V_d \times C_{ss}}{F}$$

Loading doses are larger than maintenance doses.

Loading dose may be desirable when steady state concentration should rapidly be reached (emergent situations) or for drugs with long $t_{½}$, when considerable time is required to reach steady state.

Loading dose example:
Theophylline intravenously for relief of acute asthma attack

- Theophylline V_d is 35 L for a 70 kg person
- $C_{p\ desired}$ is 10 mg/L (adult)
- F = 1 for intravenously administered drugs

$$LD = (V_d \times C_p) / F$$

$$LD = (35\ L \times 10\ mg/L) / 1 = 350\ mg\ I.V.\ for\ a\ 70\ kg\ person.$$

PK parameters are listed on Katzung & Vanderah's Basic & Clinical Pharmacology Table 3–1

Risk of toxicity when using loading dose

Sensitive individuals may be exposed abruptly to a toxic concentration of a drug.

Excessive concentration may take a long time to fall if drug involved has a long t½.

Toxic effects may result from actions at undesirable sites.

- loading doses tend to be large, based on calculation using V_{ss}
- rapid administration – LD is often administered by rapid intravenous injection.

Example: Maintenance dose calculation

Maintenance dose is administered after the loading dose is given to maintain plasma level within the therapeutic window.

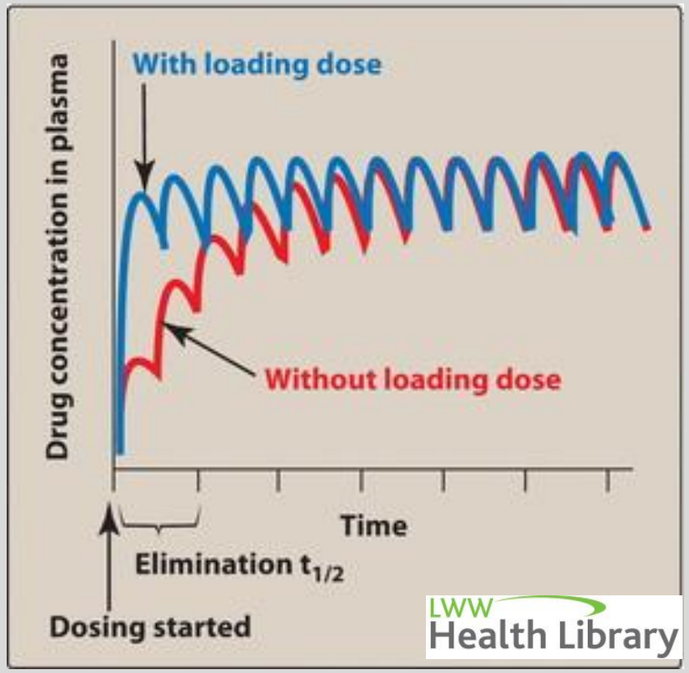
For theophylline, the maintenance dose by continuous IV infusion:

PK parameters:

- $C_{p\ desired}$ = 10 mg/L
- *CL* = 2.8 L/h/70 kg
- *F* = 1 (I.V.)
- **Dosing rate = (*CL* x $C_{p\ desired}$) / 1**

  = (2.8 L/h x 10 mg /L) / 1

  = 28 mg/h for 70 kg person



PK parameters are listed on Katzung's Basic & Clinical Pharmacology Table 3–1

Switch to oral maintenance dose when asthma attack is relieved and the patient is stable.

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

$$MD = \frac{CL \times Css_{desired} \times \tau}{F}$$

- Theophylline $F_{oral} = 0.96$
- τ (tau) dosing frequency = every 12 hours

MD = (2.8 L/h x 10 mg /L) / 0.96 x 12

= (28 mg/h / 0.96) x12h = 26.88 mg/h x12 = 322.56 mg per dose

Commercially available:

= 350 mg extended release tabs every 12 hours for a 70 kg patients

➢ Practice point:
F=0.96 is nearly 100% bioavailability.
In practice, *F*=1 would be used.
When *F*=1, it is omitted from the calculations.

Optimizing theophylline therapy:

Theophylline has a narrow therapeutic window and considerable interpatient variability → Monitor theophylline serum levels.

Pharmacokinetic and Pharmacodynamic Variables influencing plasma concentration and response

Disease states may modify a patient's response to drug therapy.

