Clinical Pharmacokinetics

OBJECTIVES

- Why clinical pharmacokinetics?
- Important parameters

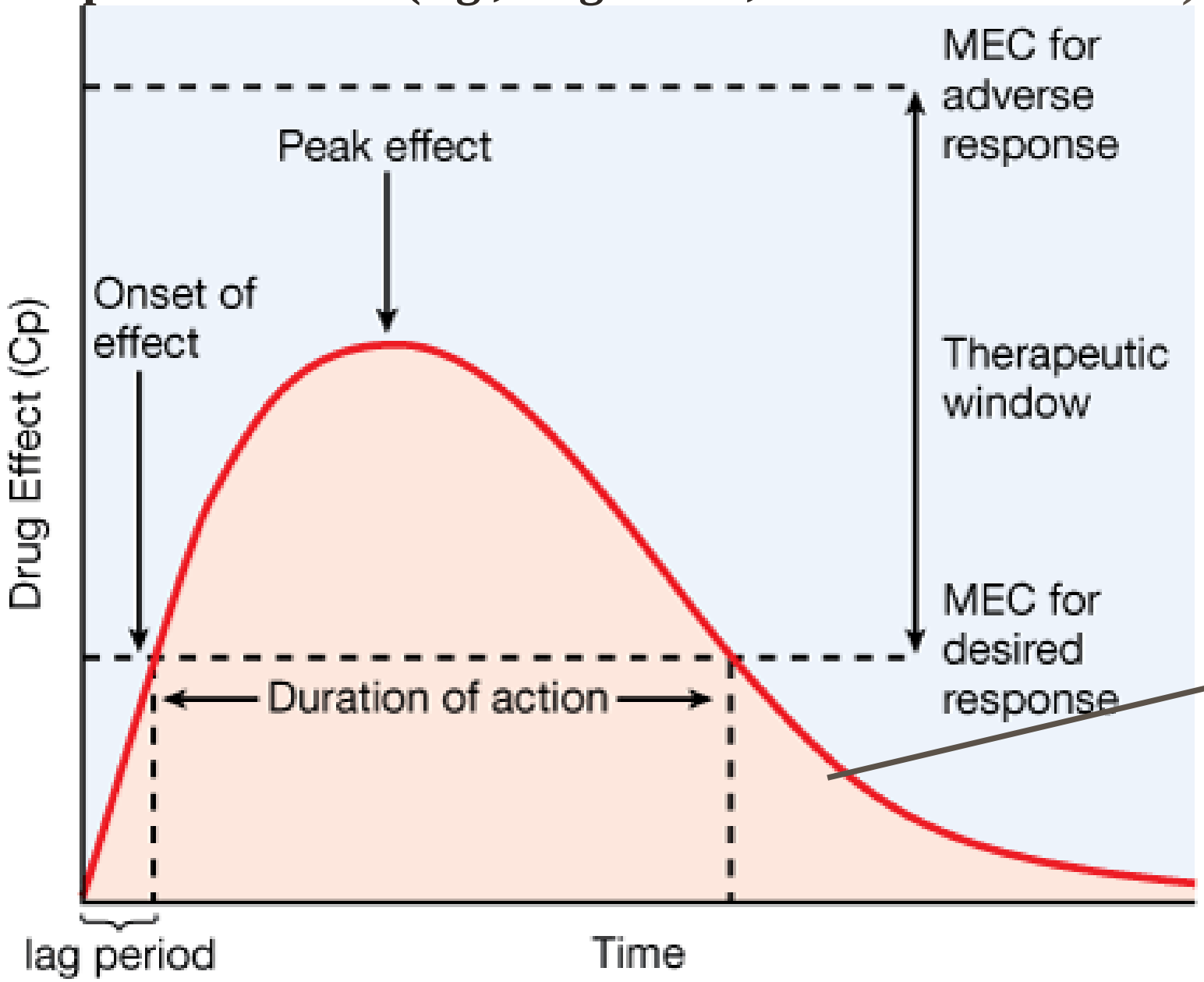
1. **Clearance**
2. **Volume of distribution**
3. **Half life**
4. **Bioavailability**

- First order and Zero order kinetics
- Concept of LOADING and MAINTAINENCE dose
- Therapeutic drug monitoring

fundamental tenet

Relationship exists between the pharmacological effects of a drug and an accessible concentration of the drug (*e.g.*, in blood or plasma).

Temporal characteristics of drug effect and relationship to the therapeutic window (e.g., single dose, oral administration).



AUC

Importance of pharmacokinetics in patient care

Improvement in therapeutic efficacy and avoidance of unwanted effects

Four most important parameters

- **half-life measure of the rate of removal of drug from body**
- **Clearance: measure of the body's efficiency in eliminating drug**
- **Volume of distribution, a measure of the apparent space in the body available to contain the drug**
- **Bioavailability: fraction of drug absorbed as such into the systemic circulation.**

Plasma half life

- The time required for the concentration of drug in the plasma to decrease to one half of its initial value.
- T1/2 does not reflect on absorption kinetics BUT reflects on the elimination(Clearance kinetics)
- for example if the initial conc. of drug is 100mg and if the half life is 1 hr, only 50mg will remain in the plasma at the end of 1 hr.

Time :	0	1hr	2hr	3hr	4hr
Cp (mg/dl):	100	50	25	12.5	6.25

- So from this table we can deduce that the half-life of this drug is _____ hour.

Importance of half life

- **denotes how quickly a drug is removed from the plasma by biotransformation or excretion**

- **Since drug require a minimum conc. in the plasma to produce pharmacological action, a drug which is eliminated quickly requires more frequent dosing**

- **indicates the duration of action of drug**

Complete drug elimination occur in 4-5 half lives.

- 1^{st} -50 %
- 2^{nd} -75%(50+25)
- 3^{rd} -87.5%(50+25+12.5)
- 4^{th} -93.75%(50+25+12.5+6.25)

Decline in plasma concentration

$T_{1/2}$ is the time taken for plasma concentration to decline by one-half, starting at (100%) plasma concentration,

- **1 x t1/2 :Plasma concentration will fall to 50%,**
- **2 x t1/2 : 25%**
- **3 x t1/2 to 12.5%,**
- **4 x t1/2 to 6.25% and in**
- **5 x t1/2 to 3.125% of the original steady-state concentration.**

If the half life of a drug is 4 hrs, What percentage of the drug administered would remain in the body after 16 hrs after administration

