

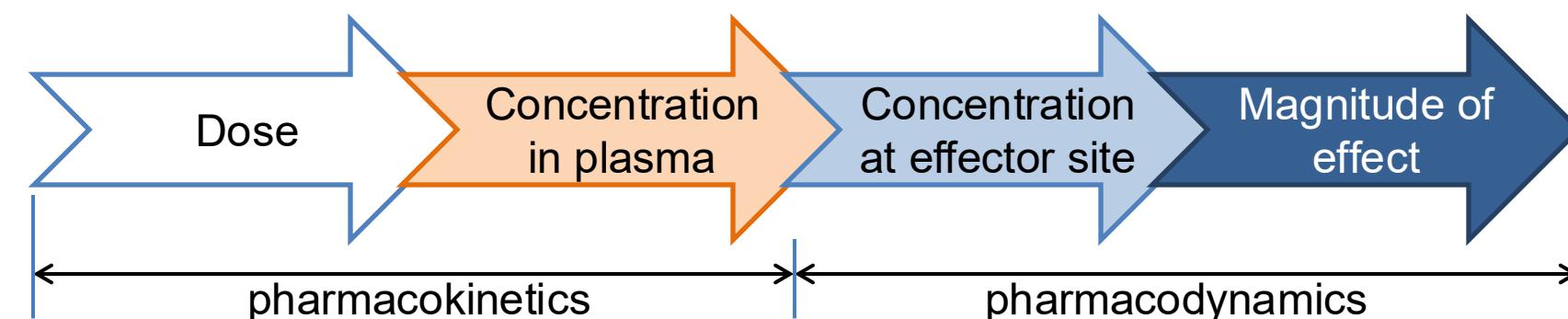
Target concentration strategy: Application of pharmacokinetics and pharmacodynamics for individualizing dose.

