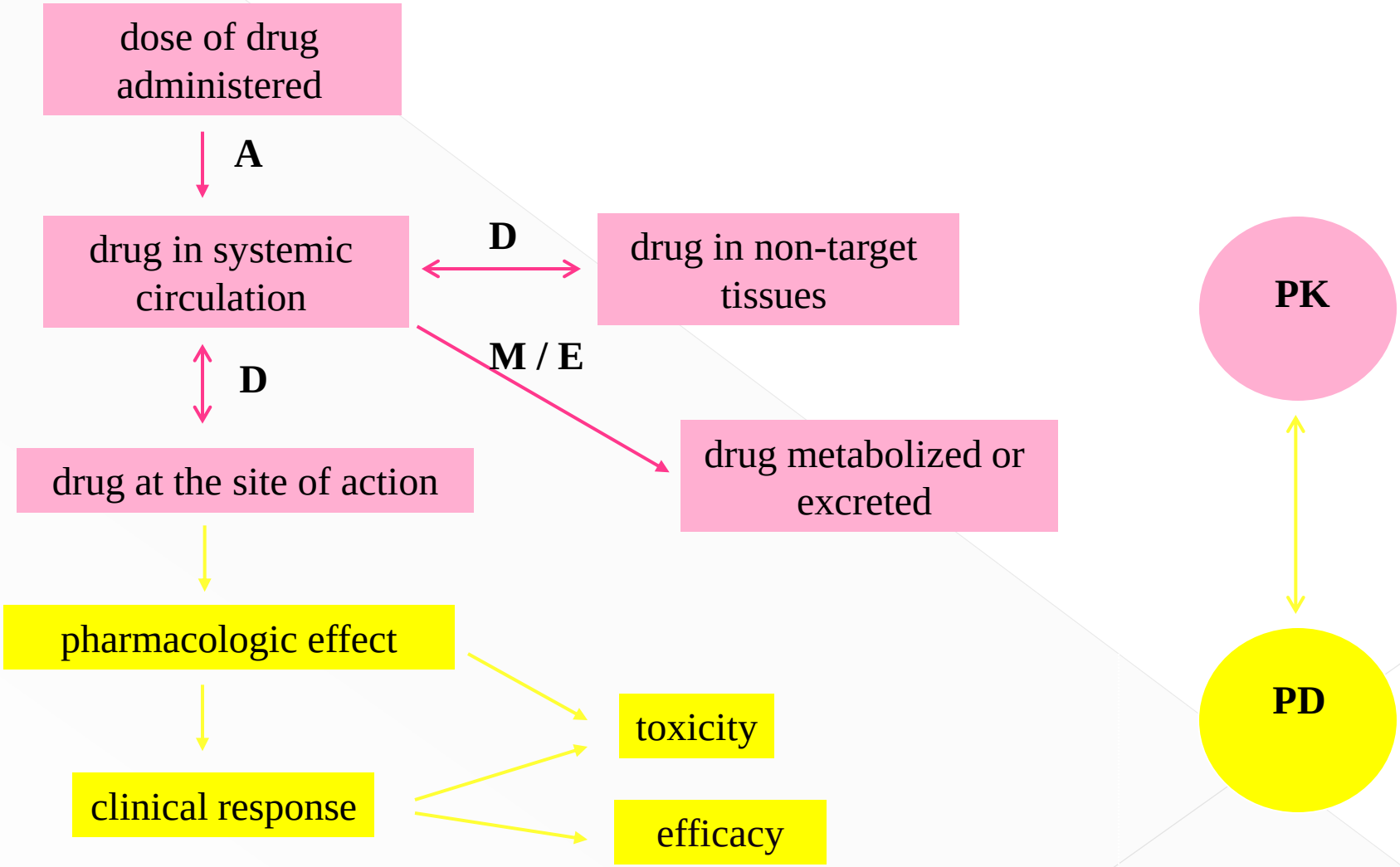
Topic #2:
Pharmacokinetics

It represents the action of the body on the drug: ADME

Overview

- To achieve the goal(s) of drug therapy, adequate drug doses must be delivered to the target tissue so that **therapeutic** yet **nontoxic** levels are obtained
- When a **medicine is selected for a patient**, the clinician must determine **the dose** that most closely would **achieve this goal**
- The time course of therapeutic drug action in the body can be understood in terms of pharmacokinetics and pharmacodynamics

What Happens After Drug Administration?



Pharmacokinetics vs. Pharmacodynamics

- Pharmacokinetics governs the dose-concentration part of the interaction
- Pharmacodynamics governs the concentration-effect part
- **Concentration** provides the **link** between pharmacokinetics and pharmacodynamics and is the **focus** of **the target concentration approach to rational dosing**

Overview (Cont'd)

- Knowing the **relationship** between **dose**, **drug concentration** and **effects** allows the clinician to take into account the various pathologic and physiologic features of a particular patient that makes him/her different from the average patient in responding to a drug

- The "standard" dose of a drug is based on trials in healthy volunteers and patients with average abilities

- This dose will not be suitable for every patient

- N.B: physiologic and pathologic processes modify specific pharmacokinetic parameters

Pharmacokinetics

- When a drug enters the body, the body begins immediately to work on the drug
- *Pharmacokinetic processes:* absorption, distribution, metabolism (biotransformation), & excretion
- *Pharmacokinetic parameters:*
  - Volume of Distribution (V_d)
  - Clearance (CL)
  - Half-Life ($t_{1/2}$)
  - Protein binding (PB)
  - Bioavailability (F)

I. Absorption

- The rate and efficacy of absorption depend on the route of drug administration
- Which is determined primarily by: drug properties (water or lipid solubility, ionization, etc.) & therapeutic objectives
- Ex…… .rapid onset of action
  - or long-term administration
  - or restriction to a local site
- Two major routes of drug administration:
  1) Enteral
  2) Parenteral

Oral administration

Advantages

- Safest, most
- convenient,
- and most economical route of administration
- Toxicities or overdose may be overcome with antidotes such as activated charcoal

??Parenteral

Others??

Disadvatages

- Limited absorption of some drugs because of their physical characteristics
- Emesis as a result of irritation to the GI mucosa
- Destruction of some drugs by digestive enzymes or low gastric pH (penicillin G)
- Irregularity or inconsistnce of absorption in the presence of food or other drugs

Factors affecting GI absorption

Numerous factors alter drug absorption. The main factors are:

1. Gastric emptying time:
   - In general, factors that **accelerate gastric emptying** time, thus permitting drugs to reach the large absorptive surface of the small intestine sooner, will increase drug absorption **(metoclopramide**)

Factors affecting GI absorption

2. Intestinal motility:

- Contact time at the absorption surface
  - The effect depends on the drug
  - and change in motility

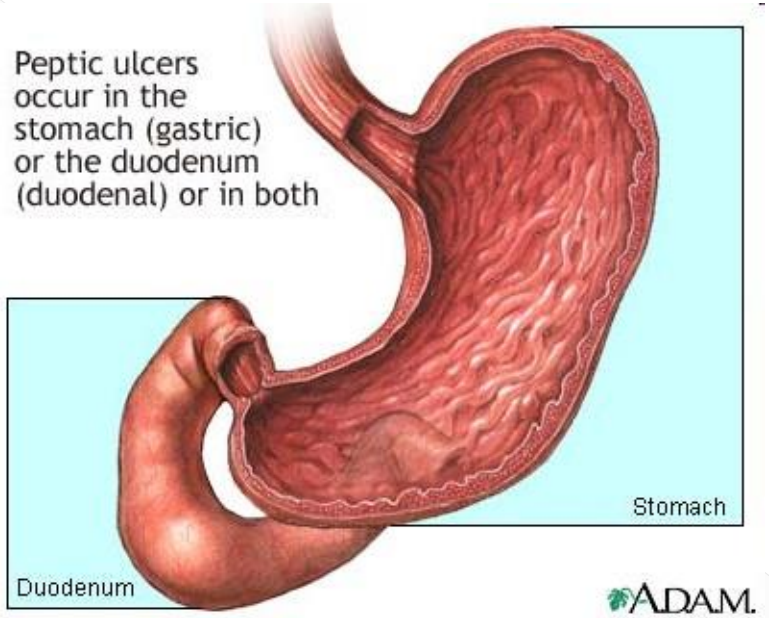
- Increased GIT motility may facilitate drug absorption.
- However, the opposite may also occur in that an increase in motility may reduce contact time in the upper portion of the intestine where most of drug absorption occurs (e.g. severe diarrhea)