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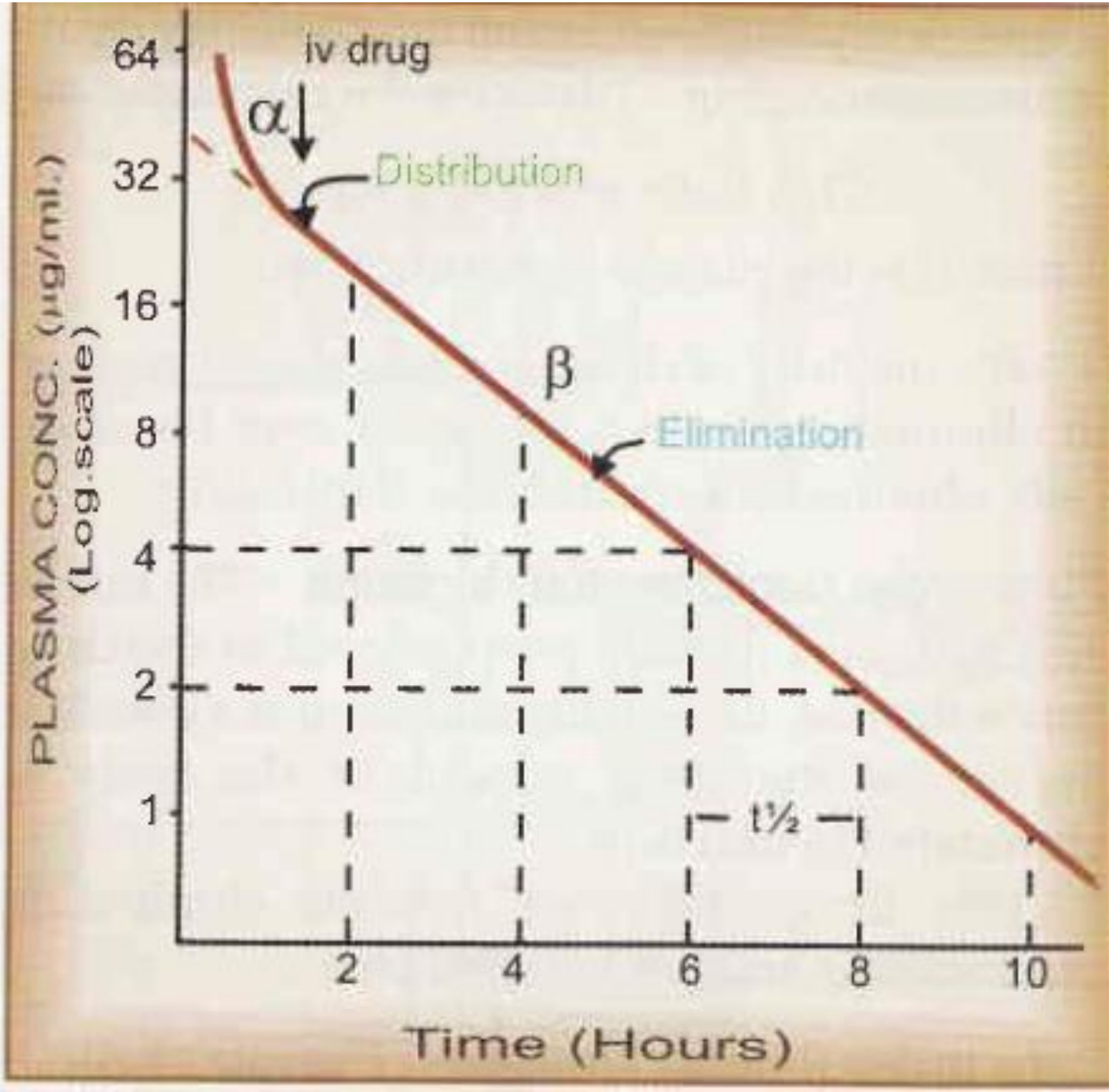
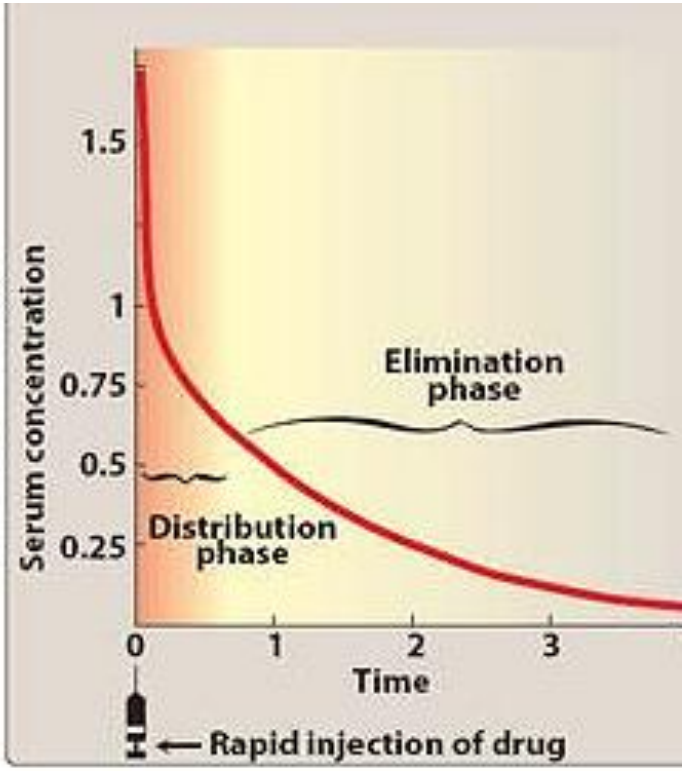
- 6.25%


iv drug
α
Distribution
β
Elimination
t½
64
32
16
8
4
2
1
PLASMA CONC. (µg/ml.)
(Log.scale)
2
4
6
8
10
Time (Hours)



Since first order kinetics is an exponential process ,mathematically ,the elimination t1/2 is

$$T1/2 = \frac{\ln 2}{\kappa}$$

- drug elimination is described by an exponential process, the time taken for a twofold decrease can be shown to be proportional to the natural logarithm of 2.

- The constant 0.693 is an approximation to the natural logarithm of 2.

Half life

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

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

A normal volunteer will receive a new drug in a clinical trial. The clearance and volume of distribution of the drug in this subject are 1.386 L/hr and 80 L ,respectively. The half life would be

a) 83 hrs
b) 77 hrs
c) 58 hrs
d) 40 hrs

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$$= \frac{0.693 \times 80}{1.386}$$

$$= 40 \text{ hrs}$$

Half life

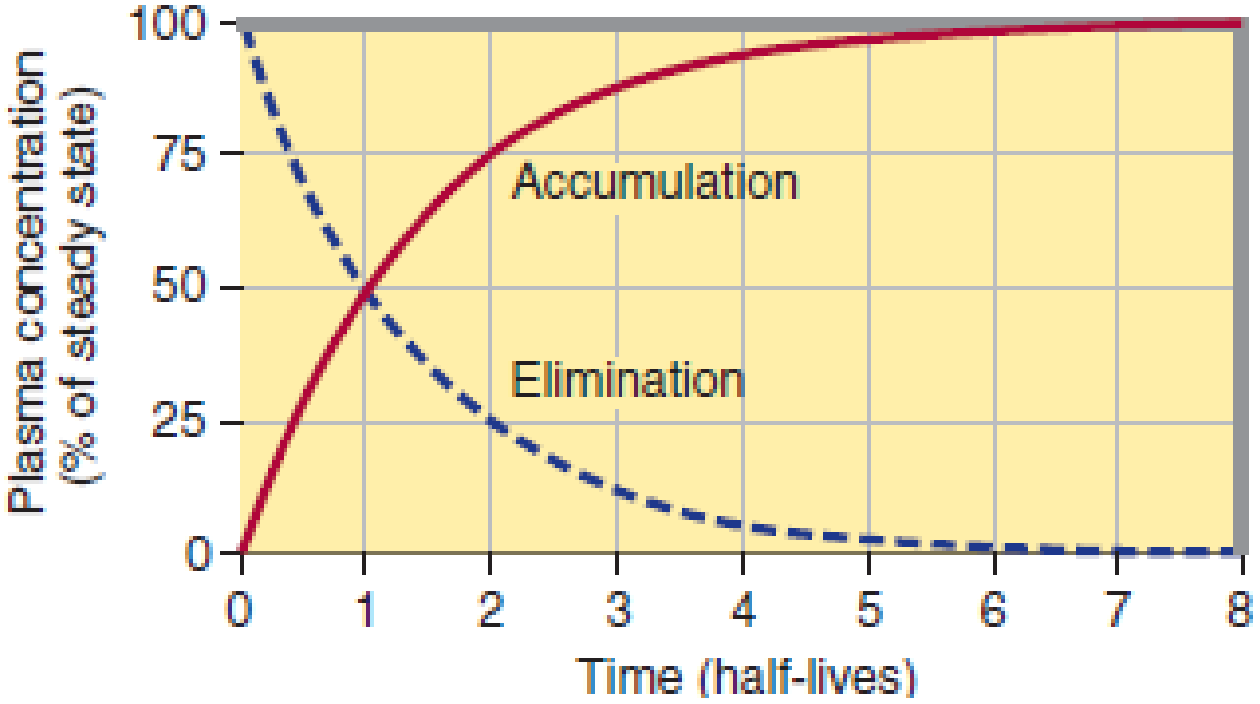
$$t_{1/2} = \frac{0.693 \ V_d}{CL_E}$$

$t_{1/2}$ = Elimination half life

V_d = Volume of distribution

CL_E = clearance

The time course of drug accumulation and elimination.



- **The "rule of thumb" that four half-lives must elapse after starting a drug-dosing regimen before full effects will be seen**
- **Solid line: Plasma concentrations reflecting drug accumulation during a constant-rate infusion of a drug. Fifty percent of the steady-state concentration is reached after one half-life, 75% after two half-lives, and over 90% after four half-lives**

Salient features of half life

1. **Half life is a derived parameter that changes as a function of both clearance and volume of distribution.**
2. **Plasma protein binding increases half –life.**
3. **Drugs widely distributed and sequestered in tissues have longer half life-Amiodarone.**
4. **Approx 4-5 half lives are required for complete elimination of the drug.**

Clinical significance

1. Determines frequency of administration or dosing interval .
2. If a drug has long half life, then it will take longer to achieve SSC and thus loading dose of a drug needs to be given
3. If a drug has short half life but there is emergency ,even then loading dose is given
4. Drugs with long half life-cumulate on prolonged daily use
5. Reduced clearance ,prolonged half life