**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 healthy 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.

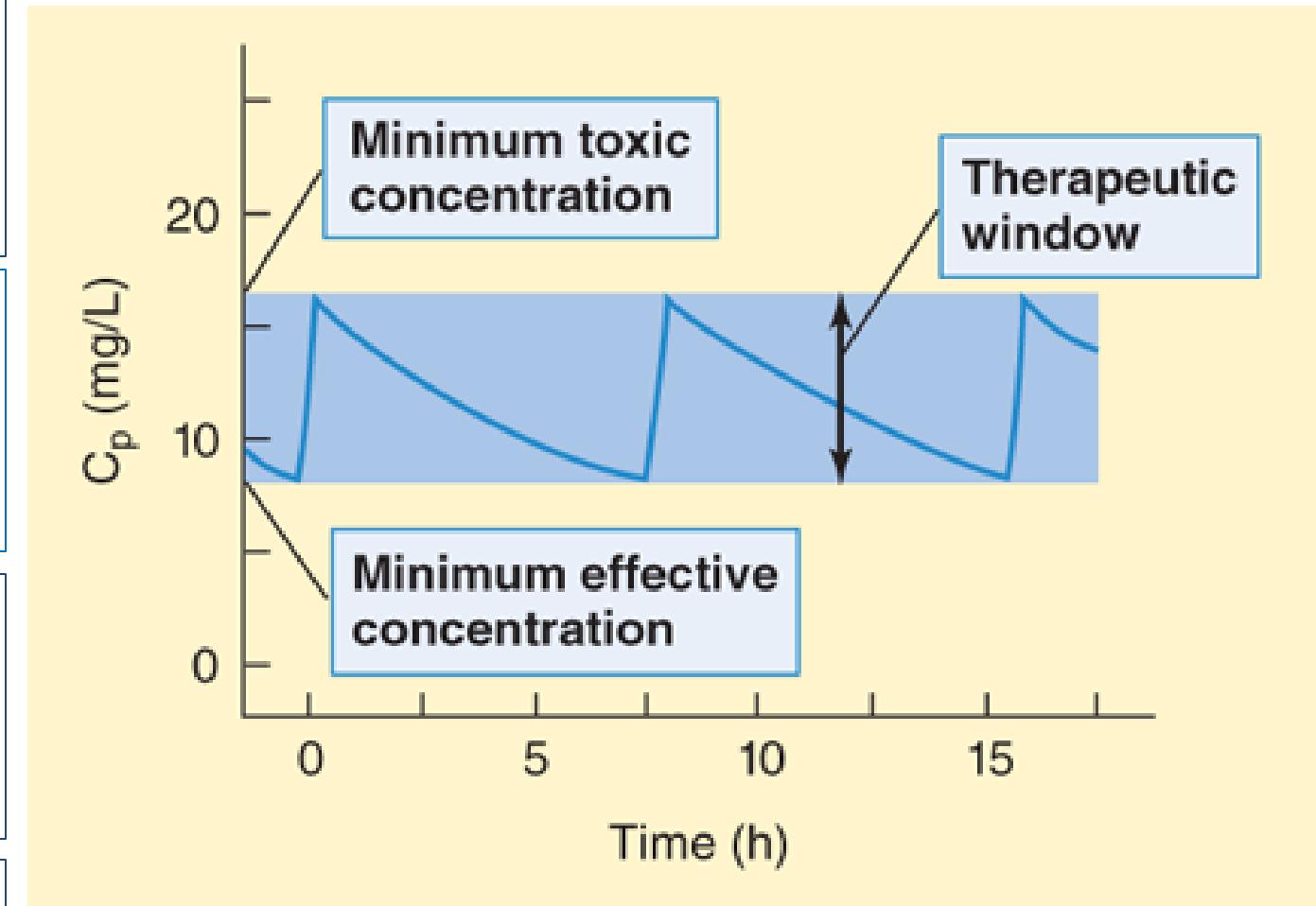
## **Trough concentration:**

The minimum drug concentrations achieved during repeated dosing cycles.

## **Minimum effective concentration:**

the minimum concentration required to produce a therapeutic effect

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.)



B. G. Katzung, M. Kruidering-Hall, R. L. Tuan, T. W. Vanderah, A. J. Trevor  
*Katzung & Trevor's Pharmacology: Examination & Board Review*, 13e  
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## Target Calculation Approach to Rational Dosing

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

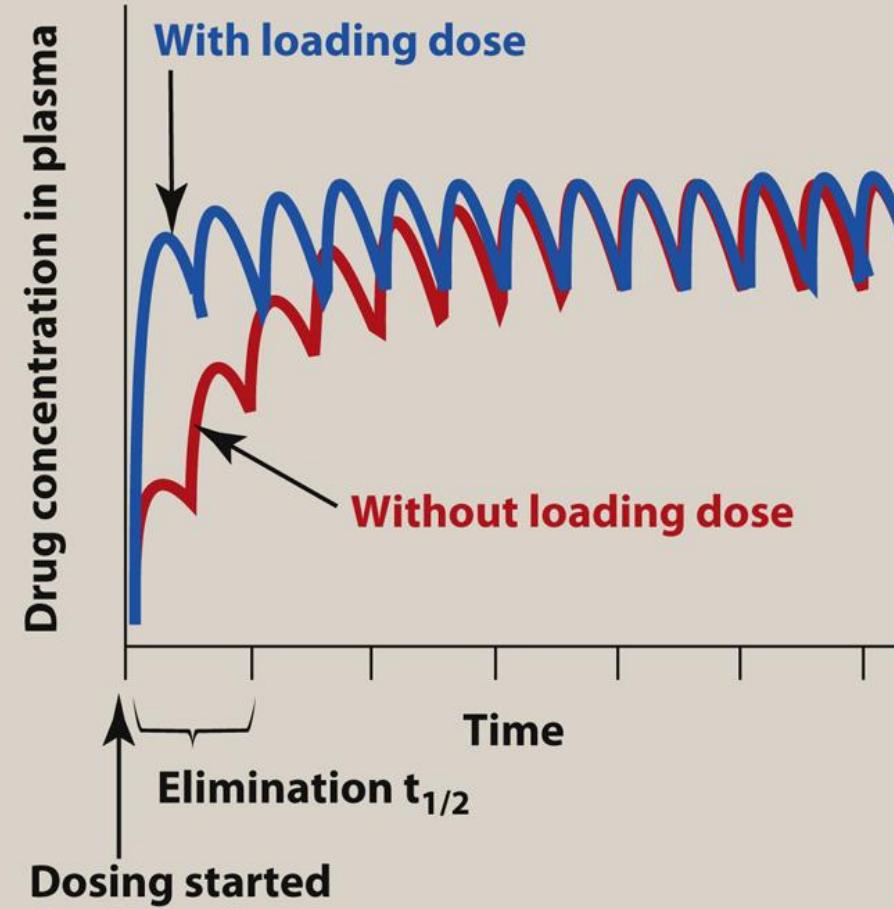
relates amount of drug in the body to drug concentration in plasma

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

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

From: 1 Pharmacokinetics

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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  $t_{1/2}$ , 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