Factors affecting GI absorption

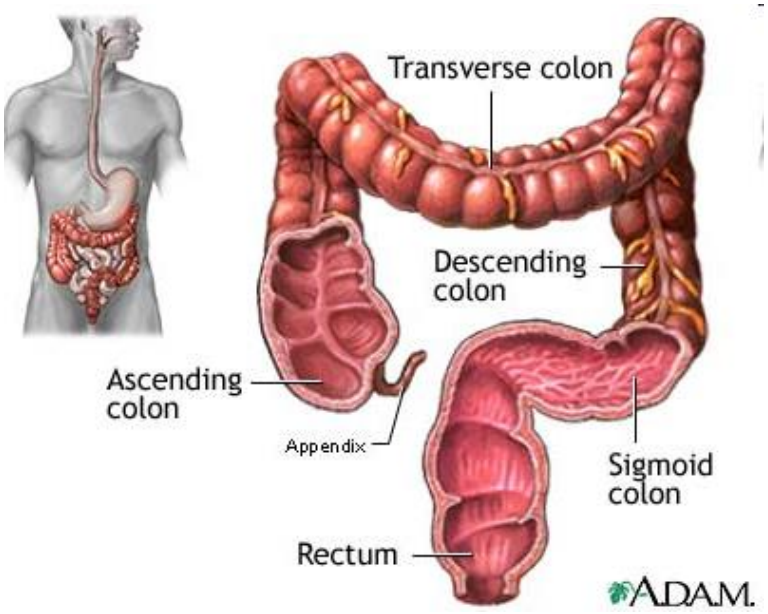
3. Food

- Absorption of **most drugs** from the GIT is reduced or delayed by the presence of food
- The absorption of several drugs (e.g. propranolol) is increased if they are taken after a meal, probably because food increases splanchnic blood flow

4. Physical state of the drug (solid forms?)



pH =1-2

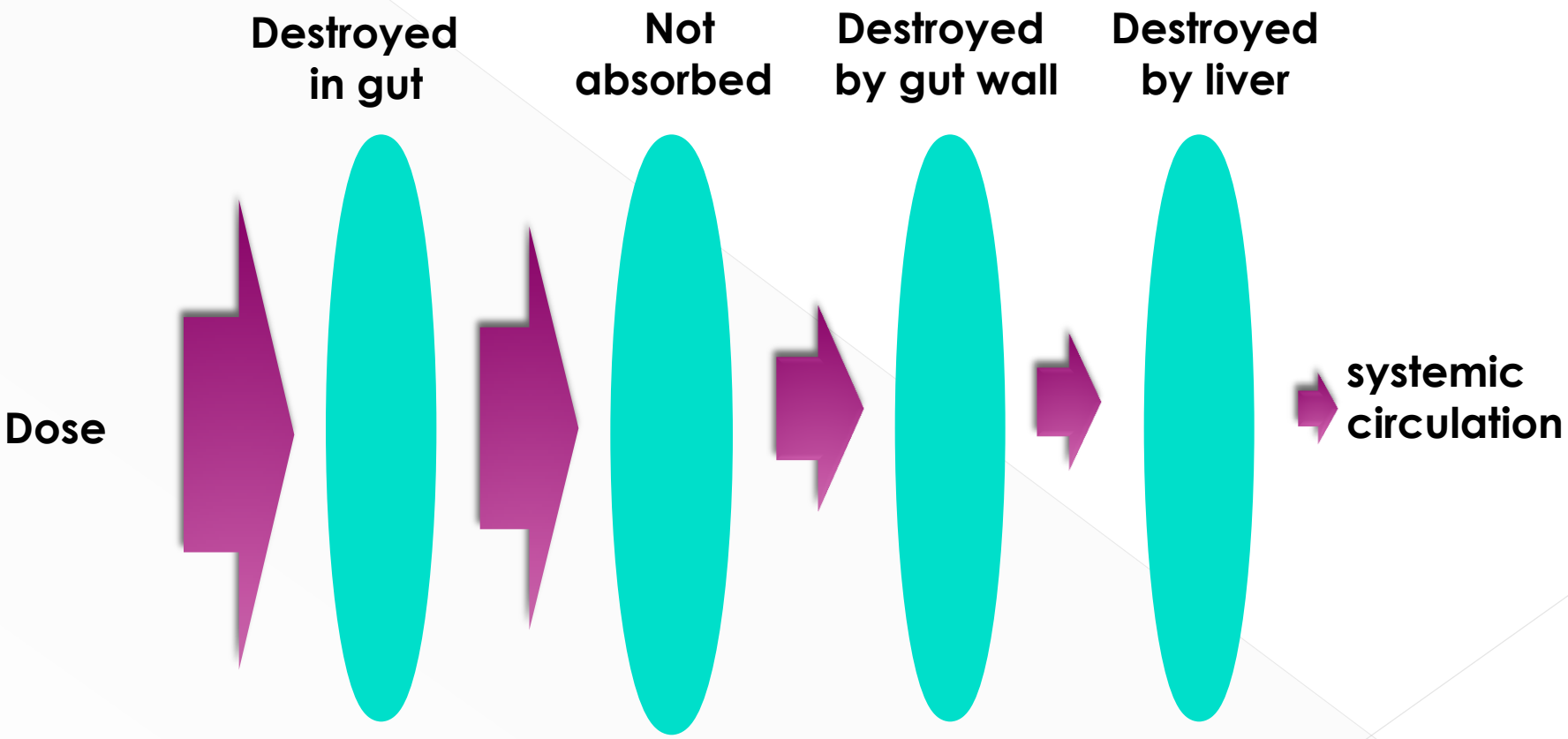


pH = 3-6

1. Proteolytic enzymes (insulin) (CYP 3A4)
2. Carrier (P-glycoprotein)

- **First pass effect?? Routes with minimal first pass?**

Oral absorption



Oral administration

- Mechanism of drug absorption:
  - Mostly **through passive transfer** at a rate determined by the ionization and lipid solubility of the drug molecules
  - **Carrier mediated transport** (e.g. Levodopa)
- Site of absorption: **small intestine (duodenum)** is the **major site** for drug absorption because of its large absorptive surface (approximately 200 m^2)

Distribution

- It the process by which a drug reversibly leaves the blood and enter the interstitium (extracellular fluid) and/ or the cells of the tissues

- Primarily depends on:
  a. Regional blood flow
  b. Capillary permeability
  c. Degree of drug binding to plasma & tissue proteins
  d. Chemical nature of the drug

Elimination

- Is the irreversible loss of drug from the body
- Excretory organs eliminate compounds that posses polar characteristics more efficiently than substances with high lipid solubility
- Lipid-soluble drugs thus are not readily eliminated until they are transformed to more polar compounds

Elimination

- It occurs by two processes:

I. **Excretion**: the kidney is the most important organ for excreting drugs and their metabolites
   - Bile
   - Lung (anesthetic gases)
   - Milk in nursing mothers

II. **Metabolism**: changes the chemical structure of a drug to produce a drug "*metabolite*", which is frequently but not universally less pharmacologically active

Metabolism

- The **liver** is the major site for drug metabolism
- The **metabolism of drugs** into **more polar metabolites** is essential for their:
  - elimination from the body,
  - as well as for termination of their biological and pharmacological activity
- Specific drugs may undergo biotransformation in other tissues, such as the **kidney** and the **intestine**

Metabolism

- The enzyme systems for drug metabolic biotransformation reactions can be grouped into two categories:

1) **Phase I: oxidative or reductive enzymes (CYP450)**
2) **Phase II: conjugative enzymes (chloramphenicol)**

Pharmacokinetics

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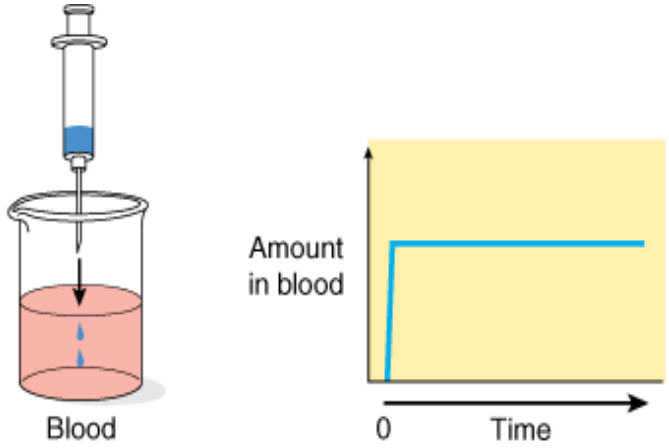
A



