Clinical Pharmacokinetics Part 1

Rational Dosing and the Time Course of Drug Action

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I am available to groups and individuals for pharmacology help and discussions by appointment.

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Links

Scholar Rx Bricks: (Required)

General Principles

Pharmacokinetics and Pharmacodynamics > Pharmacokinetics: Drug Concentration and Dosing
https://exchange.scholarrx.com/brick/drug-concentration-and-dosing

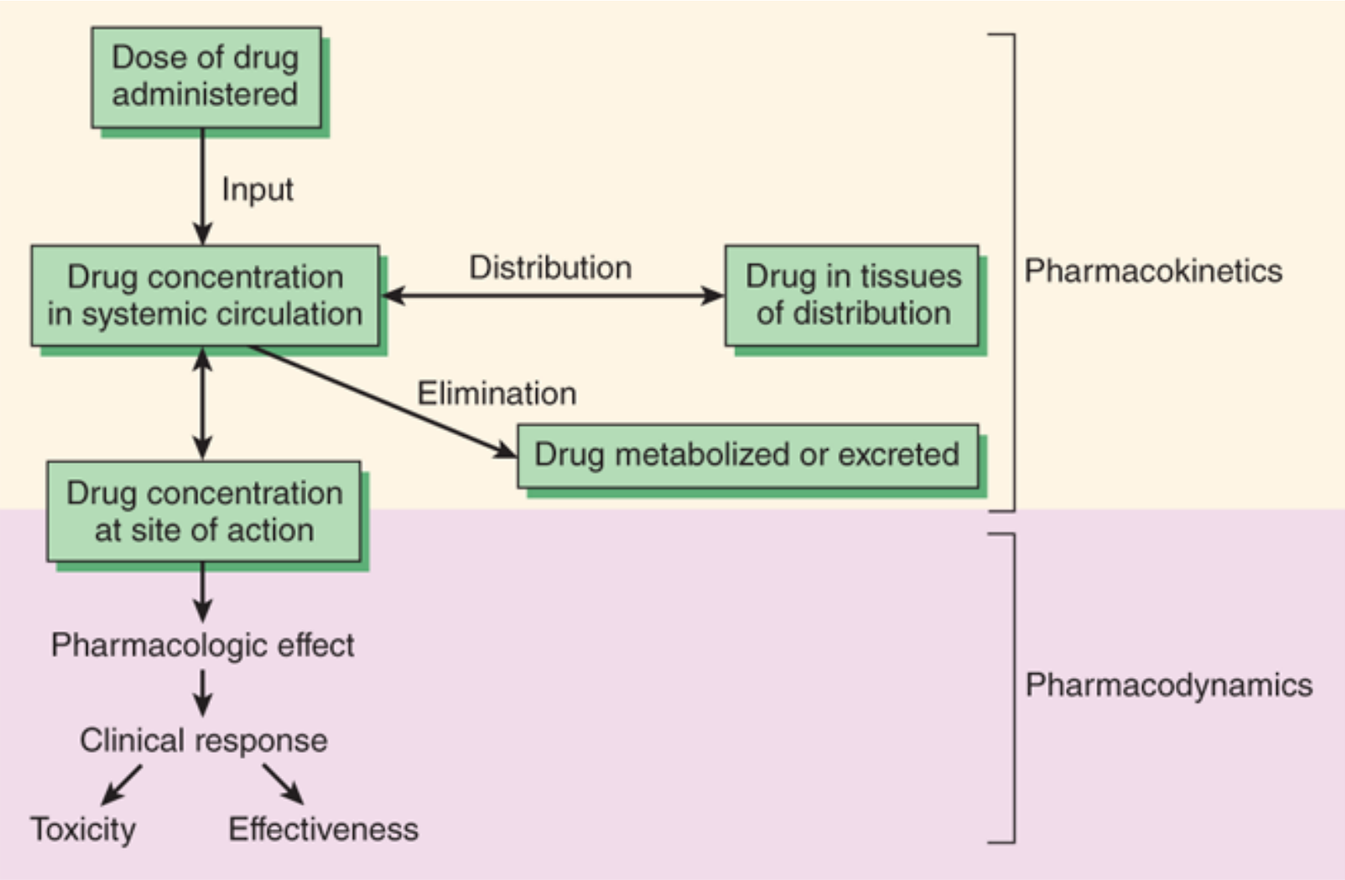
Enzymes as Drug Targets https://exchange.scholarrx.com/brick/enzymes-as-drug-targets

Katzung & Vanderah's Basic & Clinical Pharmacology, 16e, 2024; Chapter 3: Pharmacokinetics
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3382&sectionid=281747069

THE REVIEW BOOKS HAVE PRACTICE QUESTIONS

Katzung & Trevor's Pharmacology: Examination and Board Review, 14e, 2024
Chapter 3: Pharmacokinetics
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3461&sectionid=285589076

LWW Health Library Premium Basic Sciences; Lippincott Illustrated Reviews: Pharmacology, 8e, 2023: Chapter 1: Pharmacokinetics
https://premiumbasicsciences-lwwhealthlibrary-com.nyit.idm.oclc.org/content.aspx?sectionid=253324942&bookid=3222



A rational approach to achieving ***a desired beneficial effect with minimal adverse effects*** combines the principles of pharmacokinetics and pharmacodynamics to clarify the dose-effect relationship.