Factors that potentially affect Drug Absorption, *CL* and V_d

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

Absorption from GI tract	• Solubility in enteral fluid • Acid-base characteristics • Lipid solubility • Food (presence/absence)	• Coadministration with other drugs that complex with it in gut (such as antacids, cholestyramine) • Blood flow to gut • GI transit time	
Clearance, impaired organ function	Hepatic: Unpredictable (related to intrinsic hepatic clearance)	Renal: ↓*CL* for drugs excreted in urine	Heart failure or shock: Decreased perfusion of liver, kidneys → ↓*CL*
Volume of distribution	Edema, ascites, pleural effusion: ↑total body water →↑V_d for hydrophilic drugs that distribute in body water	• ↑Plasma protein binding → ↓V_d as more drug molecules remain in plasma • ↑Tissue binding →↑V_d	• ↓Skeletal muscle mass → ↓V_d • Obesity → ↑V_d for lipophilic drugs

Factors influencing pharmacokinetic parameters

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

Effects on volume of distribution	**Effect on t½**
Aging: ↓ muscle mass → ↓ distribution	↓ t½
Obesity: ↑ adipose mass → ↑ distribution	↑ t½
Pathologic fluid: ↑ distribution	↑ t½
Effects on clearance	
Cytochrome P450 induction: ↑ metabolic rate → ↑ elimination rate, ↑ CL	↓ t½ and reduction of therapeutic effect
Cytochrome P450 inhibition: ↓ metabolic rate → ↓ rate of elimination, ↓ CL	↑ t½, drug accumulation and increased risk of toxicity
Cardiac failure: ↓ clearance	↑ t½
Hepatic failure: ↓ clearance	↑ t½
Renal failure: ↓ clearance	↑ t½

Pharmacodynamic variables influencing response

- Maximum effect attainable in the target tissue (E_{max})
- Sensitivity of the tissue to the drug

Individualizing Drug Therapy

Fundamental principles to guide prescribing

The **benefits** of drug therapy should always outweigh the risk.	Select a **therapeutic objective** (goal of therapy).
Simplify the dosing per day and minimize the number of drugs as appropriate.	**Choose a drug therapy** on the patient characteristics and clinical presentation.
Genetics play a role in interpatient variability to drug response.	**Determine** the appropriate dose and dosing schedule.
Prescribers should use only a limited number of drugs with which they are **thoroughly familiar**.	**Electronic medical records** and pharmacy systems increasingly incorporate prescribing information, such as unindicated medications being prescribed, potential dosing errors, drug interactions, and genetically determined drug responses
Provide **patient education** on the disease and treatment. Repeat, extend, and reinforce the information to the patient as often as necessary.	

Therapeutic monitoring of drug plasma concentration in the individual patient: *maximizing effect while minimizing toxicity*

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

Measuring the concentration of drug in plasma has utility when there is a/an:

Relationship between the concentration of drug in plasma and the clinical effect	Significant inter- / intra-patient pharmacokinetic variability
Established target concentration	Narrow therapeutic window

Availability of a reliable, cost-effective drug assay for clinical use

Measuring drug concentrations in plasma or serum establishes the **individual** patient's pharmacokinetics.

One well-done drug concentration is more valuable than any algorithm that seeks to predict concentration or effect using patient characteristics, comorbidities, or other factors.	Poorly-done therapeutic monitoring may produce results that are misleading, and in this way are worse than having no testing at all.
The duration of an infusion and the correct timing of the sample after the infusion are critical to having results that can be assessed in light of published data and guidelines.	
The major use of measured concentrations of drugs (at steady state) is to **refine the estimate of *CL/F*** (oral clearance) for the patient being treated. *CL/F* (patient) = dosing rate / C_{ss} (measured)	

