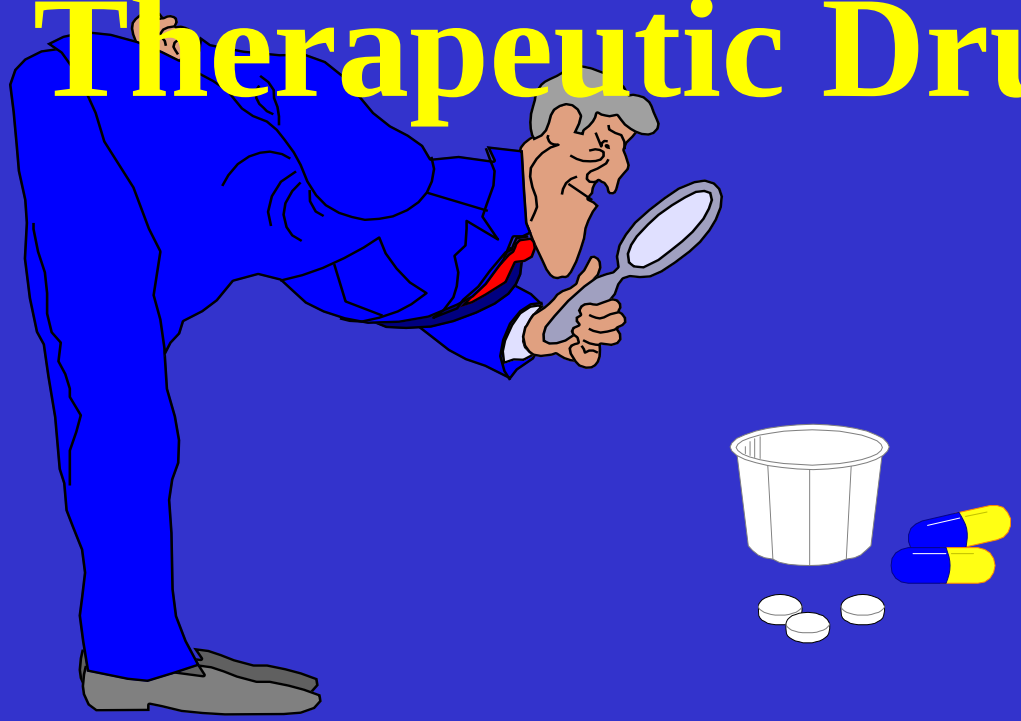
Clinical Pharmacokinetics and Therapeutic Drug Monitoring



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Outline

- Review of Concepts
  - Dose, Dosage, Clearance, Half-Life, Volume of Distribution
  - loading dose, maintenance dose and time to achieve steady state plasma concentration (Cpss)
- Therapeutic drug Monitoring
- Cases

- Discussion/Questions

What is clinical pharmacokinetics ?

- Study of the time course of a drug's movement through the body.
- Understanding of what the body does to (or with) the drug.
- Application of Therapeutic Drug Monitoring (TDM) and individualization of drug therapy.

WHY BE CONCERNED ABOUT CLINICAL PHARMACOKINETICS AND DOSAGE REGIMENS?

Pharmacokinetics and Dosage Regimens Determine:

- How much drug is in the body at any given time
- How long it takes to reach a constant level of drug in the body during chronic drug administration
- How long it takes for the body to rid itself of drug once intake of drug has stopped

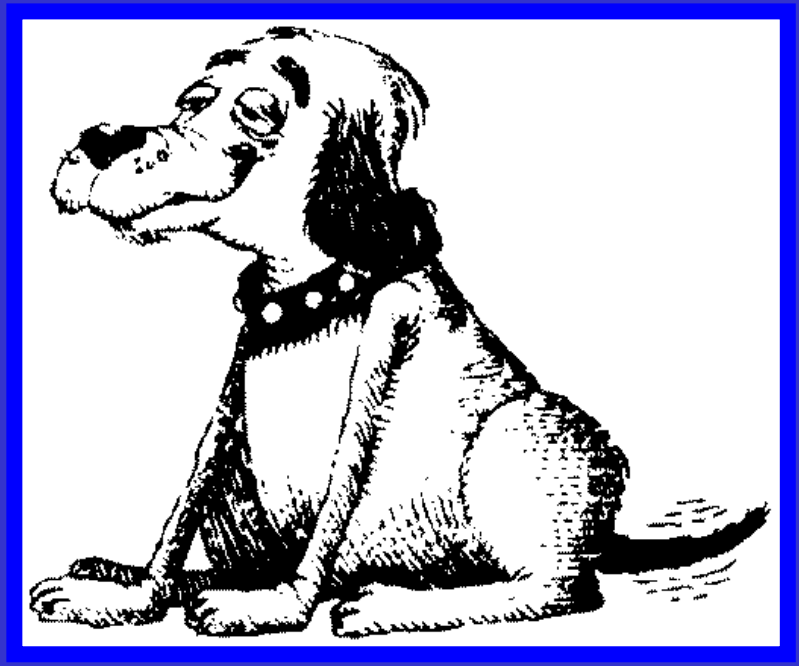
Basic Parameters

- In the next few slides the basic concepts and parameters will be described and explained.
- In pharmacokinetics the body is represented as a single or multiple compartments in to which the drug is distributed.
- Some of the parameters are therefore a little abstract as we know the body is much more complicated!