The relationship between dose and effect can be separated into pharmacokinetic (dose-concentration) and pharmacodynamic (concentration-effect) components. Concentration provides the link between pharmacokinetics and pharmacodynamics and is the focus of the target concentration approach to rational dosing. The three primary processes of pharmacokinetics are input, distribution, and elimination.

What you need to know and understand
Terms to know

Equivalence between drug products:

Pharmaceutical equivalence	Drug products that contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration
Bioequivalence	Two pharmaceutically equivalent drug products are considered to be ***bioequivalent*** when the **rates and extents of bioavailability** of the active ingredient in the two products are not significantly different under suitable test conditions.
Therapeutic equivalence	Bioequivalent drug products having similar safety and efficacy profiles.
Biosimilar	Biological (protein) product highly similar to an FDA-approved biological product and having no clinically meaningful differences in safety and effectiveness from the reference product.

Therapeutic drug monitoring for optimizing the dose of a drug ***in an individual patient*** $\Rightarrow$ ***maximizing effect while minimizing toxicity***

- Only clinically meaningful when the efficacy of a drug treatment can be enhanced by achieving a certain concentration or effect range and/or the toxicity of drug therapy can be reduced by maintaining a certain concentration or effect range:

- Measuring the concentration of drug in plasma has utility when there is a(n):

1. Relationship between the concentration of drug in plasma and the clinical effect
2. Significant inter- and/or intra-patient pharmacokinetic variability
3. Established target concentration
4. Narrow therapeutic window
5. Availability of a reliable, cost-effective drug assay for clinical use

Optimization of drug therapy is based on in-depth understanding of factors that determine an individual's response to drug treatment.

Fundamental principles should guide prescribing of drugs:

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Benefits v. Risk	The benefits of drug therapy, however defined, should always outweigh the risk.
Dose	The smallest dosage necessary to produce the desired effect should be used.
Treatment regimen	The number of medications and doses per day should be minimized.
Changes in drug regimen	Prescribers should be particularly wary when adding or stopping specific drugs that are especially liable to provoke interactions and adverse reactions.
Individual variabilities	Genetics play a role in determining variability in drug response and may become a part of clinical practice
Knowledge	Keeping abreast of the literature and unbiased opinion will provide a foundation for decision-making.
Familiarity	Prescribers should use only a limited number of drugs, with which they are thoroughly familiar.

Variation in drug distribution rate

Change in blood flow to various tissues

↓

Change in rates of

drug distribution to tissues

Thus, the effect of a drug at various sites of action can vary ***depending on perfusion of these sites***.

Extraction Ratio (*E*):

a clearance model of an organ's ***intrinsic capacity***

for eliminating a drug in a single pass through the organ at steady state

Extraction ratio compares plasma levels of free drug at steady state immediately before entering and just after exiting the organ:

$$E = \frac{(C_{in} - C_{out})}{C_{in}}$$

$$CL = Q \times \frac{(C_{in} - C_{out})}{C_{in}} \rightarrow CL = Q \times E$$

$$E = CL / Q$$

Drug clearance is determined by:

1. Blood flow (*Q*) through the eliminating organ
2. Free (unbound) fraction of drug in plasma
3. Intrinsic clearance – the intrinsic ability of clearance mechanisms of the organ (ie, hepatic enzymes to metabolize the particular drug or renal excretory processes)

Effect of reduced hepatic blood flow on systemic drug levels

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Blood flow-dependent extraction

For drugs with high E_H (>0.7)

- **Shunting of blood past the liver will result in substantial increases in drug availability in systemic circulation.**

Hepatic clearance approximates blood flow.