Summary of Clinical Pharmacokinetics, Part 2

Rational dosing and the time course of drug effects

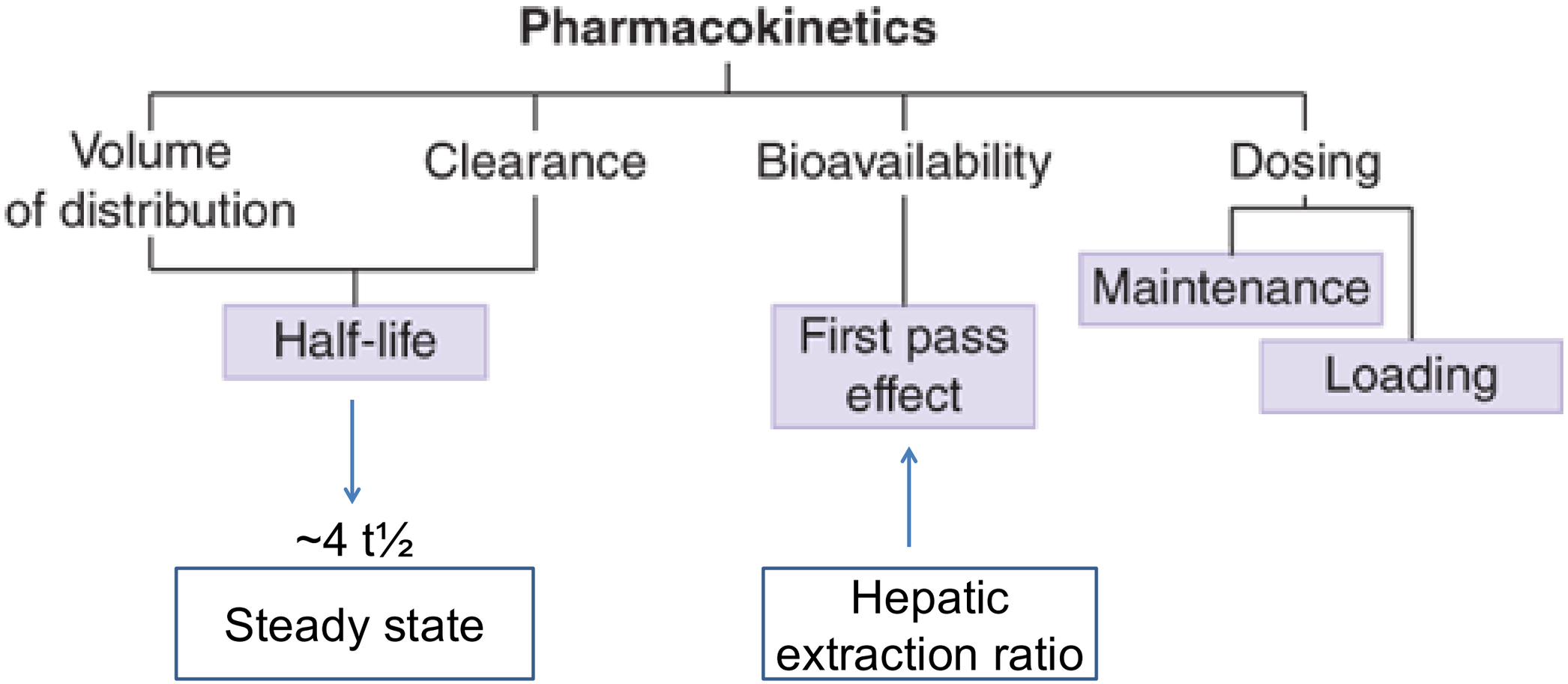


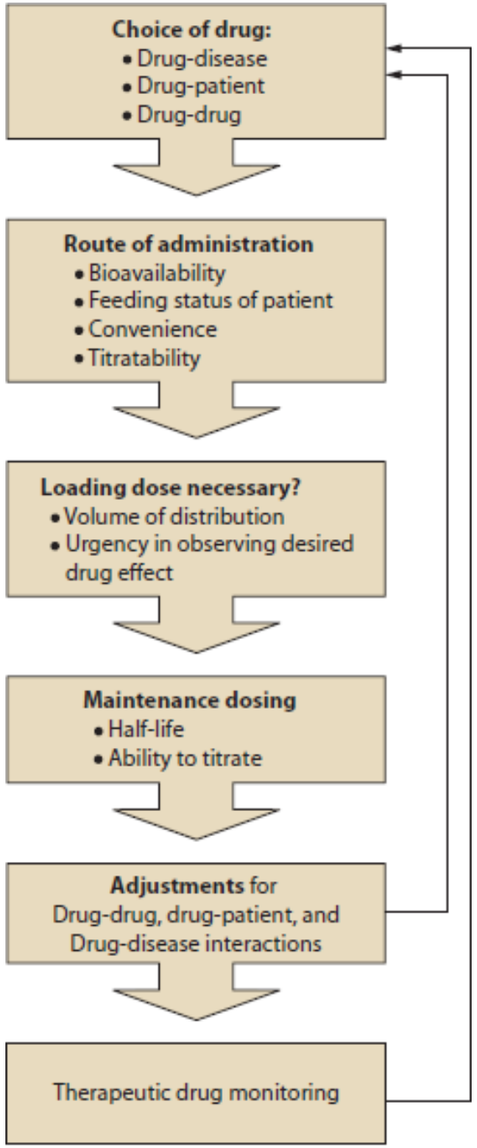
Figure from Katzung & Trevor's Pharmacology Examination & Board Review: Chapter 3

- The elimination half-life is a measure of the time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%. Half-life is a function of volume of distribution and clearance. Half-life elimination curves track the amount of drug in the body over time.
- In first-order elimination kinetics, the drug elimination rate is directly proportional to plasma free drug concentration. Most clinically relevant drugs follow first-order kinetics.
- In zero-order elimination kinetics, the metabolic enzymes eventually will become saturated as the concentration of substrate increases. The rate of drug elimination is constant (a constant amount) and independent of plasma drug concentration. A few drugs follow zero-order kinetics at therapeutic concentrations.