WARNING!!

THE STUDY OF PHARMACOKINETICS MAKES SOME PEOPLE ANXIOUS

BUT RELAX,



Pharmacokinetics Can Be Made FRIENDLY

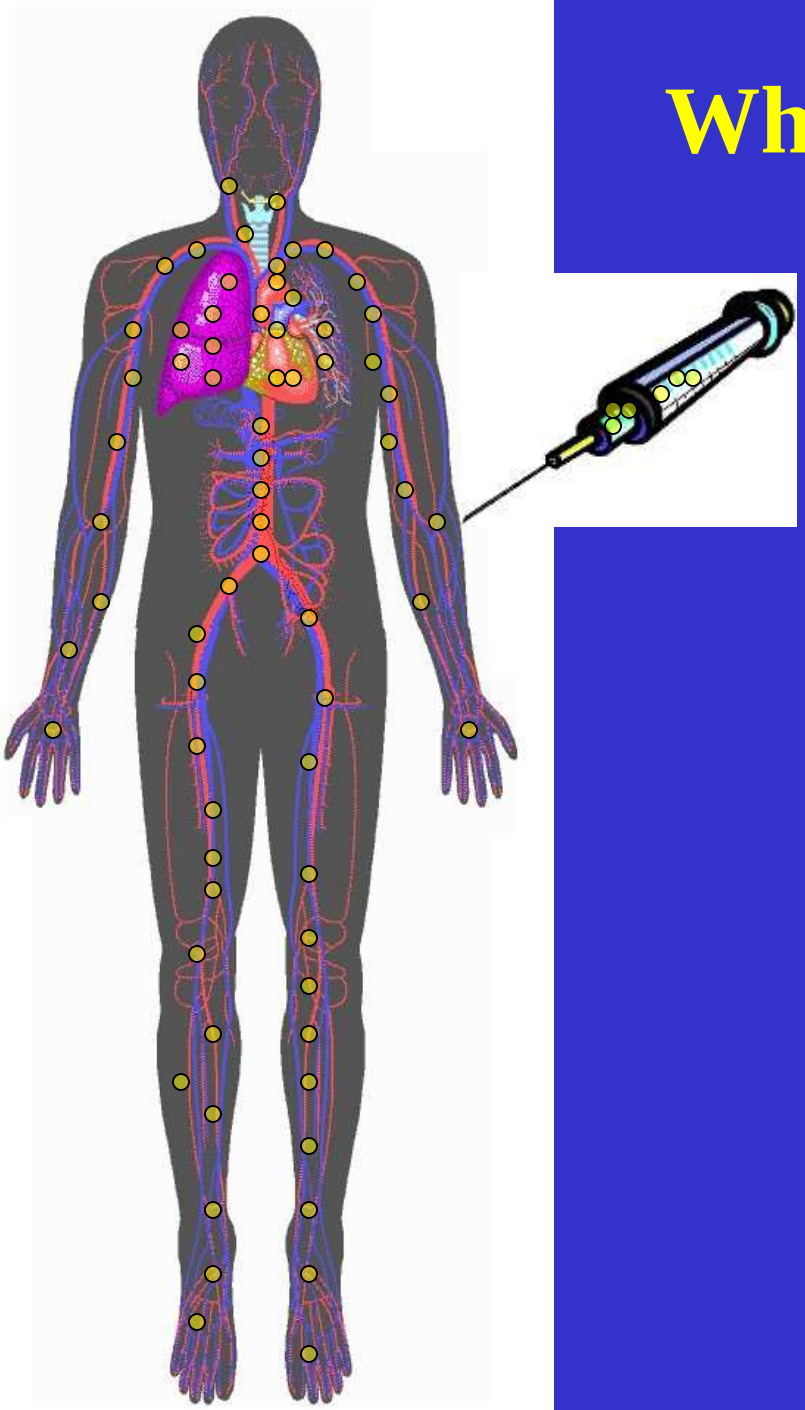
MAJOR CONCEPT #1

CONCEPT OF VOLUME OF DISTRIBUTION (V_D) OF DRUGS

Opening Question:

Mr. JR receives 500 mg of Levofloxacin by intravenous bolus (over 1 minute) and the serum concentration is measured immediately and found to be 5.0 mg/L.

What is the apparent volume of distribution?
What percent of drug is located in serum?



Where does the drug go?