Half life

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

$t_{1/2}$ = Elimination half life

V_d = Volume of distribution

CL_E = clearance

EXCEPTIONS

T ½ indicates duration of action but *not always*

1. Hit and run drugs
2. Drugs generating active metabolites
3. Drugs with ZERO ORDER kinetics

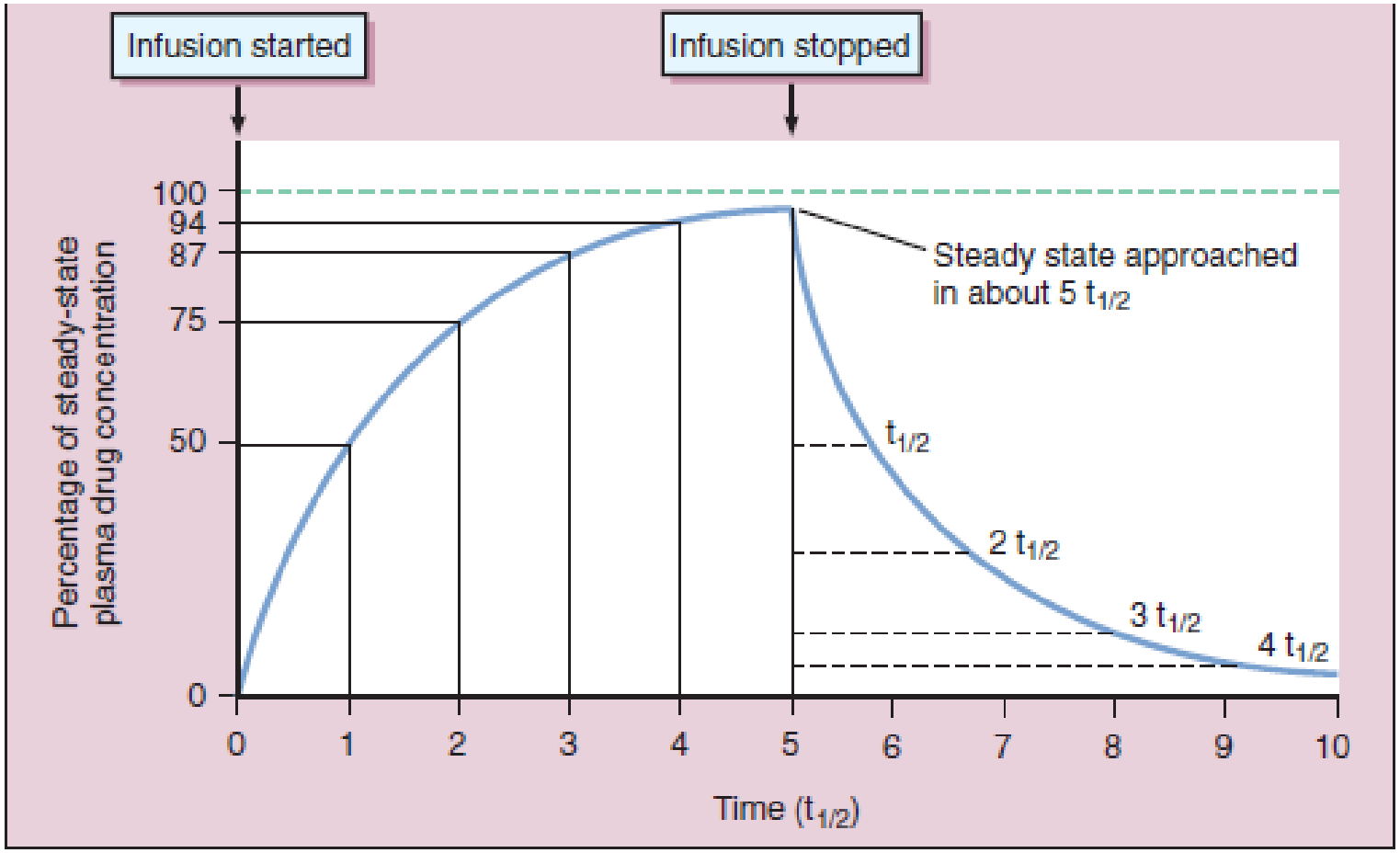
Steady state concentration

- **When a drug is infused at a constant rate, the plasma concentration rises until a state is reached at which the rate of administration of drug to the body is exactly equal to rate of elimination.**

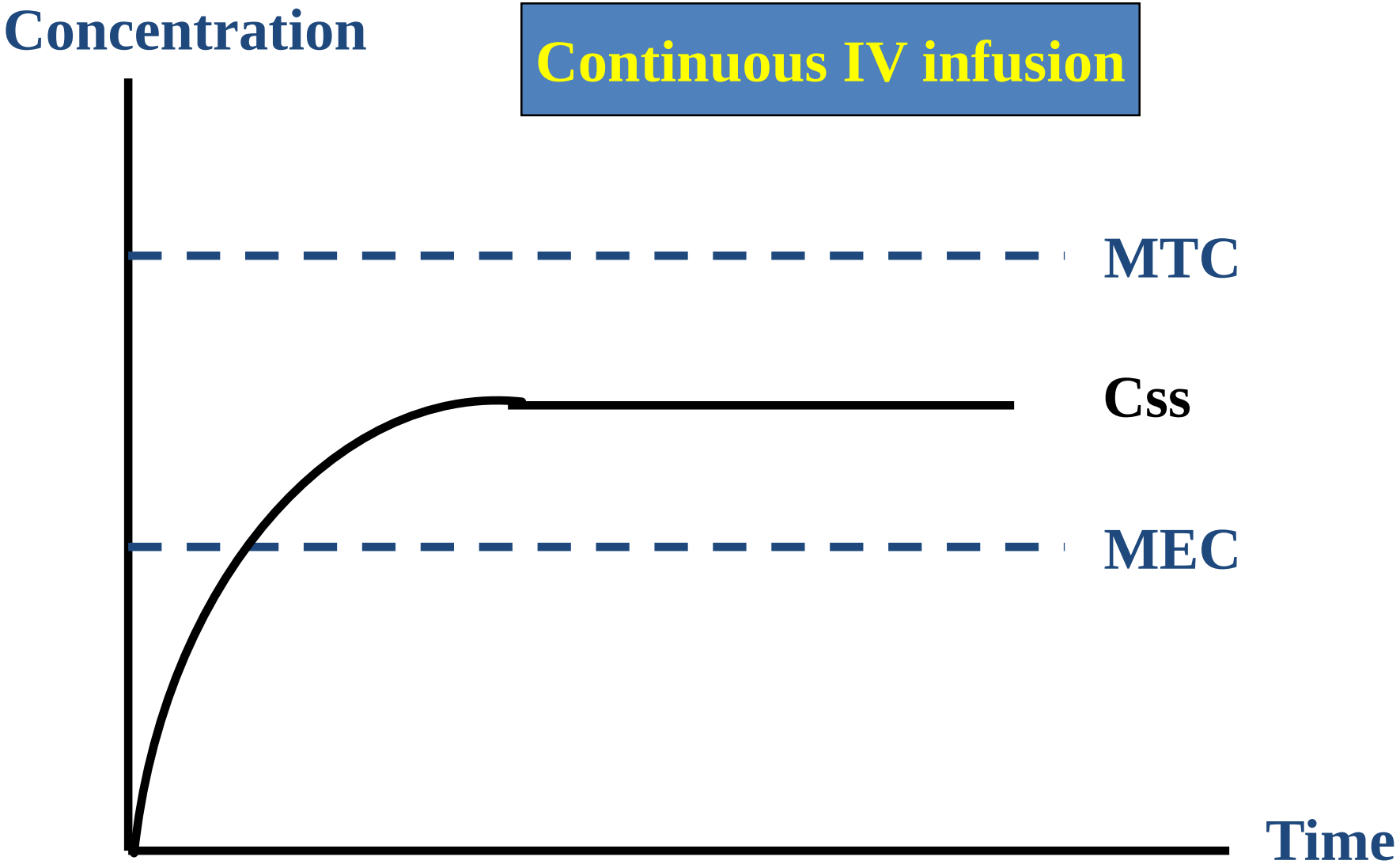
- **When attained, amount of drug in the body remains constant, plasma concentration is on a *plateau***