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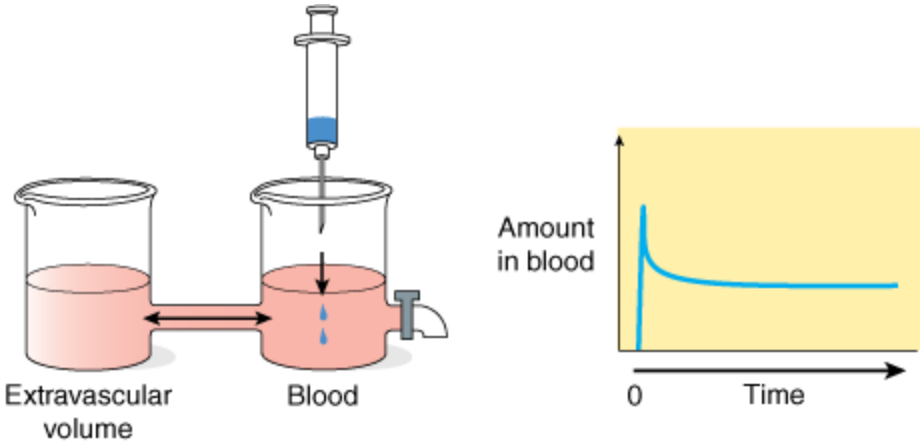

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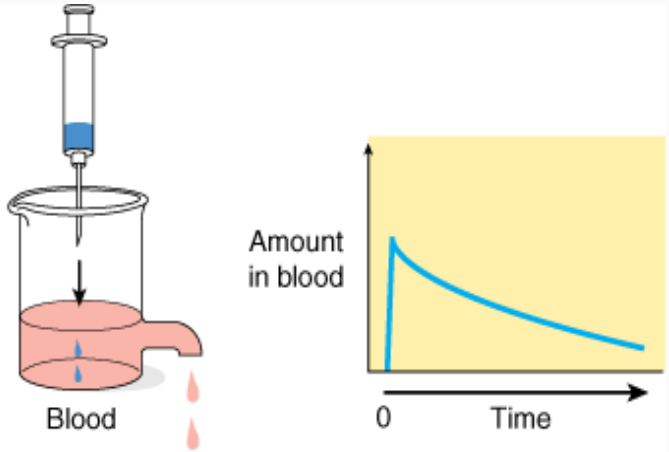

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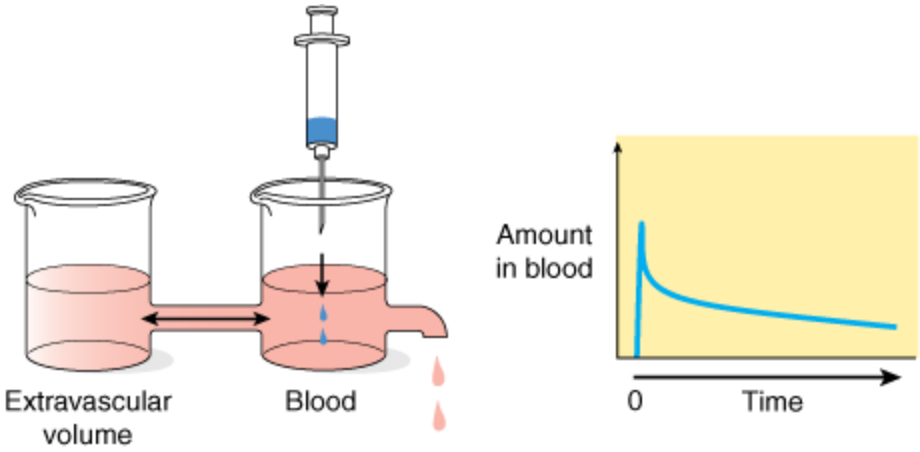
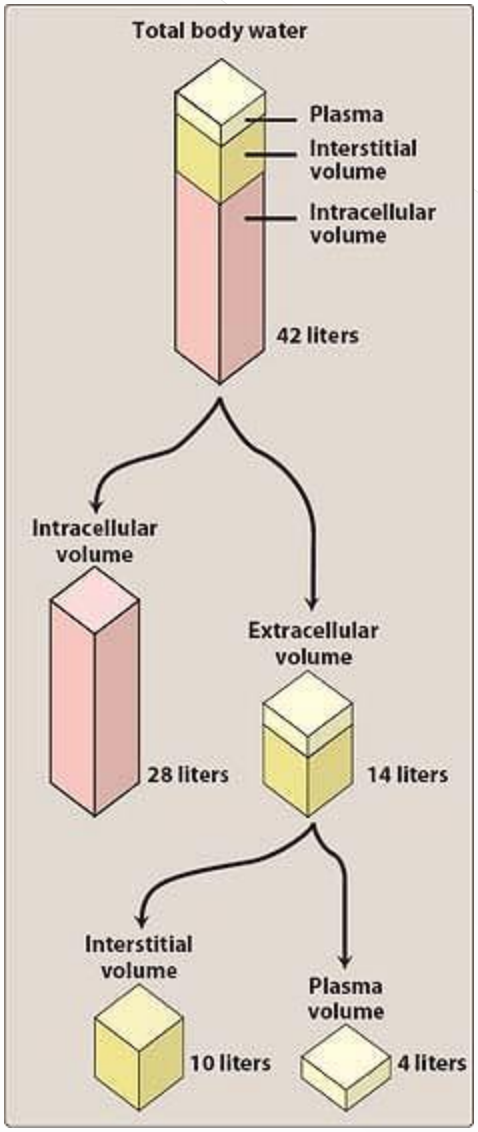


Volume of distribution (V_d)

$$V_d = \frac{\text{Amount of drug in body}}{\text{[C] in blood or plasma}}$$

- It relates the **amount of drug in the body** to the **concentration of drug (C) in blood or plasma**
- Definition: **"hypothetical"** volume of fluid into which a drug is dispersed (in which the drug is assumed to be uniformly distributed)
- **It doesn't normally reflect physiological volume**
- Necessary to **contain the dose of drug homogeneously** at the **conc found in the blood**, **plasma** (apparent V_d)

Distribution: body fluid compartments



Physical volumes (L/Kg body weight) of some body compartments to which drugs may be distributed

Digoxin Vd: 500Liter

Chloroquine Vd: 13,000Liter

Volume of distribution (V_d)

- **Drugs confined to the plasma compartment** (plasma volume 0.05L/kg BWT) (e.g. heparin and warfarin) **very large molecular weight**, or **binds extensively to plasma** proteins
- Drugs distributed in **the extracellular compartment** (extracellular volume 0.2L/kg) (e.g. aminoglycoside antibiotics): **low molecular weight and hydrophilic**
- Other sites: **In pregnancy**, the **fetus may take up** drugs and **thus increase the volume** of distribution
- (Drugs that are **extremely lipid soluble** (e.g. **thiopental**) may have **unusually high volume of distribution**)

Volume of distribution (V_d)

- *Volume of distribution is commonly calculated/expressed for a particular patient using body weight (per 70 kg body weight)*

Ex: 500 mg of *digoxin,* 70-kg subject, Vd ~ 500 L, (approximately 10 times greater than the total-body volume of a 70-kg man)??