Is it confined to blood

or

is it mostly in the blood

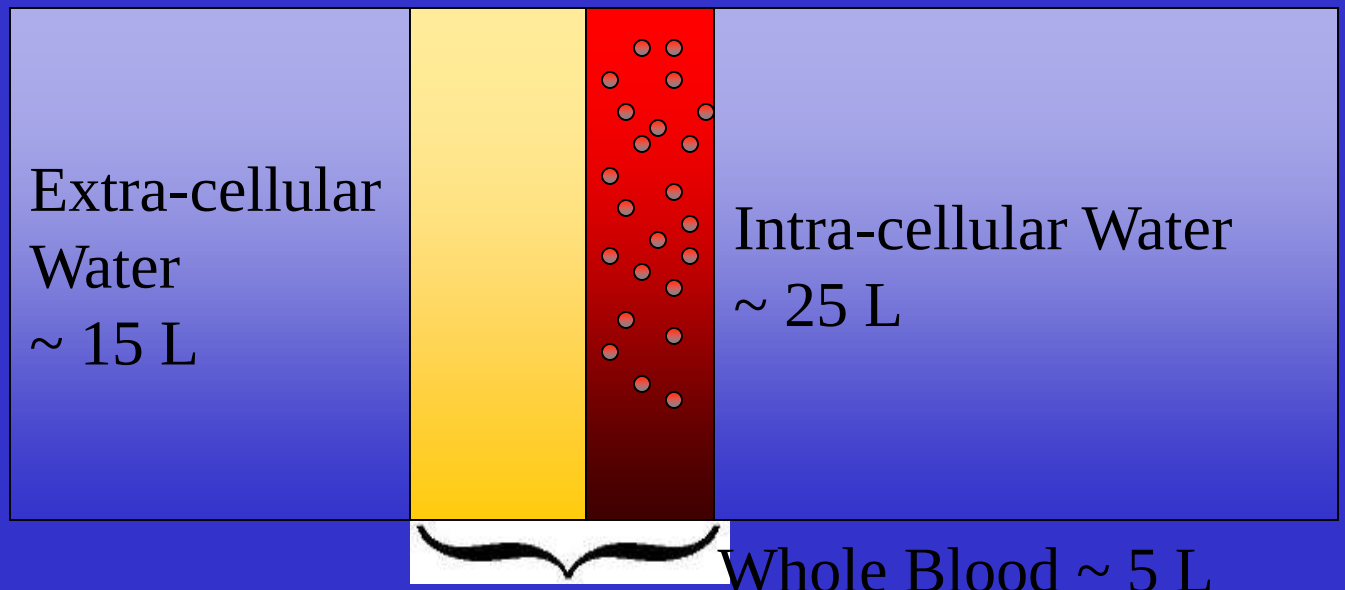
or

is it largely confined to tissues?

Barriers to Distribution

1. **GI Tract**
   - ⇨ **Intestinal wall prevents absorption**
     - **… not all drugs are absorbed**
2. **Vascular walls**
   - ⇨**limits "escape" from serum / blood**
3. **Cellular walls**
   - ⇨**limits "free" movement within the body**

Plasma or Serum ~ 55% ⬇ ⬇ **RBC's, ~ 45% of whole blood**

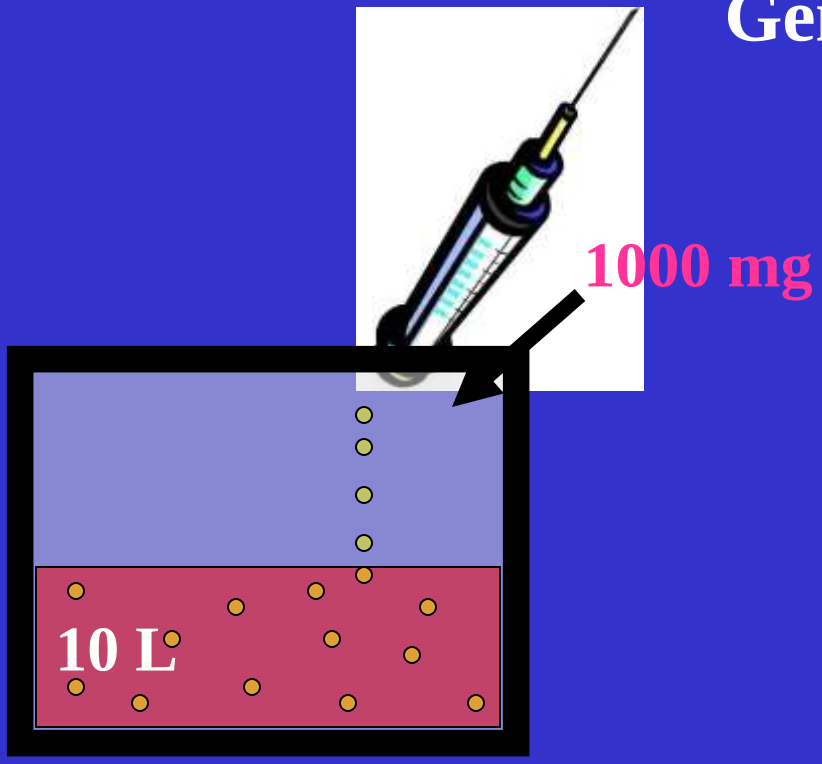


Body Water[1]