- **Stable drug effect assumed.**

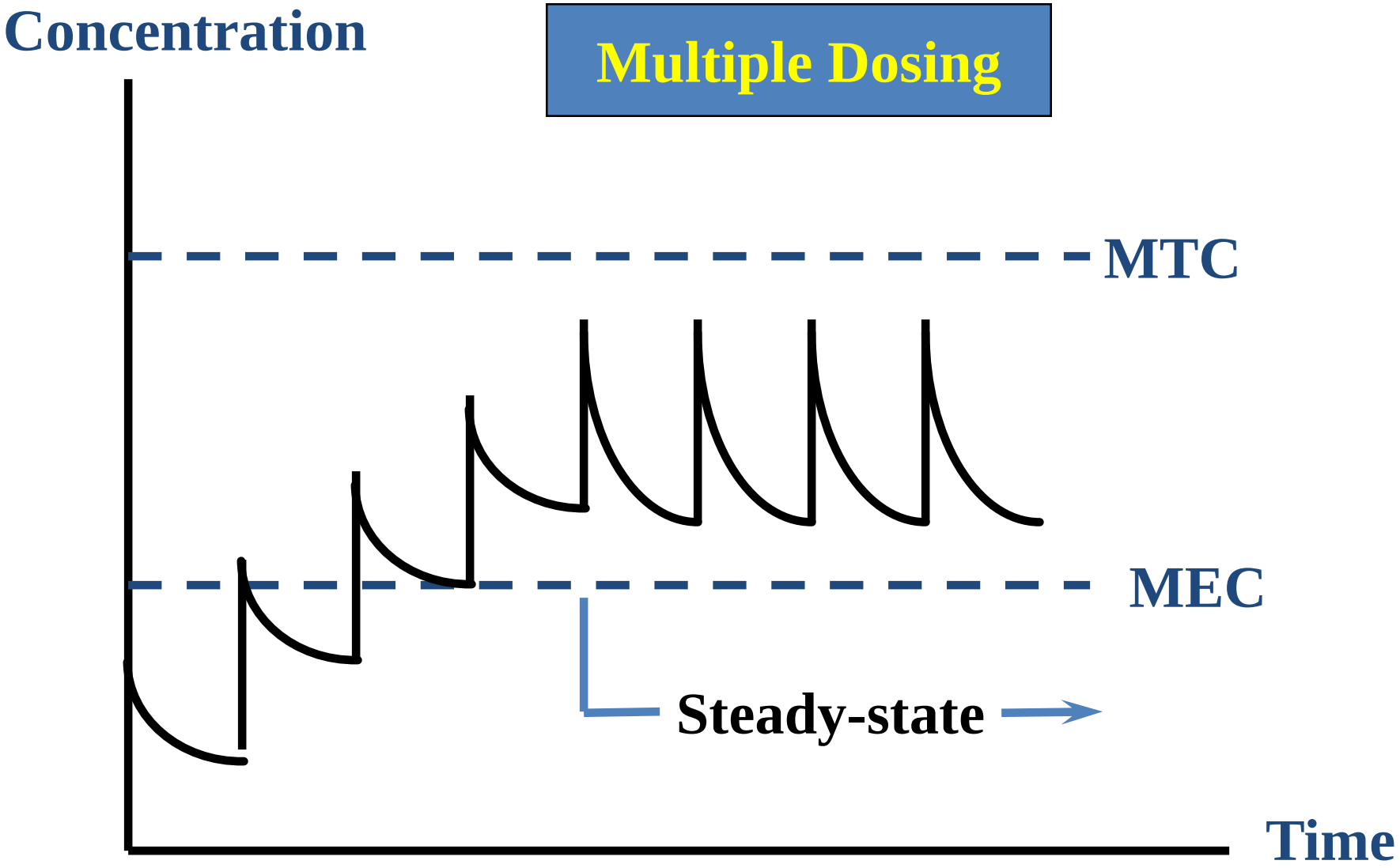
The steady-state drug concentration depends on drug dose administered per unit of time AND half-life of the drug



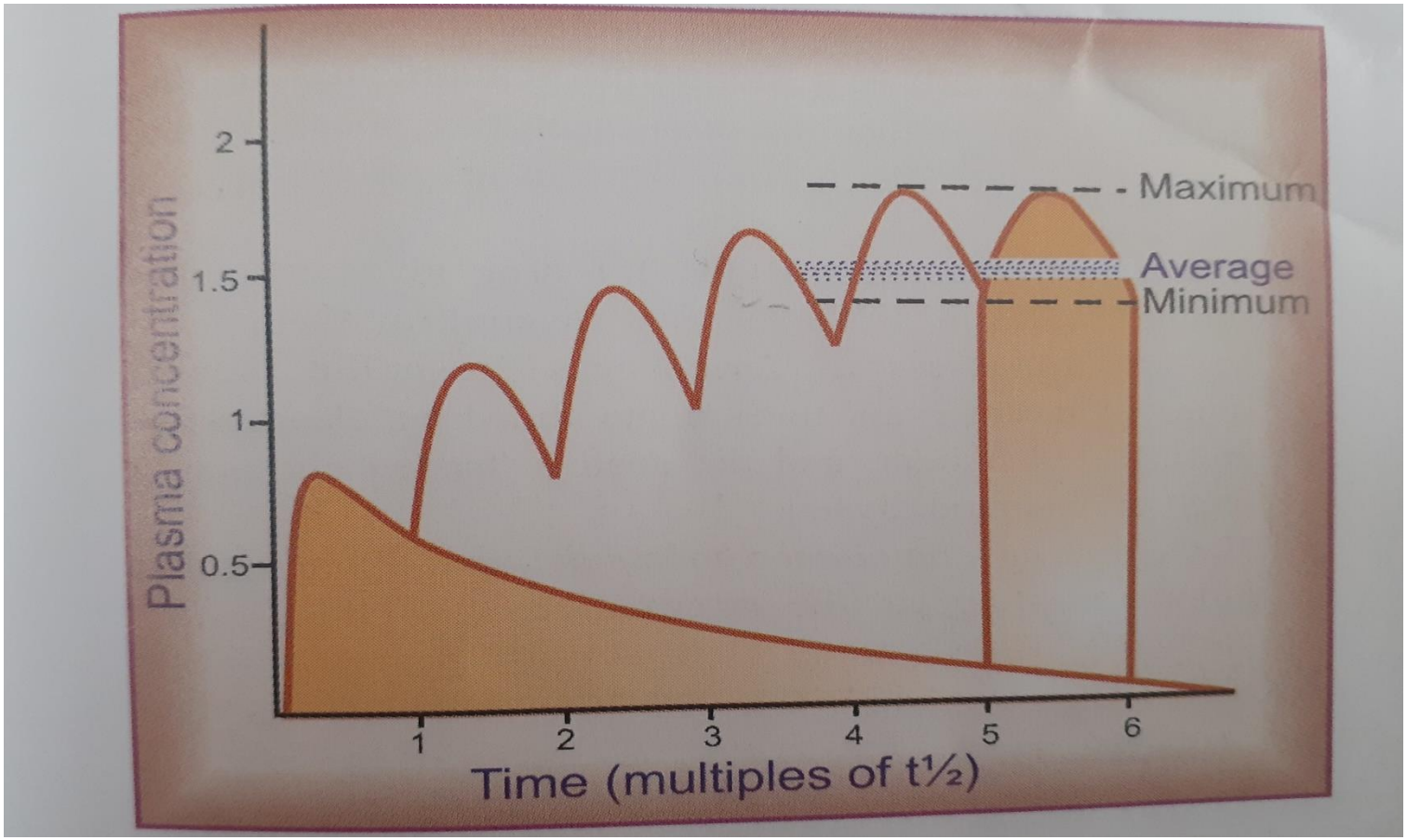
Continuous IV infusion



Multiple Dosing



- When constant dose of a drug is repeated before the expiry of 4 t ½ ,it would achieve **higher peak concentration** ,because some remnant of the previous dose will be present in the body
- This continues with every dose until progressively increasing rate of elimination (which increases with increase in the concentration)balances the amount administered over the dosing interval



When the drug is administered orally (absorption takes some time) ,average Cpss is approx 1/3rd of the way between the minimal and maximal levels in a dose interval

IMPORTANT….

When a drug is given at a constant rate (continuous or intermittent) the *time to reach steady* state depends only on the T1/2

for all practical purposes,

after 5 x t 1/2 the amount of drug in the body will be constant and the plasma concentration will be at a plateau.

Steady state concentration

Table 2.18 Increase in plasma concentration with each half life

Number of t½	Plasma concentration
One	100/2 = 50%
Two	50 + 50/2 = 75%
Three	75 + 25/2 = 87.5%
Four	87.5 + 12.5/2 = 93.75%
Five	93.75 + 6.25/2 = 96.875 ~ 97%

TABLE 7.1 Plasma $t^1/_2$ of some drugs

Drug	$t^1/_2$
adenosine	< 2 sec
dobutamine	2 min
benzylpenicillin	30 min
amoxycillin	1 h
paracetamol	2 h
midazolam	3 h
tolbutamide	6 h
atenolol	7 h
dothiepin (dosulepin)	25 h
diazepam	40 h
piroxicam	45 h
ethosuximide	54 h

Clearance

- Concept to consider when designing a rational regimen for long-term drug administration.
- Elimination rate constant (Kel) characterizes the elimination process and may simply be regarded as the *fractional rate of drug removal per unit time*
- $k_{el} = \frac{0.693}{t1/2}$