In fact, digoxin distributes preferentially to muscle and adipose tissue and to its specific receptors (Na^+,K^+-ATPase), leaving a very small amount of drug in the plasma to be measured

Volume of distribution (V_d)

- **<u>Factors influencing the volume of distribution</u>:**
- Drug pKa
- Degrees of binding to high-affinity receptor sites
- Extent of plasma and tissue proteins
- The partition coefficient of the drug in fat (lipid solubility)

- **<u>Vd may be affected by</u>:**
- Patient's age
- Patient’s gender
- Patient’s body composition
- The presence of disease

Volume of distribution (V_d)

- **<u>In general, a small Vd occurs when</u>:**
- Lipid solubility is low
- High degree of plasma protein binding
- Low level of tissue binding

- **<u>A high Vd occurs when</u>:**
- Lipid solubility is high
- Low degree of plasma protein binding
- High level of tissue binding

Clearance (CL)

- Is the **main PK parameter describing elimination** & is the most **important concept** to consider when **designing a rational regimen** for **long-term drug administration**

- **Definition:** the volume of plasma/fluid that is cleared from drug (removed from the body per unit time)

$$CL = \frac{\text{Rate of elimination}}{C} \qquad (2)$$

Clearance (CL)

- **Total body (systemic) clearance** ,Cl_{total}, is the **sum** of the clearance from **various drug metabolizing** (mainly the **live**r) and **drug excreting** organs (mainly **the kidney**) [**Additive process**]:

$$CL_{total} = CL_{hepatic} + Cl_{renal} + CL_{pulmonary} + Cl_{other}$$

- Units of clearance are volume/time (e.g**. L/h or ml/min)**

Clearance (CL)

- For most drugs, clearance is constant over the concentration range encountered in clinical settings, ie, **elimination is not saturable**
- The rate of drug elimination is **directly proportional** to concentration:

$$\text{Rate of elimination} = CL \times C \qquad (4)$$

- This is referred to **as *first-order* elimination**.
- When **clearance is first-order**, it can be found from **the AUC** of the **time-concentration profile after a dose**:

CL = Dose / AUC

Clearance (Cl)

- Drug clearance depends on:

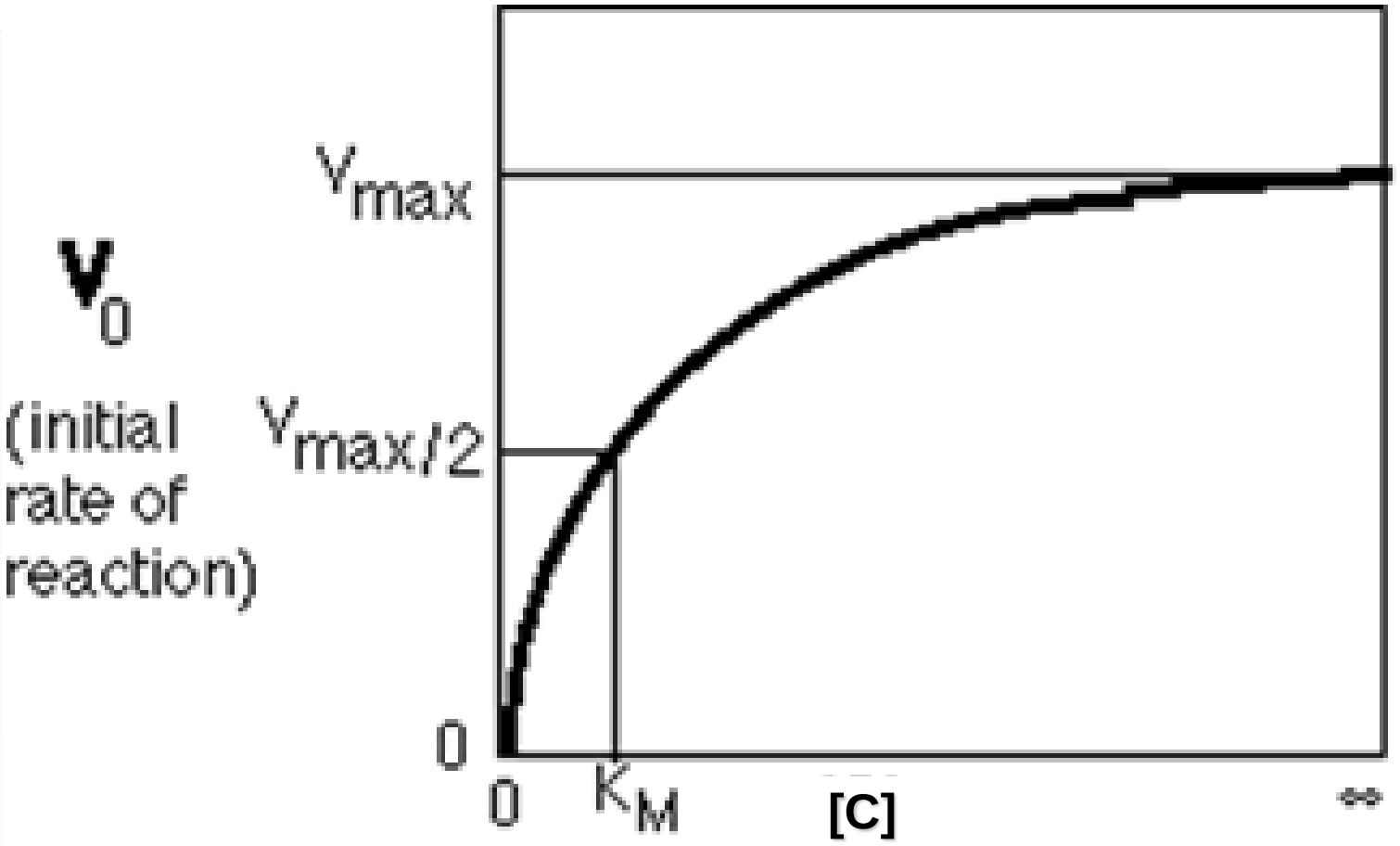
1) **Extraction ratio**: a measure of the efficiency with which an organ of elimination can remove the drug from the blood

2) **Blood flow rat**e: the rate of drug delivery to the eliminating organ

Clearance = Flow × Extraction ratio

Capacity limited elimination

- Also known as **nonlinear, & Michaelis-Menten elimination**
- **Clearance depend** on **the drug conc (cl is changed with concentration)**.
- Examples: phenytoin, ethanol, aspirin
- All active processes **are saturable**
- If **dosing rate** exceeds elimination capacity, **steady state cannot** be achieved: **the conc** will **keep on rising** as long as dosing continues
- **AUC cannot be used** to **describe** the **elimination** of such drugs



Rate of elimination = $\dfrac{\textbf{Vmax * C}}{\textbf{Km + C}}$

CL will **vary** depending on the **concentration of drug** that is achieved:

- **Linear** if values of **drug concs** are **much less than *K*m**
- **Nonlinear** when **drug concs exceed *K*m**

Fig. 1

Enzyme kinetics: increase in reaction velocity with increase in substrate concentration. As the substrate concentration increases, saturation of substrate binding to the enzyme active site eventually occurs and a maximal reaction velocity (V_{max}) is reached. The substrate concentration at a reaction velocity which is half V_{max} is called the K_m and is a measure of the affinity of the enzyme for the substrate. The reaction velocity (v) at any particular substrate concentration (S) is given by