Tissue	% Water	%Weight	Water per 70 kg (L)
Skin	72	18	9.1
Muscle	75	42	22.1
Brain	75	2	1.1
Skelton	22	16	2.5
Adipose	10	~10	0.7
Other		12	6.5
Total		100	42

1. Skelton, H. Arch Int. Med 1927; 40: 140.

General Principles of Distribution

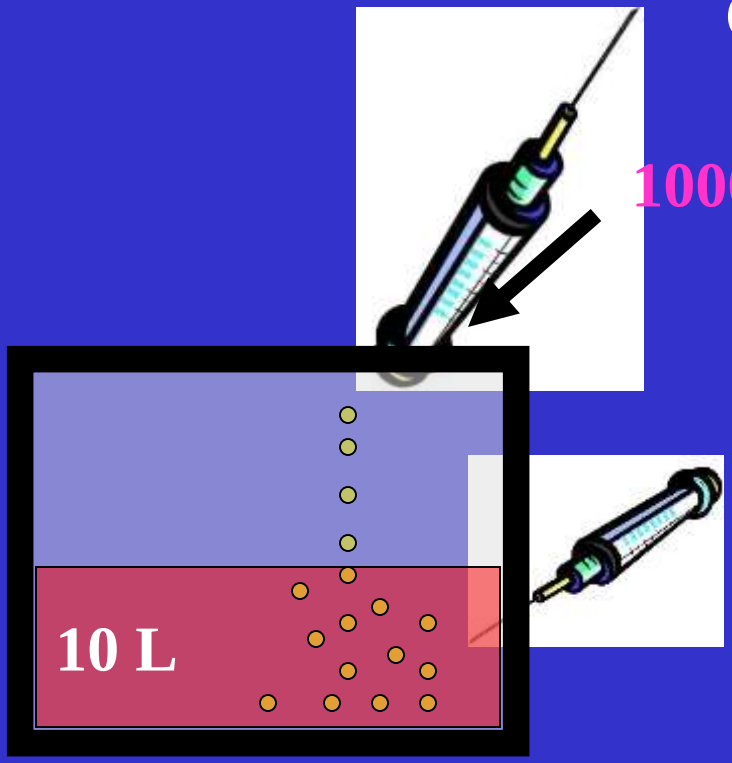


If you add 1000 mg of a drug
to 10 L of water,
what is the final concentration?

Following complete mixing
Concentration (C) = 1000 mg/ 10L
= 100 mg/L

C = Amount / volume
Volume = Amount / C

General Principles of Distribution



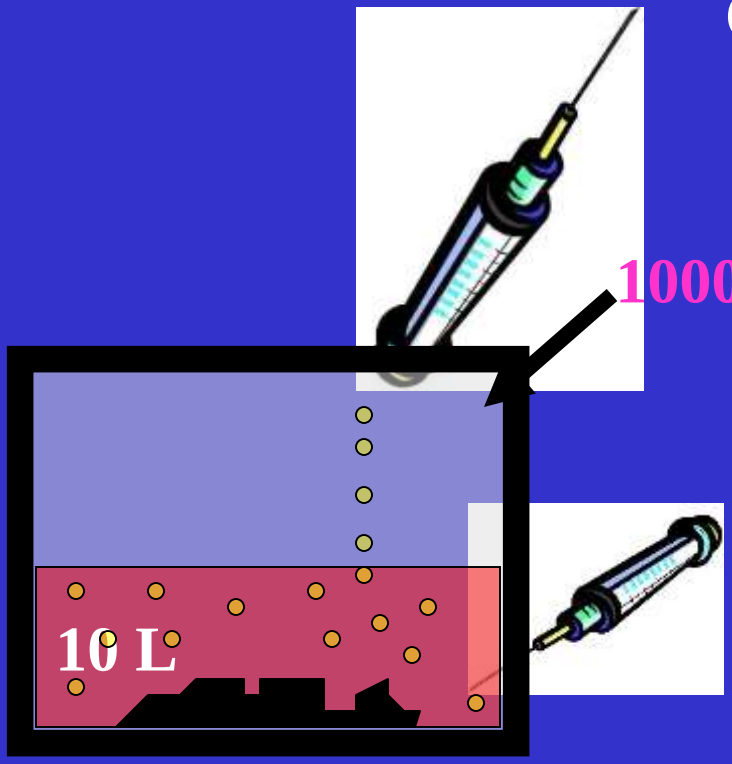
If you add 1000 mg of a drug
to 10 L of water,
what is the final concentration?

C = Amount / volume
Volume = Amount / C

Could the concentration change
as a function of time after addition?

If you knew that you had added
1000 mg of drug and then drew a sample
from a corner of the vessel before
complete mixing occurred,
what would you conclude?