Calculate the elimination rate constant for a drug having T1/2 of 1.7 hrs

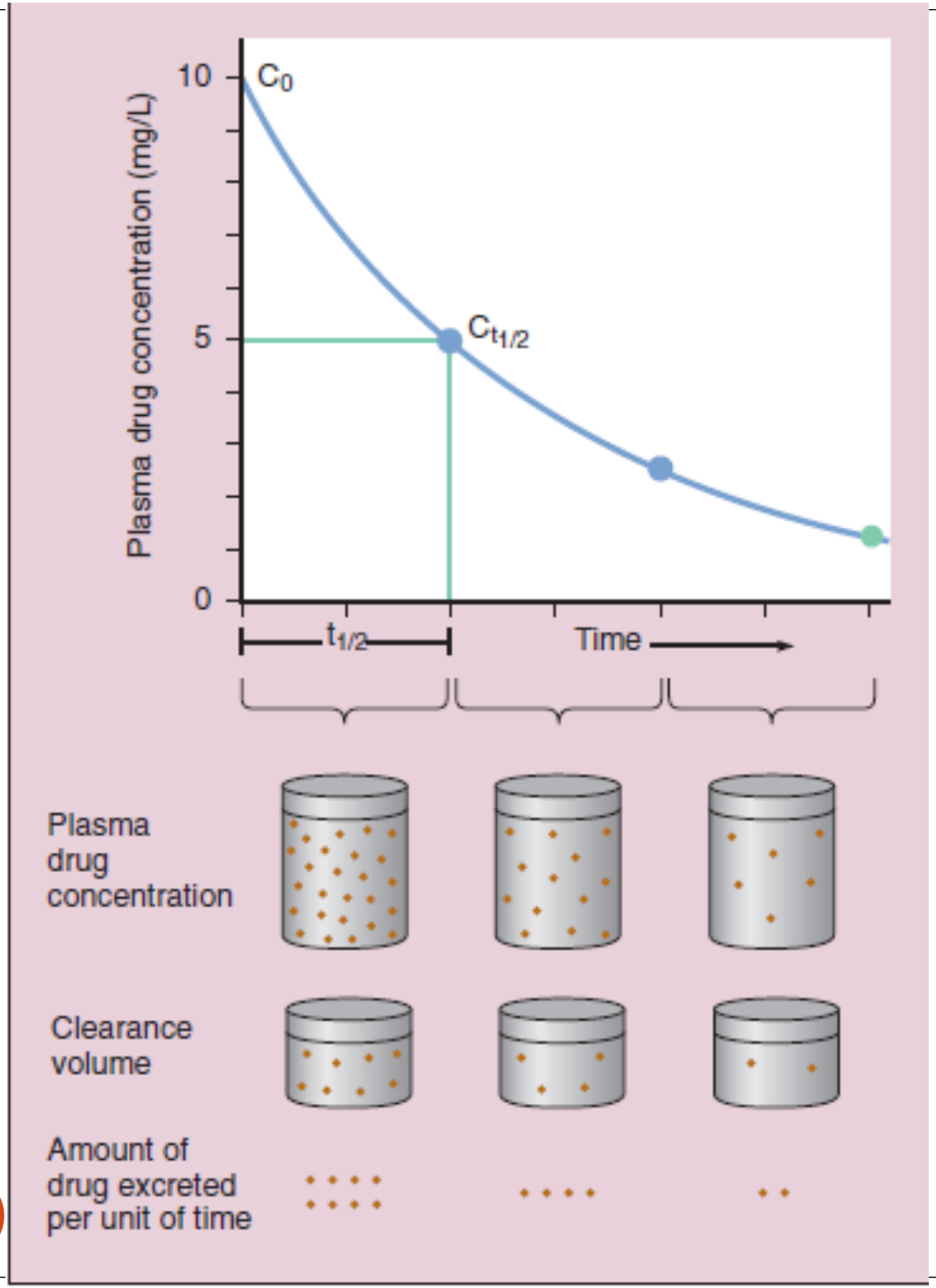
0.4/hr

Drug half-life and clearance

The elimination half-life (t1/2) is the time required to reduce the plasma drug concentration (C) by 50%.

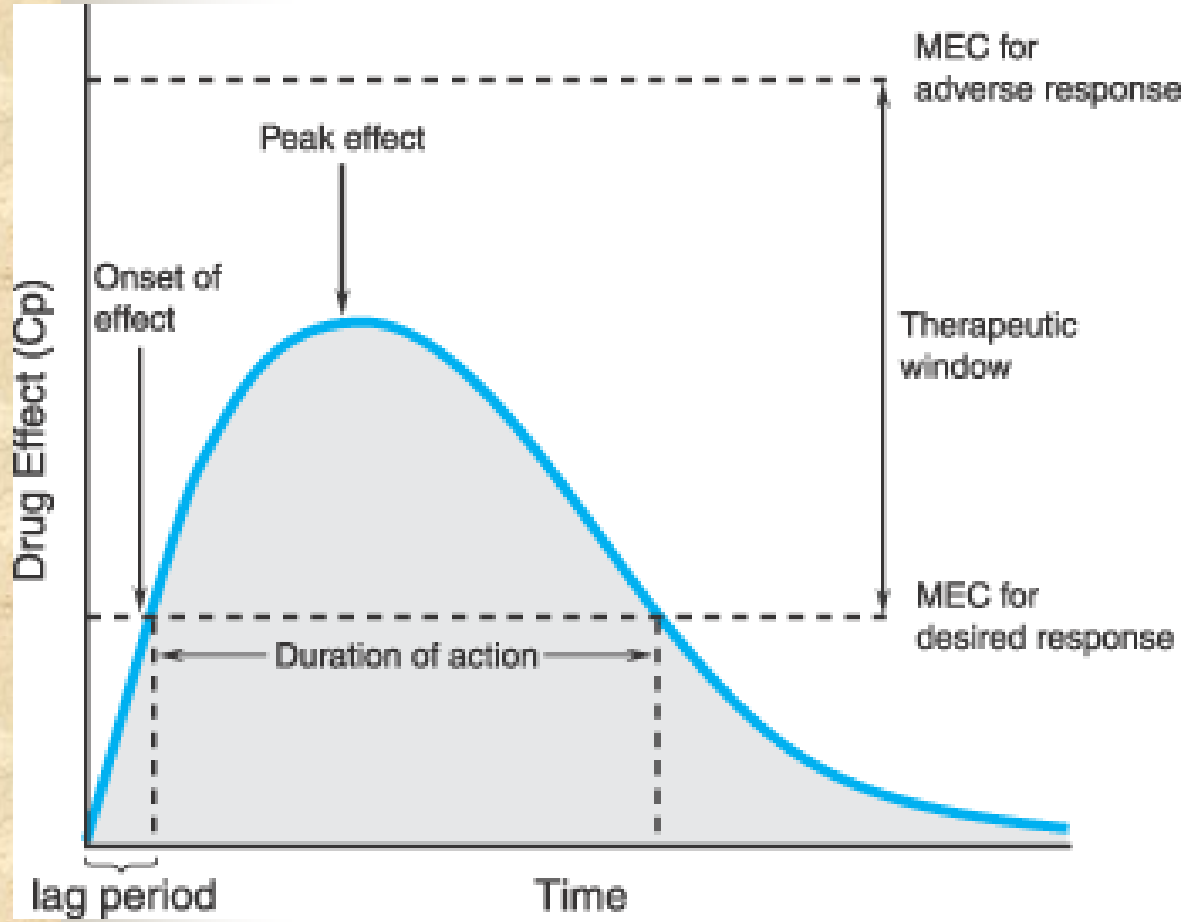
- **$t1/2 = \frac{0.693}{ke}$**
- **where 0.693 is the natural logarithm of 2 and ke is the elimination rate constant.**

The clearance (Cl) is the volume of fluid from which a drug is eliminated per unit of time.



Drug half life and clearance

$$CL = \text{Dose}/AUC$$



For a single dose of a drug ,For first order kinetics

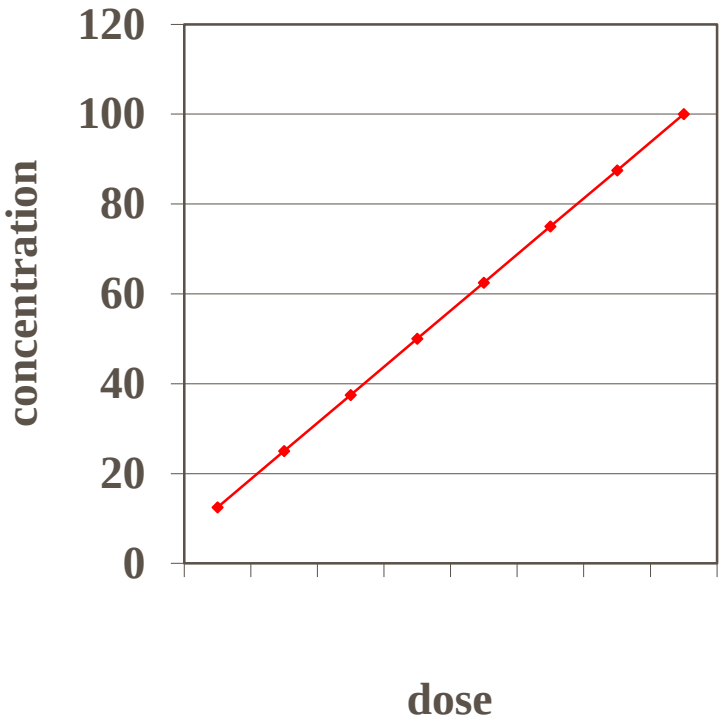
The order of reaction

First-order processes by which a **constant *fraction*** of drug is metabolized in unit time.