$$v = \frac{V_{max} \times S}{K_m + S}$$

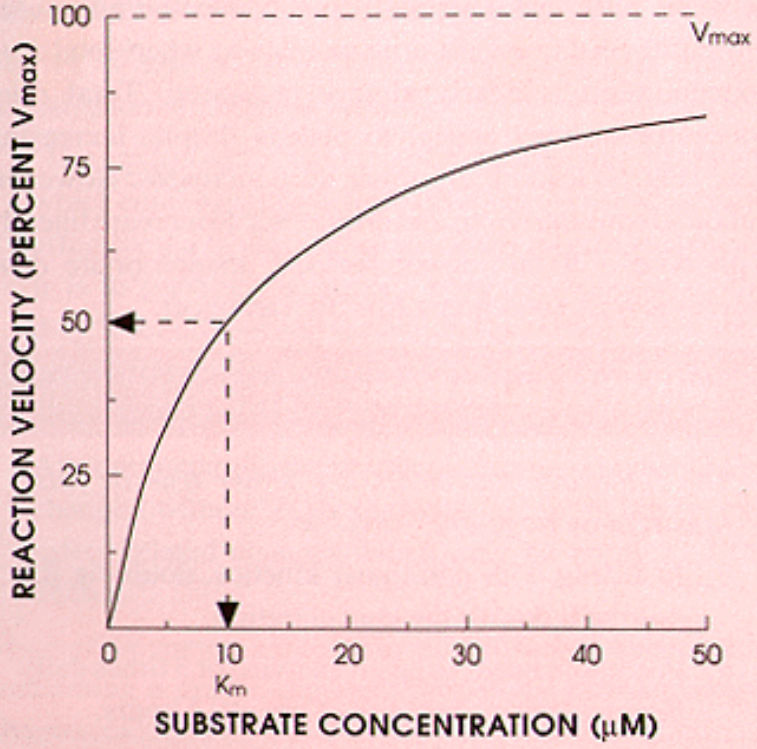
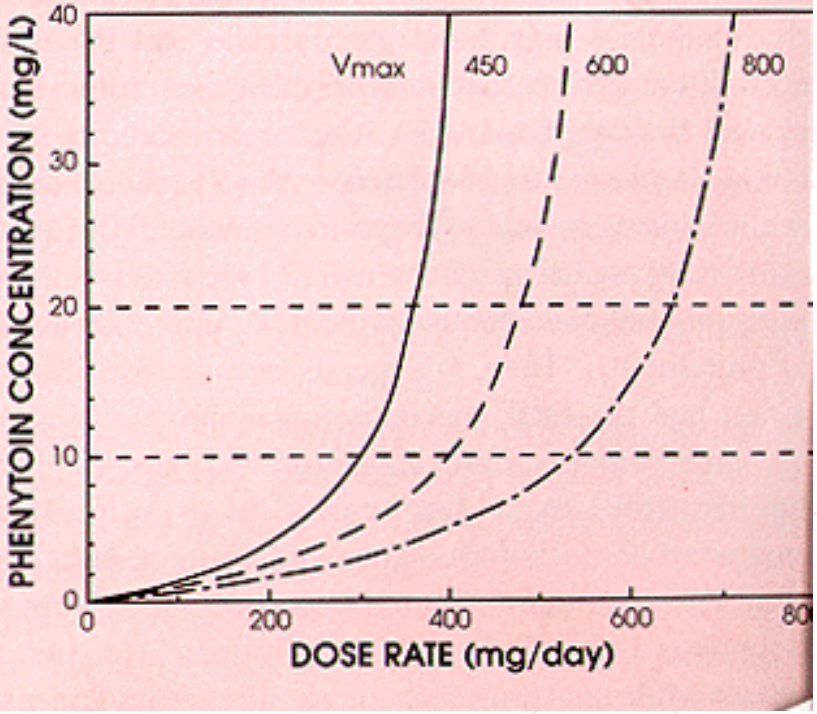
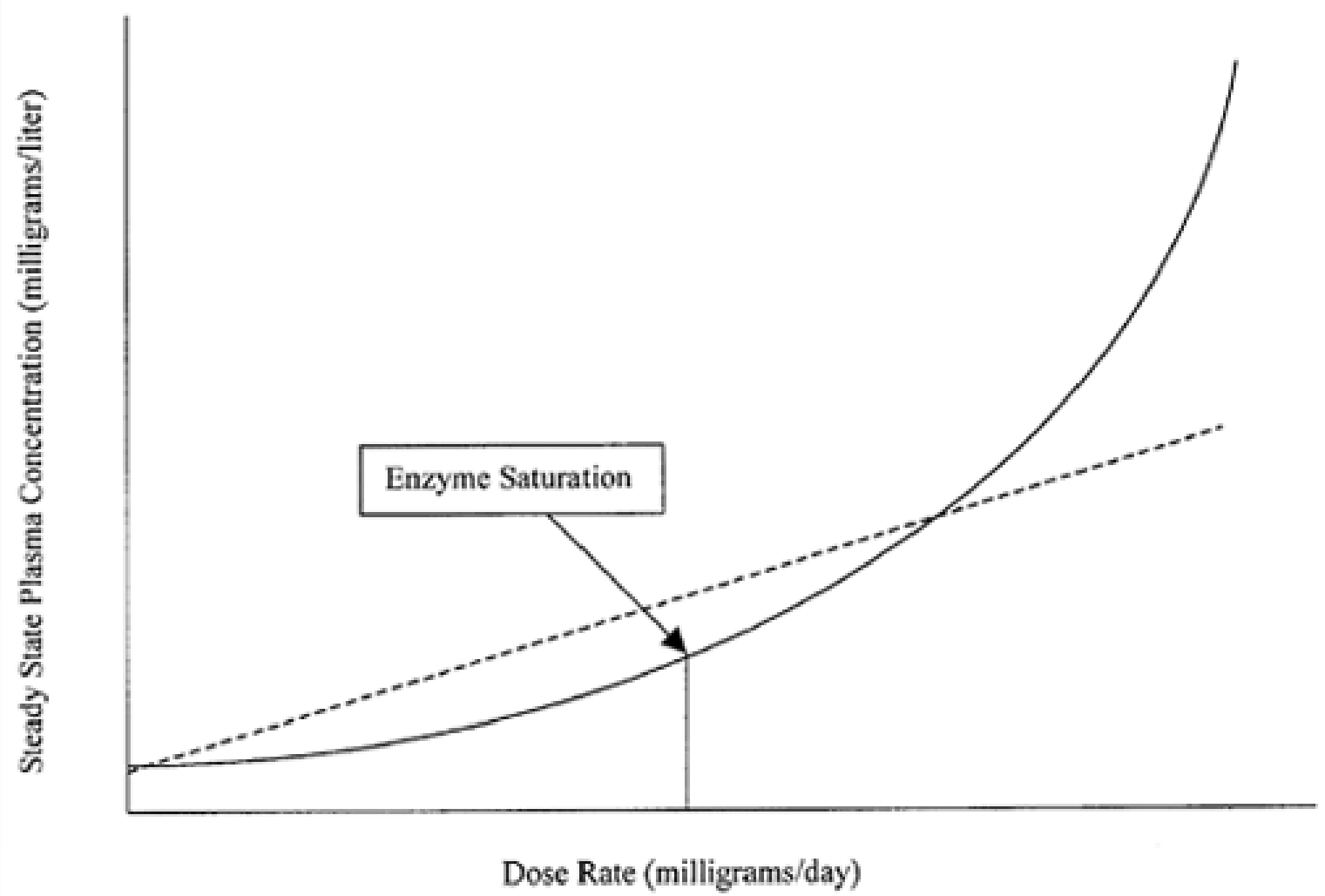


Fig. 2

Saturation of drug metabolism: increase in steady state phenytoin concentration with increasing dose rate. In the therapeutic range (10-20 mg/L), small increments in dose cause large increases in plasma phenytoin concentration. The values used for K_m (5 mg/L) and V_{max} (shown) are typical of those found in individuals with epilepsy. The therapeutic range for phenytoin is shown by the horizontal lines. The function used to generate the data is adapted from equations 3 and 5:

$$C_{ss} = \frac{\text{dose rate} \times K_m}{V_{max} - \text{dose rate}}$$




Steady State Plasma Concentration (milligrams/liter)
Enzyme Saturation
Dose Rate (milligrams/day)