General Principles of Distribution



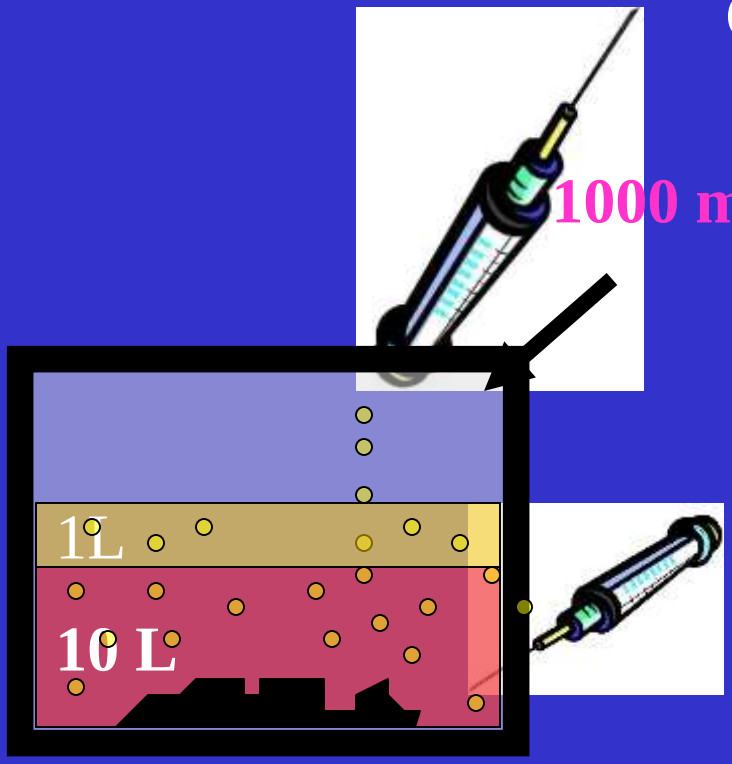
Charcoal

Again you add 1000 mg of a drug to 10 L of water, but now there is some charcoal in the water that may bind the drug.
The observed concentration after complete mixing is 50 mg/L

Since
Volume = Amount / C
then the
apparent volume of distribution is:
= 1000 mg/50 mg/L
= 20L …???

BUT The **real** volume is 10L

General Principles of Distribution



Charcoal

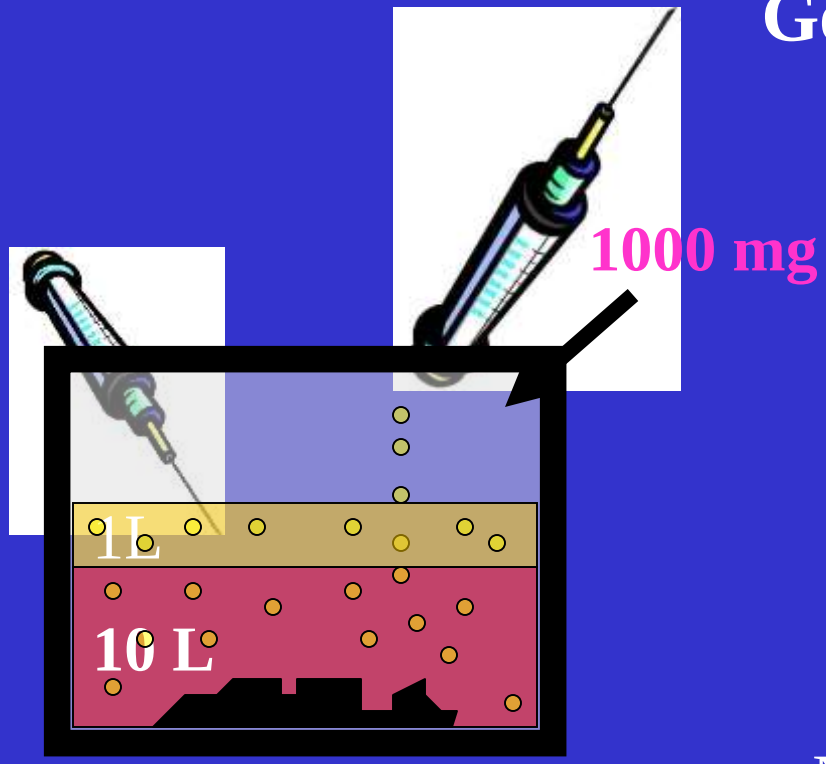
Again you add 1000 mg of a drug but this time in addition to the charcoal and 10L of water there is 1 L of oil.

You measure the concentration in the oil (150 mg/L) and in the water (25 mg/L).

Now calculate the volume:

Based on the concentration in the water
Volume = Amount / C
then the
apparent volume of distribution is:
= 1000 mg/25 mg/L
= 40L

General Principles of Distribution



Charcoal

Again you add 1000 mg of a drug but this time in addition to the charcoal and 10L of water there is 1 L of oil.