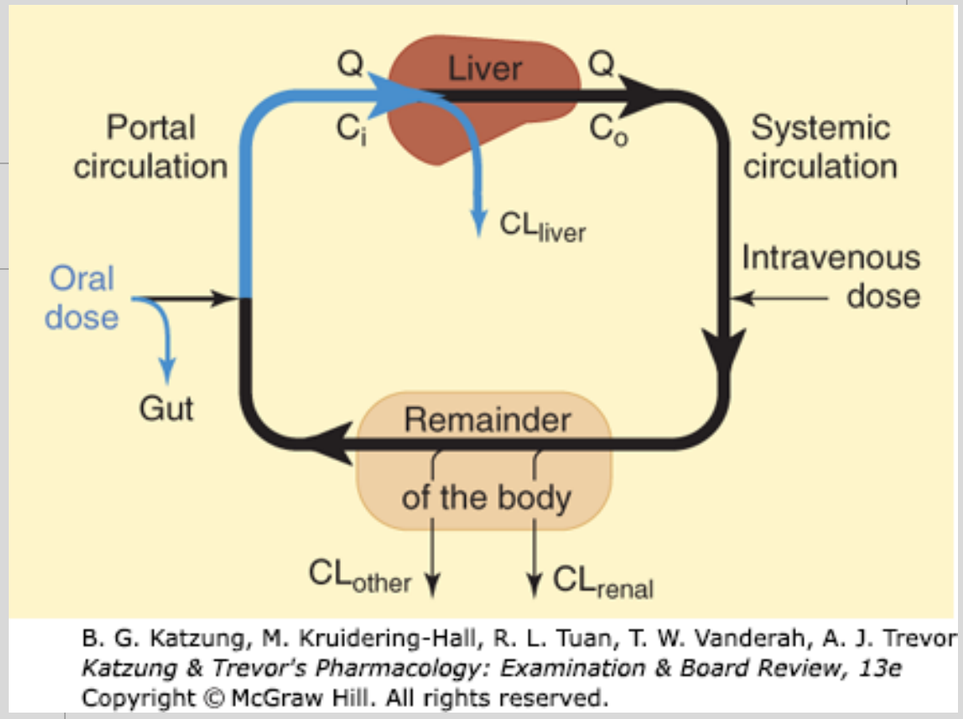
Capacity-limited extraction

For drugs with low E_H (<0.3)

- **Shunting of blood past the liver will cause little change in bioavailability.**

Clearance will be proportional to:

the unbound fraction and the drug's intrinsic clearance.



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Saturable elimination: Clinical correlates

If dosing rate exceeds elimination capacity, steady state cannot be achieved …the concentration will keep rising as long as dosing continues.

Changing the dosing rate for a drug with nonlinear kinetics is difficult and unpredictable.

Three drugs exhibit zero-order kinetics at therapeutic *concentrations*:

Ethanol, **aspirin** (anti-inflammatory doses), and **phenytoin**.

Most drug elimination pathways will become saturated if the dose is high enough→…→ toxicity.

Therapeutic Window:

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

Peak concentration:

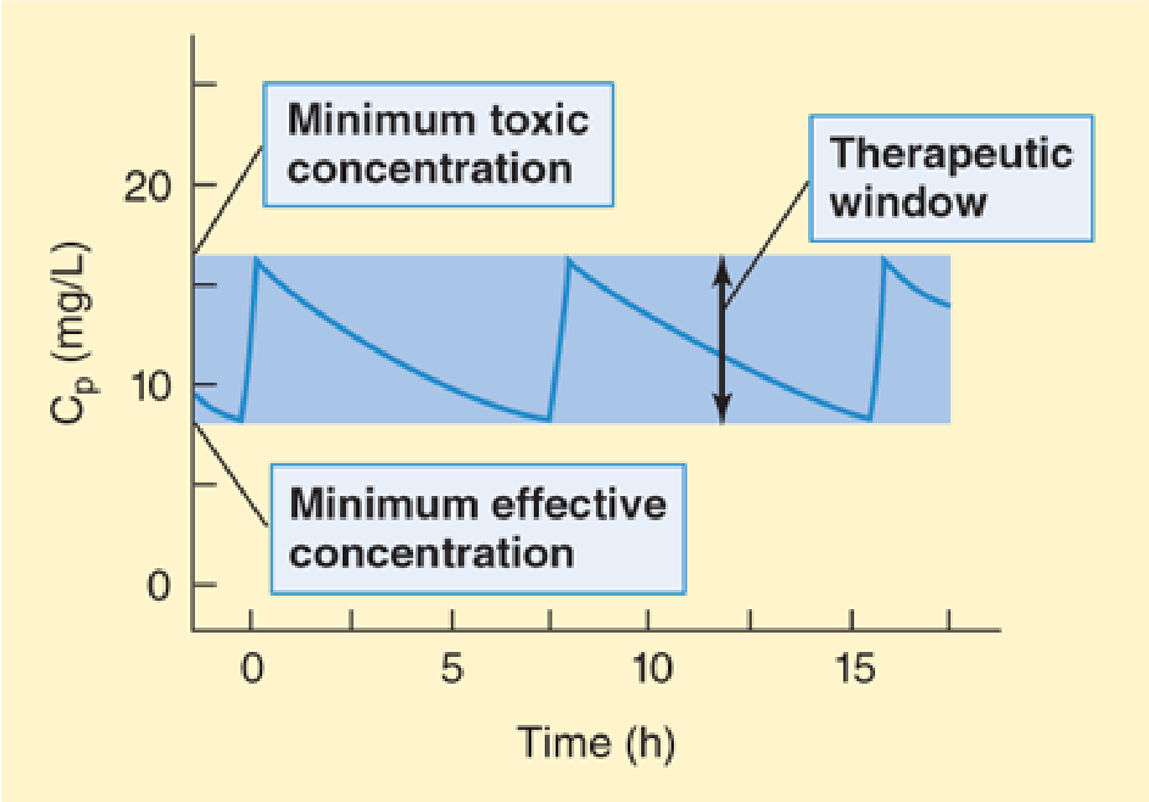
The maximum concentration (C_{max}) achieved during repeated dosing cycles.

Trough concentration:

The minimum drug concentrations achieved during repeated dosing cycles.

Minimum effective concentration:

the minimum concentration required to produce a therapeutic effect



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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

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.	