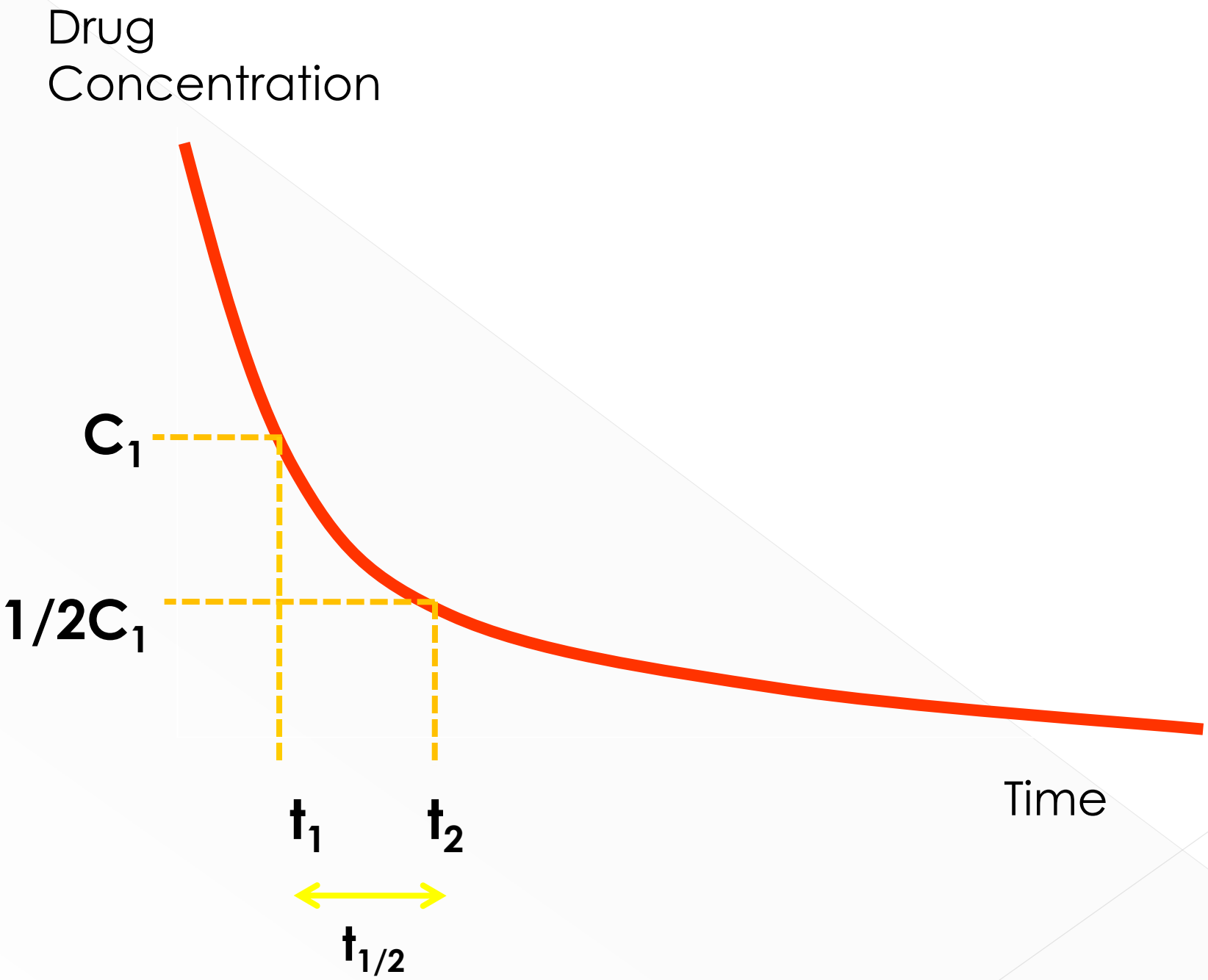
Flow-dependent elimination

- The elimination of this drugs depends primarily on the rate of drug delivery (i.e. Blood flow) to the organ of elimination
- Examples: morphine, pethidine, propranolol, verapamil
- Known as "**high extraction"** drugs since they are **almost completely extracted** from **the blood by the organ on the first pass through it**
- **Blood flow** to **the organ is** the main **determinant of drug delivery (plasma protein binding??)**
- N.B: Renal elimination….Creatinine clearance

Half-Life ($t_{1/2}$)

- **Definition**: it is the time required for the plasma concentration or the amount of drug in the body to **change** by one-half (i.e. 50%)
- During elimination or during constant infusion
- Same amount???
- The half-life is a derived parameter that changes as a function of both **clearance and volume of distribution.** A useful approximate relationship between the clinically relevant half-life, clearance, and volume of distribution is given by:

$$t_{1/2} = \frac{0.693 \times V_d}{CL}$$


Drug
Concentration
C_1
$1/2C_1$
t_1
t_2
$t_{1/2}$
Time

Half-Life ($t_{1/2}$)

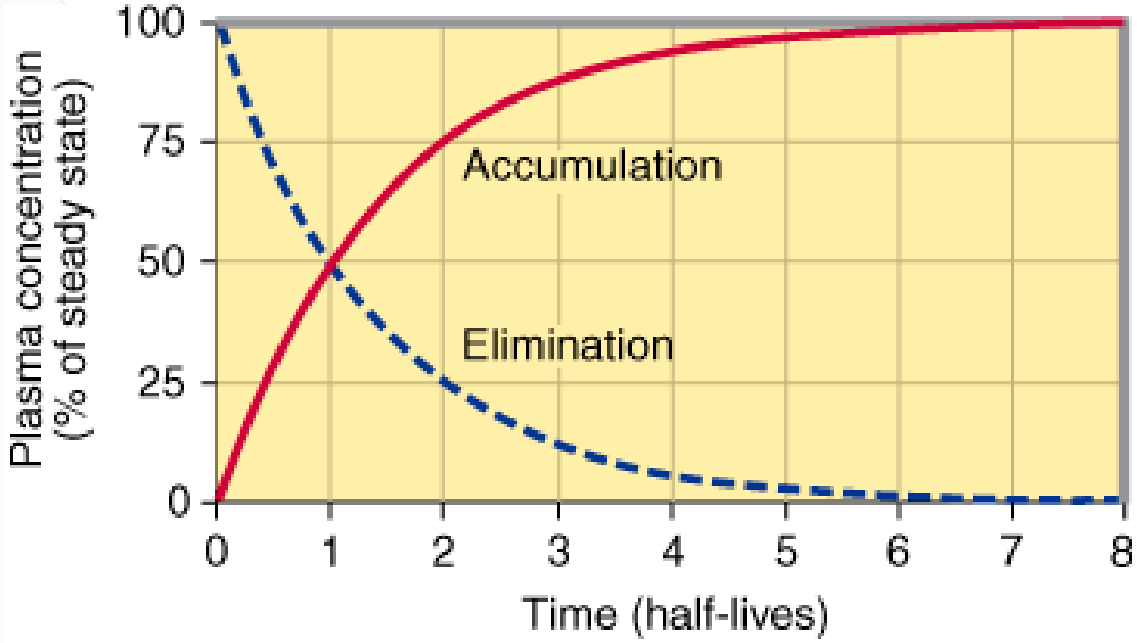
- Long or short half life drugs
- Change in half-life may reflect a change in both the clearance (kidney failure…decrease CL…increase t1/2) and volume of distribution (fluid retention…increase vd…increase t1/2)
- If **both clearance and volume of distribution** changes in **proportion**, the **half-life may be unaltered** but **average (steady state) concentration would change** ***(e.g digoxin) (elderly, decrease renal function (decreased CL...increase t1/2), and muscle mass (decreased Vd…increase t1/2))……net change on t1/2 is not that much***

Half-Life ($t_{1/2}$)

- **Sometimes,** $T_{1/2}$ can be a **poor index** of drug elimination….as for ex. **disappearance of drug may be the result of formation of undetected metabolites**

- **Half-life provides a good indication of:**
  - **The *time required to reach "ss" after a dosage regimen is <u>initiated</u> or <u>changed</u>*** (i.e., four $T_{1/2}$ to reach approximately 94% of a new "ss")
  - ***The time for a drug to be removed from the body, <u>means to estimate the appropriate dosing interval</u>***

Knowledge about half-life is useful in determining the time to reach/attain steady state (ss) or to decay from steady state conditions



50% Css	1 $t_{1/2}$
75% Css	2 $t_{1/2}$
~99% Css	4 - 5 $t_{1/2}$

4-5 half lives to reach steady state

Drug accumulation

- If the dosing interval is shorter than four half-lives, accumulation of drug in the body will occur
- accumulation is inversely proportional to the fraction of the dose lost in each dosing interval

$$\text{Accumulation factor} = \frac{1}{\text{Fraction lost in one dosing interval}}$$

$$= \frac{1}{1 - \text{Fraction remaining}} \quad (7)$$

- Ex: what is the accumulation factor for a drug given every half-life? Answer = 2