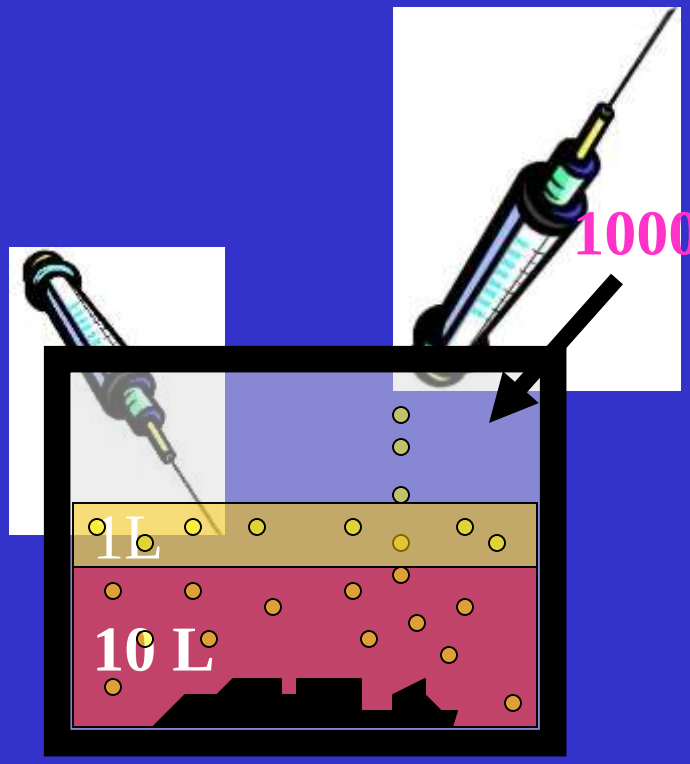
You measure the concentration in the oil (150 mg/L) and in the water (25 mg/L).

Now calculate the volume:

Based on the concentration in the oil
Volume = Amount / C
then the
apparent volume of distribution is:
= 1000 mg/150 mg/L
= 6.66 L

General Principles of Distribution

Mass Balance



Charcoal

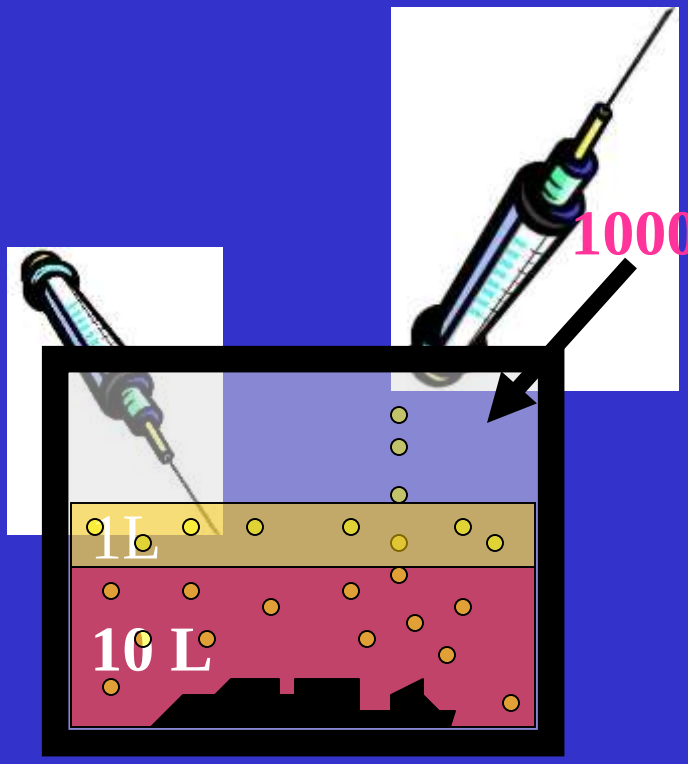
Water:
Concentration 25 mg/L
True Volume: 10L
Amount of Drug = 250 mg
Apparent Volume = 40L

Oil:
Concentration 150 mg/L
True Volume: 1L
Amount of Drug = 150 mg
Apparent Volume = 6.66 L

Charcoal: (therefore)