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

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

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

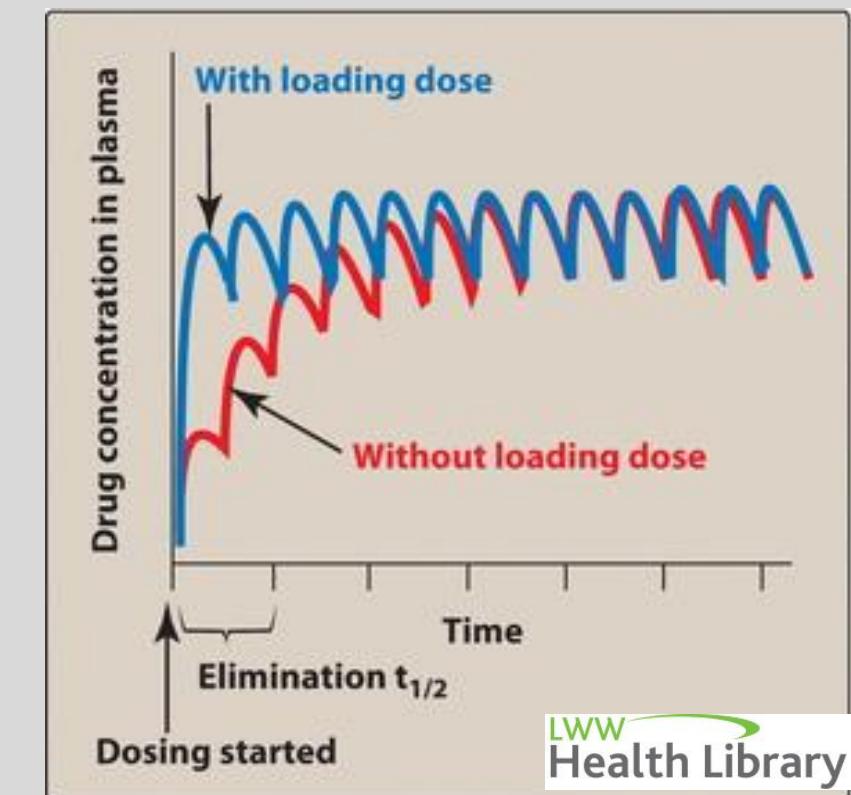
## Example: Maintenance dose calculation

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:

- $C_p \text{ desired} = 10 \text{ mg/L}$
- $CL = 2.8 \text{ L/h}/70 \text{ kg}$
- $F = 1 \text{ (I.V.)}$
- **Dosing rate =  $(CL \times C_p \text{ desired}) / 1$**   
 $= (2.8 \text{ L/h} \times 10 \text{ mg/L}) / 1$   
 $= 28 \text{ mg/h for 70 kg person}$



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

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

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

$$MD = (2.8 \text{ L/h} \times 10 \text{ mg/L}) / 0.96 \times 12$$

$$= (28 \text{ mg/h} / 0.96) \times 12 \text{ h} = 26.88 \text{ mg/h} \times 12 = 322.56 \text{ mg per dose}$$

Commercially available:

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

Optimizing theophylline therapy:

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

➤ 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.

## 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.

## 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.

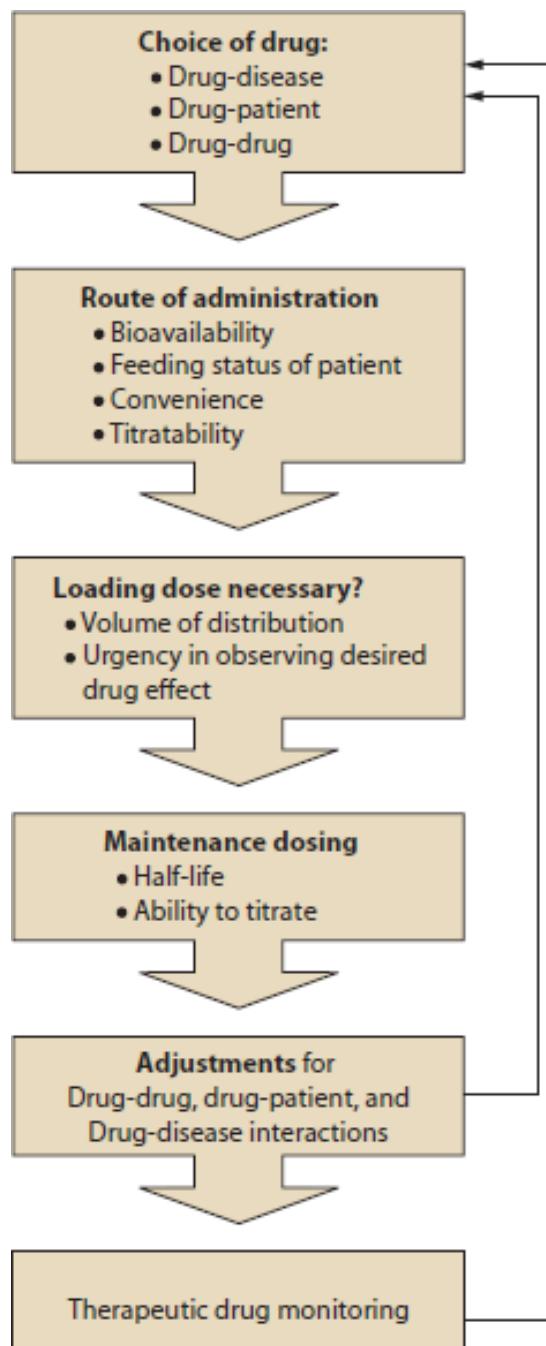
The major use of measured concentrations of drugs (at steady state) is to **refine the estimate of CL/F** (oral clearance) for the patient being treated.

$$CL/F \text{ (patient)} = \text{dosing rate} / C_{ss} \text{ (measured)}$$

## Summary of Clinical Pharmacokinetics, Part 2

- 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.

# *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.

Source: Jesse B. Hall, Gregory A. Schmidt, John P. Kress: *Principles of Critical Care*, 4th Edition: [www.accessmedicine.com](http://www.accessmedicine.com)  
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