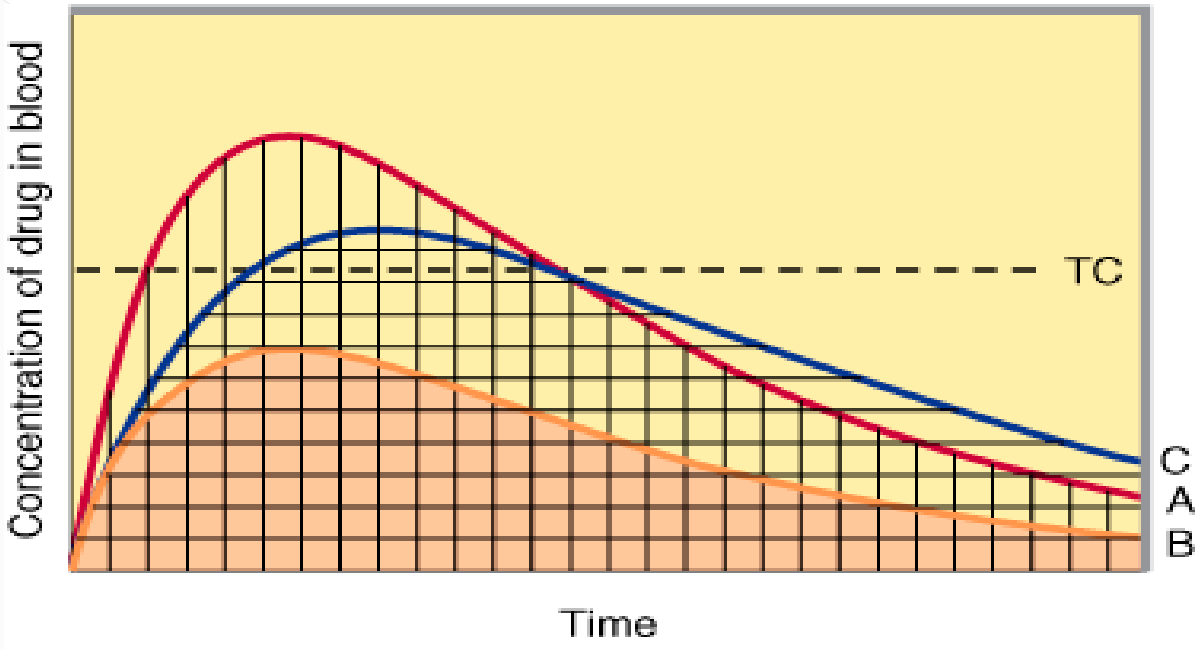
Bioavailability

- Definition: the **fraction** of **unchanged drug** reaching the **systemic circulation** following **administratio**n by **any route**
  - Bioavailability is 100% for drugs delivered IV
  - Bioavailability for drugs administered orally ≤100%??
    1. Extent of absorption-incomplete
    2. First-pass elimination
- The **area under the curve (AUC) (of concentration time curve)** is a common measure of bioavailability of a drug given by a particular route

Bioavailability

- The rate and the efficiency of absorption differ depending on the drug's route of administration
- The **amount absorbed divided** by the **amount administered** constitutes the drug's bioavailability (F)…..Table 3.3 (self study)
- Both the rate and extent of drug absorption can influence clinical effectiveness of the drug (see Fig. 3-4)

Bioavailability



A: Drug rapidly and completely available

B: Only half of availability of A but rate equal to A

C: Drug completely available but rate only half of A

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Bioavailability (Cont'd)
Rate of Absorption

- **Rate of absorption** determined by:
  1. Site of administration
  2. Drug formulation (e.g. particle size, salt form, crystal polymorphism, **enteric coating**, & the presence of excipients)

N.B: in multiple dosing regimen, different dosage forms may yield the same *average* blood level, although one may show higher max and min levels

Bioavailability (Cont'd)

Rate of Absorption

- Drug absorption is said to be *zero-order* when the rate is said to be independent of the amount of drug remaining in the gut (eg, gastric emptying, **controlled-release formulation**)

- When full dose is dissolved in GIT fluids, the rate of absorption is usually proportional to the GIT concentration (***first order absorption***)

Bioavailability
Extent of Absorption

I. First-pass elimination (in gut, gut wall, liver)

II. Solubility of the drug
- Hydrophilic drugs (e.g. atenolol) are unable to cross the lipid-rich cell membranes
- Hydrophobic drugs (e.g. acyclovir) are totally insoluble in aqueous body fluids

III. Reverese transporter (p-glycoprotein)

IV. Chemical instability (e.g. Penicillin G and insulin)

Bioavailability
First pass elimination

Magnitude of first pass hepatic effect:

Extraction ratio (ER)

ER = CL liver / Q

Q is the hepatic blood flow (usually about 90 L per hour [1500 ml/min] for 70kg person)

Systemic bioavailability (F) may be determined from the extent of absorption (f) and the extraction ratio (ER):

F = f x (1-ER)

Ex: morphine is completely absorbed; hepatic **extraction ratio is 0.67…..(1-ER) = 0.33….F=33%**

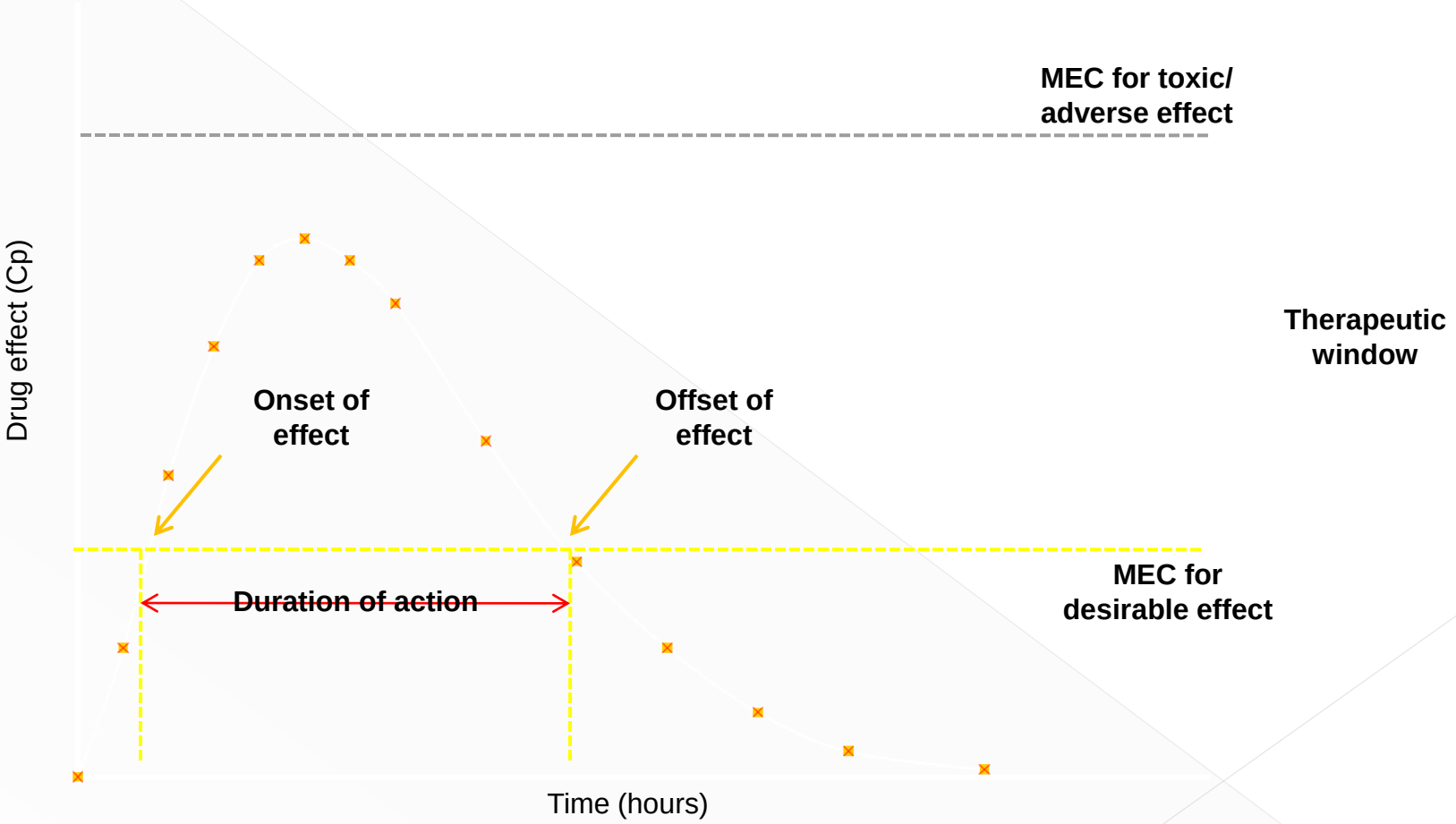
Bioavailability
First pass elimination

- High extraction ratio drugs show inter-patient bioavailability variation because of sensitivity to:
  - Hepatic function
  - Blood flow
  - Hepatic disease
- Lidocaine and verapamil…low bioavailable….but lidocaine never given P.O (CNS toxicity, convulsions)
- Alternative route of administration: convenience, increase conc. at action site, prolong duration of absorption
- Rectal?

The Target Concentration Approach to Designing a Rational Dosage Regimen

- Is based on the assumption that there is a target concentration (TC) that will produce the desired therapeutic effect
- By considering drug's PKs, it is possible to individualize the dose regimen to achieve the target concentration
- The **initial TC**: **lower end** of the **therapeutic range**
- Sometimes it depends on **the specific therapeutic objective** (Ex. Digoxin: 2ng/ml for AF *or* 1ng/ml for HF)

The **intensity** of a drug's effect is related to its concentration above a minimum effective concentration, whereas the **duration of effect** reflects the length of time the drug level is above this value



Maintenance dose

- In most **clinical situations**, drugs are administered in a series of **repetitive doses or** as a **continuous infusion** to **maintain a *steady-state concentration*** of drug in the body

- Just enough drug is given in each dose to replace the drug eliminated since the preceding one:

$$Rate_{in} = Rate_{out}$$

  - Dosing rate= elimination rate

Maintenance dose

- Clearance is the most important pharmacokinetic term to be considered in defining a rational steady state drug dosage regimen:

$$\textbf{Dosing rate}_{ss} = \textbf{Elimination Rate}_{ss}$$

Dosing rate = CL ×TC

- Thus if the TC in known, the CL in the patient determines the dosing rate….(the equation is for I.V.)