Amount = 600 mg

General Principles of Distribution



Charcoal

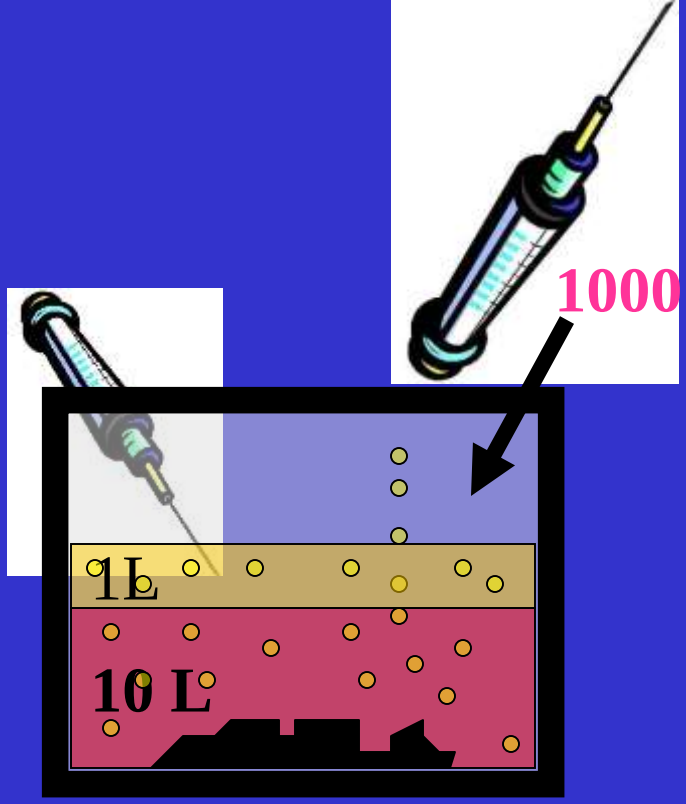
Conclusions

1. **The calculated Apparent Volume depends on the fluid being sampled.**

2. **The volume depends on the host, and the physical/chemical properties of the drug or metabolite**

3. **The calculated Apparent Volume rarely reflects a real physiologic volume.**

General Principles of Distribution



Charcoal

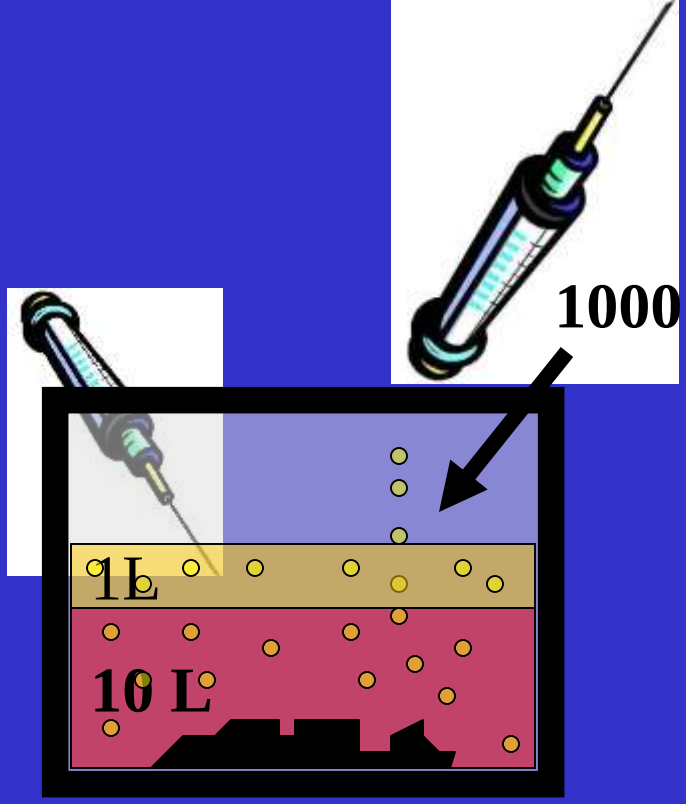
…so what is the Apparent Volume of Distribution?

it is the volume of *sampled* fluid need to *account* for the total amount of drug in the body … at distribution equilibrium … (following complete mixing).

The volume is not associated with a particular space or anatomical area or tissue.

It is a proportionality constant relating concentration and amount in the body.

General Principles of Distribution



…so, if it is not real, how useful is it?

Uses:

- **It tells us how much drug must be added to the body so as to achieve a specified concentration in the sampled fluid.**
- **In a general way it tells us where the drug is stored in the body or where it might be found.**