Zero-order processes by which a constant *amount* of drug is metabolized in unit time.

Linear Pharmacokinetics/1st order

- Linear = rate of elimination is proportional to amount of drug present
- Dosage increases result in proportional increase in plasma drug levels



t1/2 is constant

CL does not change

Zero-order process/(saturation kinetics)

As the amount of drug in the body rises, any metabolic reactions or processes that have limited capacity become saturated.

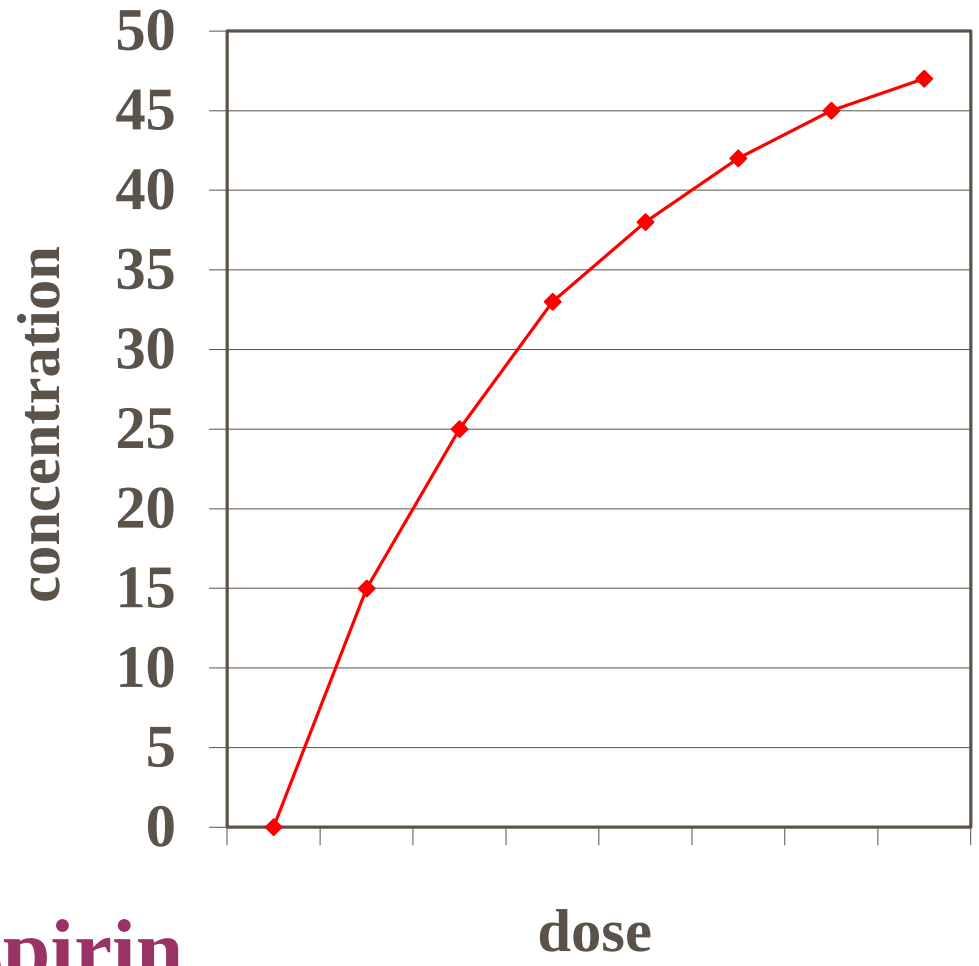
In other words : Rate of the process reaches a maximum amount at which it stays constant, e.g. due to limited activity of an enzyme

t1/2 increases with dose

CL Decreases as dose is increased

Nonlinear Pharmacokinetics

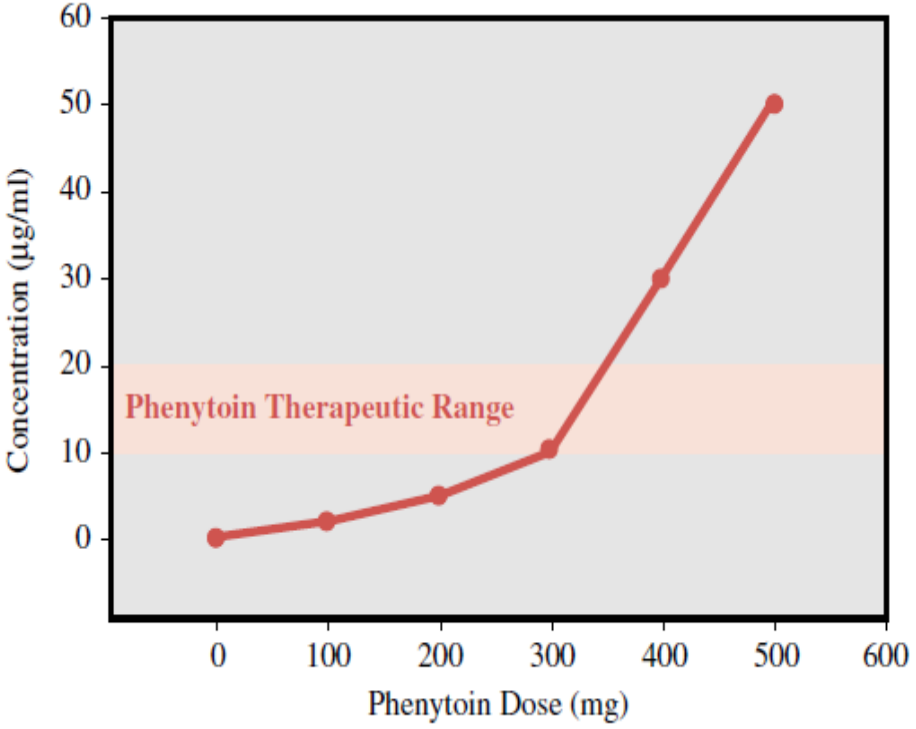
- **Nonlinear = rate of elimination is constant regardless of amount of drug present**
- **Dosage increases saturate metabolizing sites and result in non-proportional increase in drug levels**



Alcohol, Phenytoin, Aspirin

1st order to Zero Order Kinetics

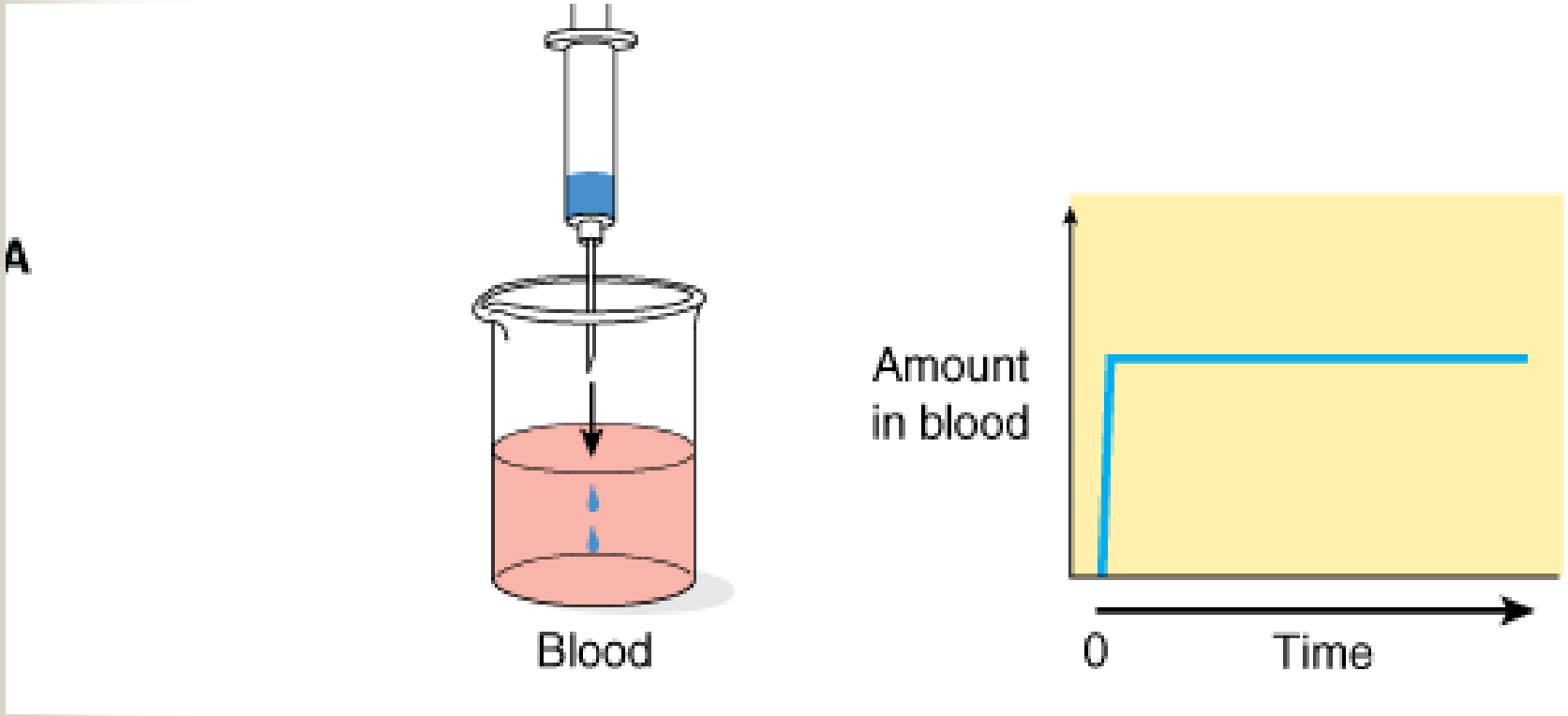
- **Follows linear kinetics until enzymes become saturated.**
- **Enzymes responsible for metabolism /elimination become saturated resulting ir non-proportional increase in drug levels.**