- When a drug that exhibits first-order pharmacokinetics is administered to a patient continuously or intermittently, the drug will accumulate until it reaches a plateau – a dynamic equilibrium = steady-state plasma drug concentration.
- The time to reach the steady state is a function of the elimination half-life of the drug. Four half-lives is 94% of steady state concentration and provides full therapeutic effect. If the half-life or the dosing rate changes, it will again take 4 half-lives to approach the new steady state plasma concentration.
- The therapeutic goal of the target concentration strategy is to maintain steady state drug levels within the therapeutic range to provide therapeutic efficacy and minimum toxicity. This approach links pharmacokinetics and pharmacodynamics.

- A loading dose rapidly raises the plasma drug concentration to the target concentration. The volume of distribution relates the total amount of drug in the body to plasma drug concentration: LD = (V_d x $C_{desired}$)/F
- The maintenance dose is administered after the loading dose to maintain the desired steady state concentration: MD = (CL x $C_{desired}$)/F.
- Disease states may modify pharmacokinetic parameters and pharmacodynamic actions and response to drug therapy.
- Optimization is based on in-depth understanding of factors that determine an individual's response to drug treatment.
- *Fundamental principles should guide prescribing of drugs.*

Flowchart for a suggested method of design for a rational drug dosing regimen.



- Individualization of drug therapy involves careful consideration of the patient's unique clinical status for each step along the path of drug prescription and dosing.
- The initial choice of drug, route of administration, loading dose, and maintenance dose calculations involve consideration of desired drug effects, titratability, and convenience.
- Modifications of the dosing regimen may be required to accommodate the individual characteristics of the patient, including allergies, age, sex, and race; potential drug-drug interactions; and potentially confounding disease states.
- Once a drug regimen is designed and implemented, therapeutic drug monitoring is indicated to ensure adequate drug effect and to minimize potential adverse events.
- The results of therapeutic drug monitoring may indicate the need for further modification of the drug regimen.

Legend: Flowchart for a suggested method of design for a rational drug dosing regimen. This illustration serves to depict the process of drug prescription and dosing as a perpetual cycle of actions. Individualization of drug therapy involves careful consideration of the patient's unique clinical status for each step along the path of drug prescription and dosing. The initial choice of drug, route of administration, loading dose, and maintenance dose calculations involve consideration of desired drug effects, titratability, and convenience. Modifications of the dosing regimen may be required to accommodate the individual characteristics of the patient, including allergies, age, sex, and race; potential drug-drug interactions; and potentially confounding disease states. Once a drug regimen is designed and implemented, therapeutic drug monitoring is indicated to ensure adequate drug effect and to minimize potential adverse events. The results of therapeutic drug monitoring may indicate the need for further modification of the drug regimen.

Citation: CHAPTER 125 Critical Care Pharmacology, Hall JB, Schmidt GA, Kress JP. *Principles of Critical Care, 4e;* 2015, Figure 125-5. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=1340&sectionid=80028183 Accessed: August 25, 2021

References

- Access Medicine Goodman & Gilman's The Pharmacological Basis of Therapeutics 14e; 2023; Chapter 2: Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, Metabolism, and Elimination
- Access Medicine Harrison's Principles of Internal Medicine, 21e, 2022; Chapter 67: Principles of Clinical Pharmacology
- Access Medicine Katzung's Basic & Clinical Pharmacology 16e, 2024: Chapter 3: Pharmacokinetics & Pharmacodynamics: Rational Dosing & the Time Course of Drug Action, and Chapter 66: Rational Prescribing & Prescription Writing
- Access Medicine Principles and Practice of Hospital Medicine, 2e, 2017; Chapter 9: Principles of Evidence-Based Prescribing

NEW YORK INSTITUTE OF TECHNOLOGY

College of Osteopathic Medicine

Lecture Feedback Form:

https://comresearchdata.nyit.edu/redcap/surveys/?s=HRCY448FWYXREL4R