Maintenance dose

- If the drug is given by a route that has a bioavailability less than 100%, then the dosing rate must be modified. For oral dosing:

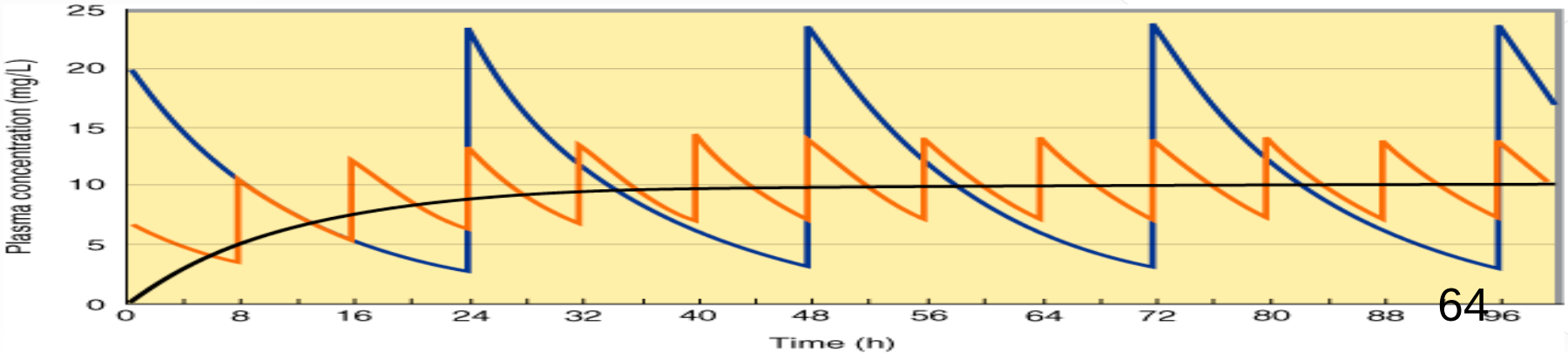
$$\textbf{Dosing rate}_{oral} = \textbf{Dosing rate}_{i.v}/F_{oral}$$

- If **intermittent doses** are given, the maintenance dose is calculated from:

Maintenance dose = Dosing rate X Dosing interval

Maintenance dose

- Ex: a target plasma theophylline conc. to relieve bronchial asthma Is 10mg/L
- CL is 2.8L/h/70kg
- F = 1 (I.V infusion)
- **Dosing rate** = CL x TC = 2.8L/h/70kg X 10mg/L = 28 mg/h/70kg
- For oral theophylline? F=0.96
- **Maintenance dose** = Dosing rate/F X Dosing Interval (8h)
- (28mg/h/0.96) X 8h = 233mg



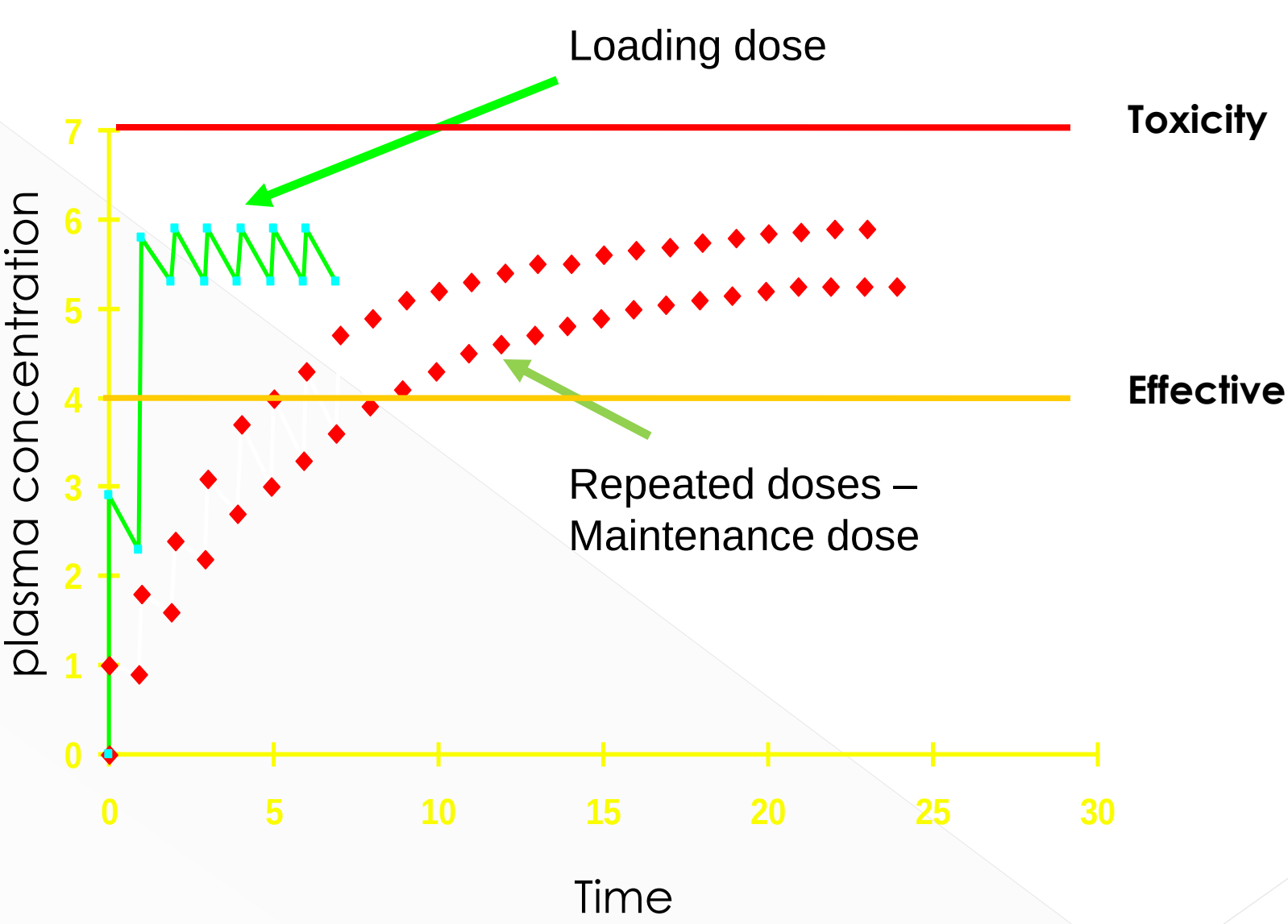
Loading dose

- **When the time** to reach **steady state** is **appreciab**le, as it is for **drugs with long half lives**, it may desirable to administer a loading dose that **promptly rises the concentration of drug in plasma to the TC**

- The Vd is the factor that relates the amount of drug in the body to the concentration…..

- The appropriate magnitude for the loading dose is:

Loading dose = TC × Vd



- To match steady state concentration:

Loading dose = Maintenance dose X Accumulation factor

Therapeutic drug monitoring (TDM)

The basic principles outlined above can be applied to the interpretation of *clinical drug concentration measurements* on the basis of three major pharmacokinetic variables: ***absorption, clearance, and volume of distribution (and the derived variable, half-life)***; and two pharmacodynamic variables: ***maximum effect attainable*** in the target tissue and the **sensitivity of the tissue to the drug**. **Diseases** may **modify all of these parameters**, and the ability to predict the effect of disease states on pharmacokinetic parameters is important in properly adjusting dosage in such cases.

The target concentration strategy

DRUG CONCENTRATION (KINETIC-DYNAMIC)

1. Choose the target concentration, TC.
2. Predict volume of distribution (Vd) and clearance (CL) based on standard population values (eg, Table 3–1) with adjustments for factors such as **weight and renal function.**
3. Give a loading dose or maintenance dose calculated from TC, Vd, and CL.
4. Measure the patient's response and drug concentration.
5. Revise Vd and/or CL based on the measured concentration.
6. Repeat steps 3–5, adjusting the predicted dose to achieve TC.