Differences between ist order and zero order kinetics

	First order	Zero order
1. Plasma t½, if dose is increased	Unchanged	Increased
2. Clearance if dose is increased	Unchanged	Reduced
3. Elimination, if dose is increased	Increased i.e. constant fraction of drug is eliminated in unit time (α plasma conc^{n})	No change i.e. constant amout is eliminated in unit time (independent of plasma conc^{n})
4. Dose increment	Same as initial dose	Must be smaller
5. Competitive inhibition	Rare	Common due to saturation of enzymes
6. Examples	Most of the drugs i.e. common	Phenytoin, alcohol i.e. rare

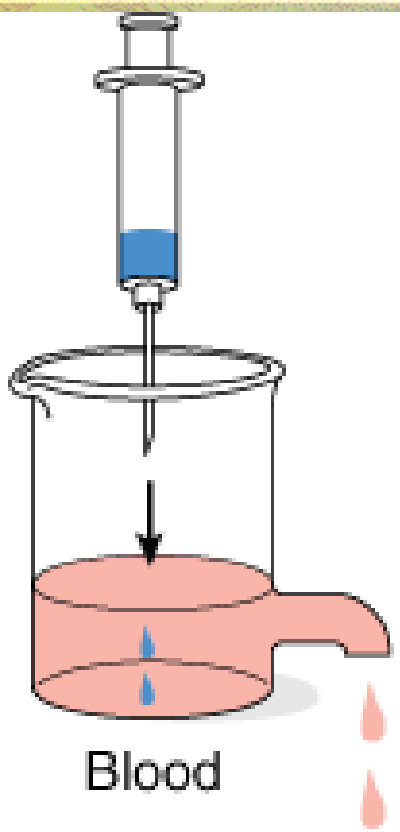
Models of drug distribution & Elimination

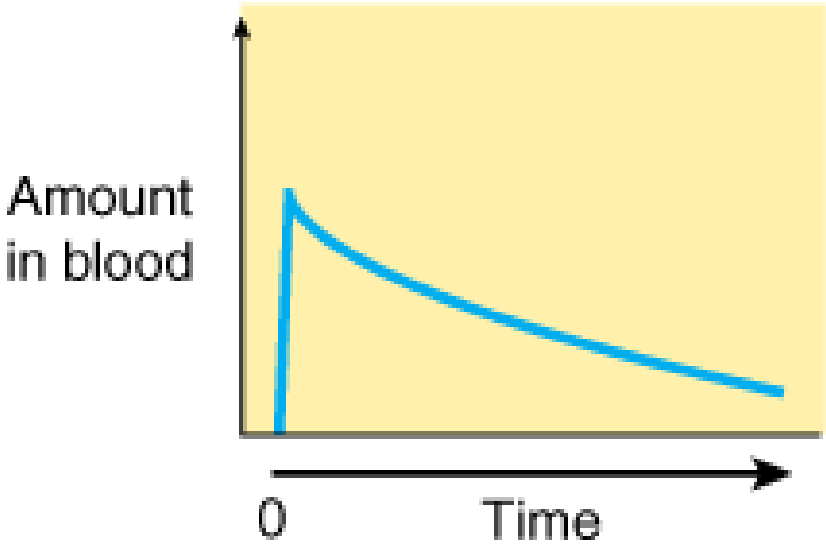


No route of elimination present

Steep rise followed by a plateau

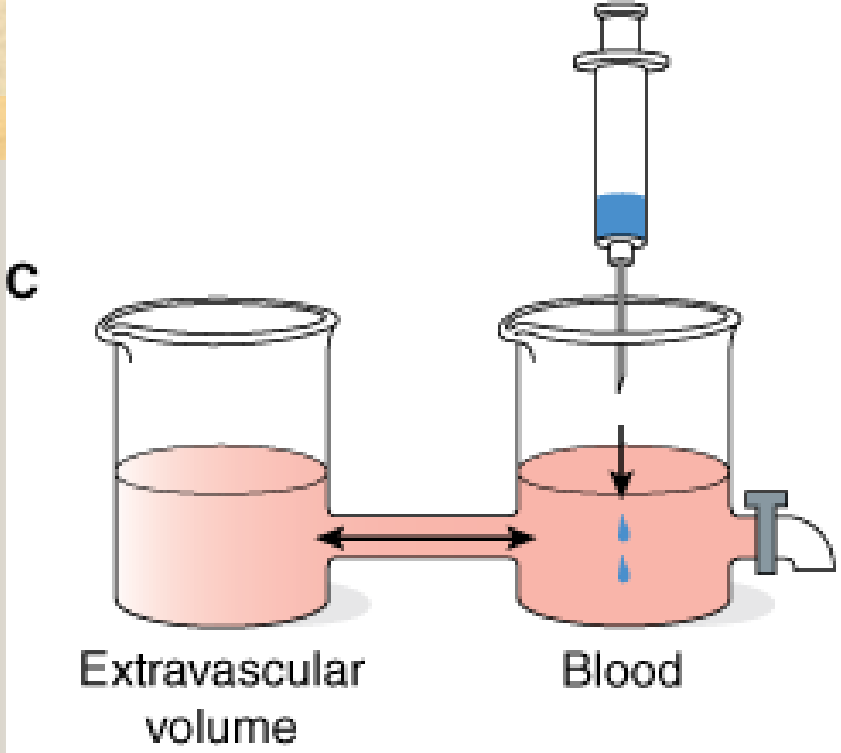
B

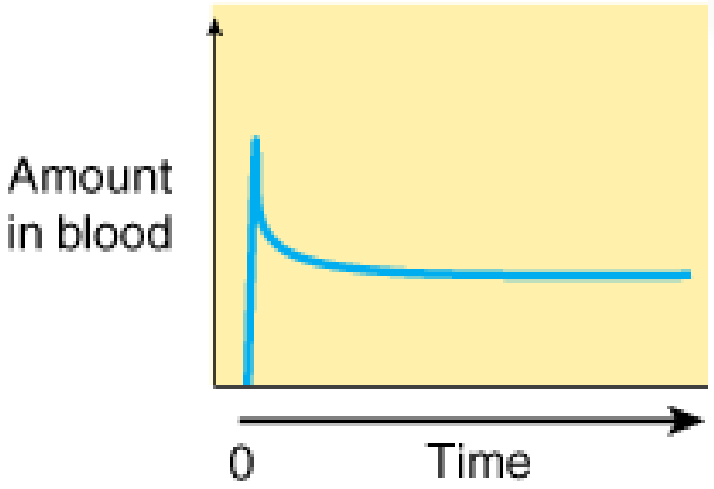




Route of elimination present

Slow decay after a sharp rise to maximum

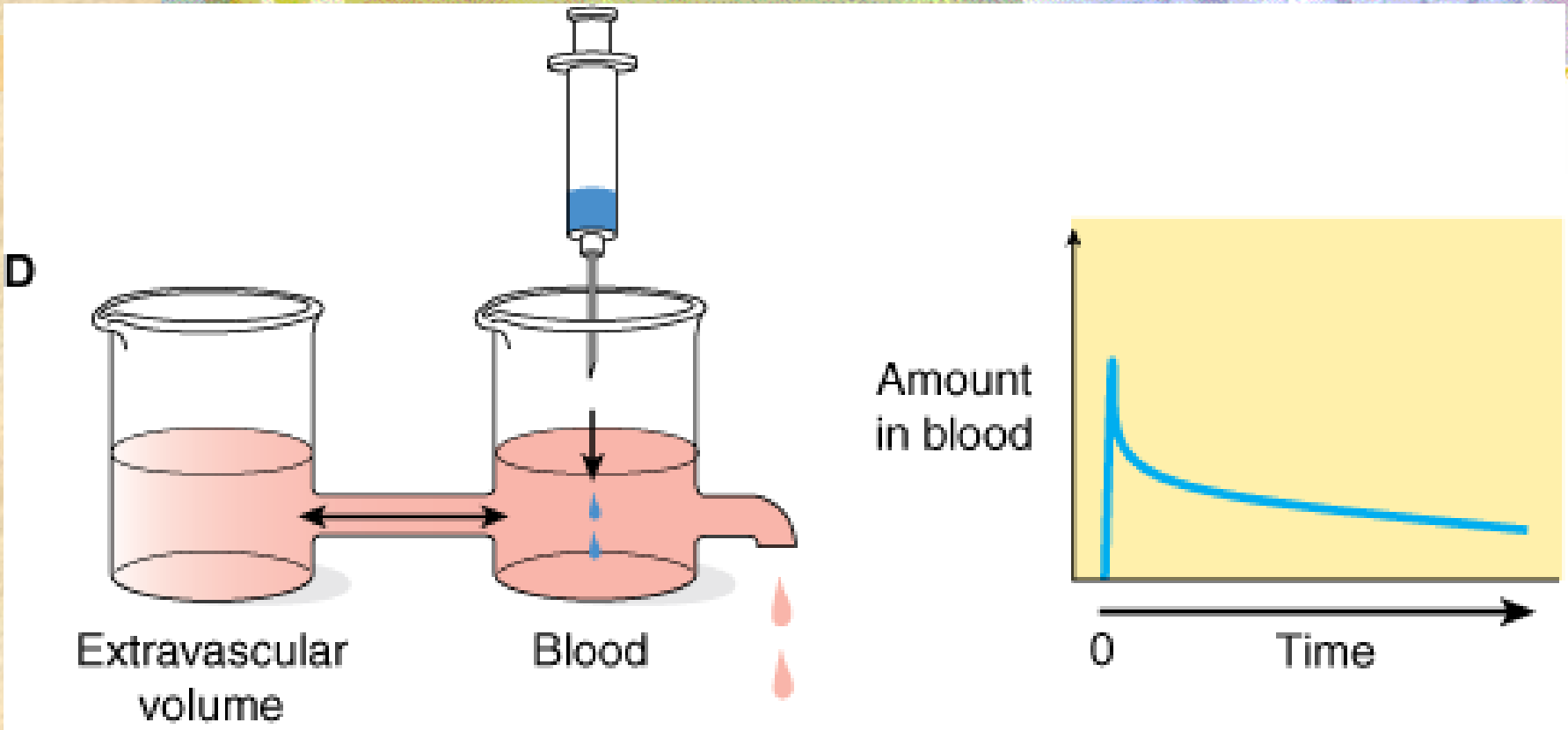




Compartment model

Drug equilibrates rapidly with the second compartment

Drug level declines in the blood to a new steady state



Realistic combination of elimination mechanisms and extravascular equilibration

Which of the following factors is TRUE concerning drug distribution?

(A) drug with a higher degree of plasma protein binding will have a lower volume of distribution.

(B) All drugs distribute to the same degree in all tissues.

(C) The binding of drugs to tissues has no relationship to the distribution of drug in the body.

(D) In general, lipophilic drugs distribute to a lesser extent than hydrophilic drugs.

Two types of dosing

Loading Dose

One or a few quickly repeated doses that may be given at the beginning of therapy with the aim of achieving the target concentration rapidly

Maintenance dose

This dose is one that is to be repeated at specified intervals after the attainment of target Cpss so as to maintain the same by balancing elimination

Loading Dose

The appropriate magnitude for the loading dose is

$$\text{Loading dose} = \text{target } C_p \cdot V_{ss} / F$$

may be desirable

- If the time required to attain steady state by the administration of drug at a constant rate (four elimination half-lives) is long relative to the temporal demands of the condition being treated.
- T1/2 of lidocaine is 1 -2 hrs. Arrhythmias encountered after MI may be life-threatening, , one cannot wait 4 - 8 hrs to achieve a therapeutic concentration of lidocaine by infusion of the drug at the rate required to attain Css .
- Hence, use of a loading dose of lidocaine in the CCU is a standard practice

may be desirable

- **Drugs to be given orally but have long T1/2**

Digoxin

Chloroquine

Long acting Sulphonamides

Doxycycline

disadvantage

1. Particularly sensitive individual may be exposed abruptly to a toxic concentration of a drug.
2. Moreover, if the drug involved has a long half-life, it will take a long time for the concentration to fall if the level achieved is excessive.

Drug XX

- Target plasma concentration 30 mg/L
- Volume of distribution 20 L
- Half life 4 hours

- Calculate the loading dose

Drug XX

- Target plasma concentration 30 mg/L
- Volume of distribution 20 L
- Half life 4 hours

- Calculate the loading dose

Loading dose = Vd x target plasma concentration

= 20 L x 30 mg/L

= 600 mg

Loading dose depends on volume of distribution

Maintenance dose rate depends on clearance

Maintenance Dose

In most clinical situations,(where there is no urgency) drugs are administered in a series of repetitive doses or as a continuous infusion to maintain a Css associated with the therapeutic window

Maintenance Dose

$$\text{Dosing rate} = \text{target } C_p \cdot CL/F$$

The application of pharmacokinetic principles in the treatment of individual patients in optimizing drug therapy is referred to as ***Clinical pharmacokinetics.***

THERAPEUTIC DRUG MONITORING

Plasma concentration may not be worth measuring.

Where dose can be titrated against a quickly and easily measured effect

- **blood pressure (antihypertensives)**
- **body weight (diuretics)**
- **INR (oral anticoagulants)**
- **blood sugar (hypoglycaemics)**

'hit and run drugs'

Plasma concentration has no correlation with effect. This is the case with drugs that act irreversibly .

Such drugs destroy or inactivate target tissue (enzyme, receptor) and restoration of effect occurs only after days or weeks, when resynthesis takes place,

- Some monoamine oxidase inhibitors,
- aspirin (on platelets),
- anticholinesterases
- anticancer drugs

Where is TDM Required?

1. As a guide to the effectiveness of therapy,

- plasma gentamicin and other antimicrobials against sensitive bacteria,
- plasma theophylline for asthma,
- blood cyclosporine to avoid transplant rejection

2. When the desired effect is suppression of infrequent sporadic events such as epileptic seizures or episodes of cardiac arrhythmia

3. To reduce the risk of adverse drug effects, e.g.otic damage with aminoglycoside antibiotics or adverse CNS effects of lithium, when therapeutic doses are close to toxic doses (low therapeutic index)

4.When lack of therapeutic effect and toxicity maybe difficult to distinguish. Digoxin is both a treatment for, and sometimes the cause of, cardiac supraventricular tachycardia; a plasma digoxin measurement will help to distinguish whether an arrhythmia is due to too little or too much digoxin

5. When there is no quick and reliable assessment of effect, individual variations are large e.g. lithium for mood disorder.

6.To check patient compliance on a drug regimen

7. When there is failure of therapeutic effect at a dose that is expected to be effective, e.g.anticonvulsants

8.To diagnose and treat drug overdose.

CHRONIC PHARMACOLOGY

Chronic diseases: chronic therapy

- Interference with self regulating systems: tolerance
- Feedback system
- Regulation of receptors
- Rebound phenomena
- Abrupt withdrawl
- Specific cell injury
- Metabolic changes
- Dangers of interaction with other drugs

A decrease in renal and liver function, as seen in the elderly, would prolong drug half-life, ____ plasma protein binding, and ____ volume of distribution.

a) Increase; Increase

b) Decrease; Decrease

c) Increase; Decrease

d) Decrease; Increase

Which of the following drug permeation mechanisms is used for peptides, amino acids, glucose, and other large or insoluble molecules?

a) Aqueous diffusion

b) Lipid diffusion

c) Carrier molecules

d) Endocytosis and exocytosis

A competitive antagonist affects the agonist _____ and a non-competitive antagonist affect the agonist _____.

a) Potency; Efficacy

b) Efficacy; Potency

c) Duration; Speed

d) Speed; Duration

Reasons for taking a drug history from patients

- Are a cause of disease. Abrupt Withdrawal can cause disease. benzodiazepines, antiepilepsy drugs.
- interact causing adverse effect/ therapeutic failure.
- Can give diagnostic clues, e.g. ampicillin causing rash in infectious mononucleosis
- Cause false results in clinical chemistry tests
- Assists choice of drugs in the future.
- Can leave residual effects after administration has ceased, e.g. chloroquine, amiodarone.
- Drugs available for independent patient self medication are increasing in range and importance.