L/70 kg

50,000 — Quinacrine

20,000 — Chloroquine

10,000

5,000

1,000 — Nortriptyline, Digoxin

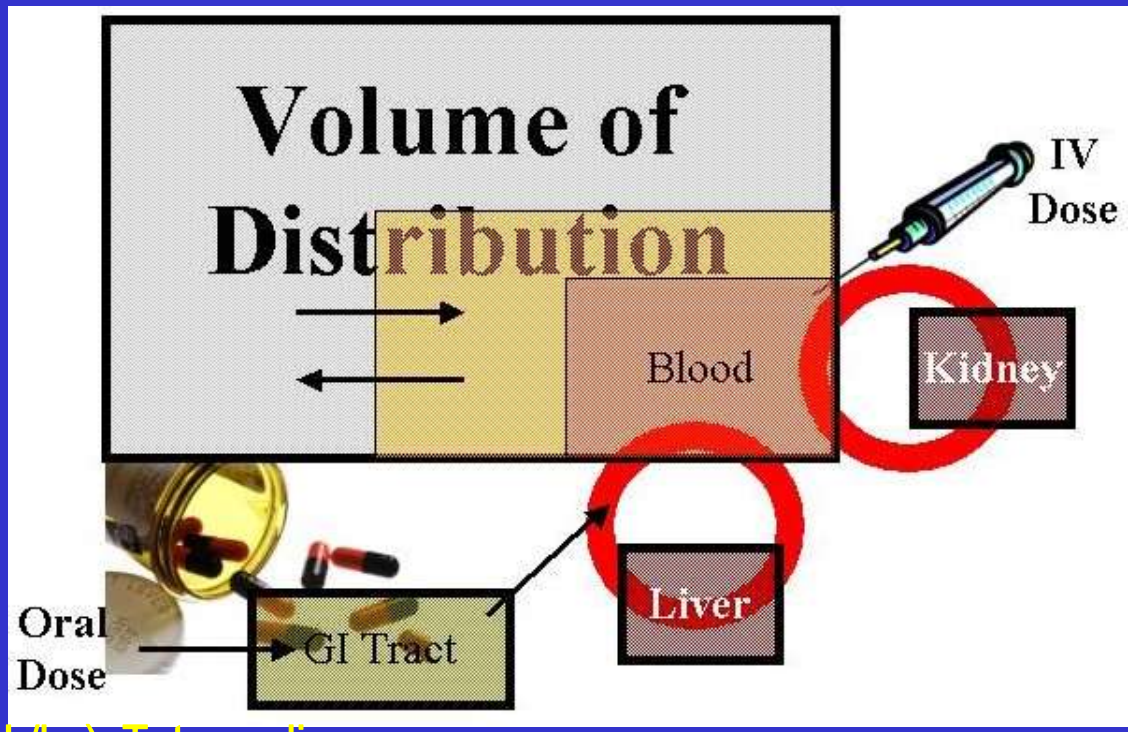
500

100 — Propranolol, Quinidine, Quinolones (1- 2 L/kg), Tetracycline, Phenobarbital

50 — Phenytoin, Theophylline (0.45 L/kg), Aminoglycodises (0.25 L/kg), ASA

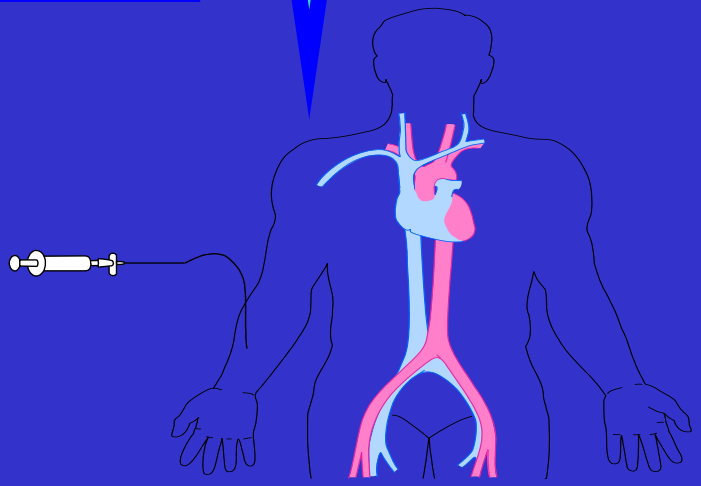
10 — Warfarin

5



CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: DEFINITION OF V_D

Dose Body with DRUG



Obtain Plasma Sample

Assay for $[C]_P$

Calculate Volume (This volume is called V_D)

By DEFINITION: $V_D = D/[C]_P$

(where D is amount of drug in body and $[C]_P$ is concentration of drug in plasma)

Equations

Conc = Dose / V

V = Dose/Conc

Answers.

1. **What is the Volume of distribution of levo?**
   Dose =
   Initial [ ] =
   Levo Volume: =

2. **Proportion in Serum: =**

Equations

Conc = Dose / V

V = Dose/Conc

Answers.

1. **What is the Volume of distribution of levo?**
   Dose = 500 mg
   Initial [ ] = 5 μg/mL (mg/L)
   Levo Volume: = Dose / Conc
   = 500 / 5
   = 100 L

2. **Proportion in Serum: =**

Equations

Conc = Dose / V

V = Dose/Conc

Answers.

2. Proportion in Serum:

Weight :	80 kg
Levo Volume:	500 mg/ 5 mg/L
Blood Volume:	8% of body weight
Hematocrit:	0.45

Blood volume: =

Serum (55%): =

Levo Volume: =

Proportion in Serum: =

Equations

Conc = Dose / V

V = Dose/Conc

Answers.

2. Proportion in Serum:

Weight : 80 kg
Levo Volume: 500 mg/ 5 mg/L
Blood Volume: 8% of body weight
Hematocrit: 0.45

Blood volume: = 0.08 x 80 kg = 6.4 L
Serum (55%): =6.4 x 0.55 = 3.5 L
Levo Volume: = 500 mg/ 5 mg/L = 100 L

Proportion in Serum: =

Equations

Conc = Dose / V

V = Dose/Conc

Answers.

2. Proportion in Serum:

Weight : 80 kg
Levo Volume: 500 mg/ 5 mg/L
Blood Volume: 8% of body weight
Hematocrit: 0.45

Blood volume: = 0.8 x 80 kg = 6.4 L
Serum (55%): =6.4 x 0.55 = 3.5 L
Levo Volume: = 500 mg/ 5 mg/L = 100 L

Proportion in Serum: = 3.5 L/100.0 L
= 3.5%

- how to make sense of the previous lesson

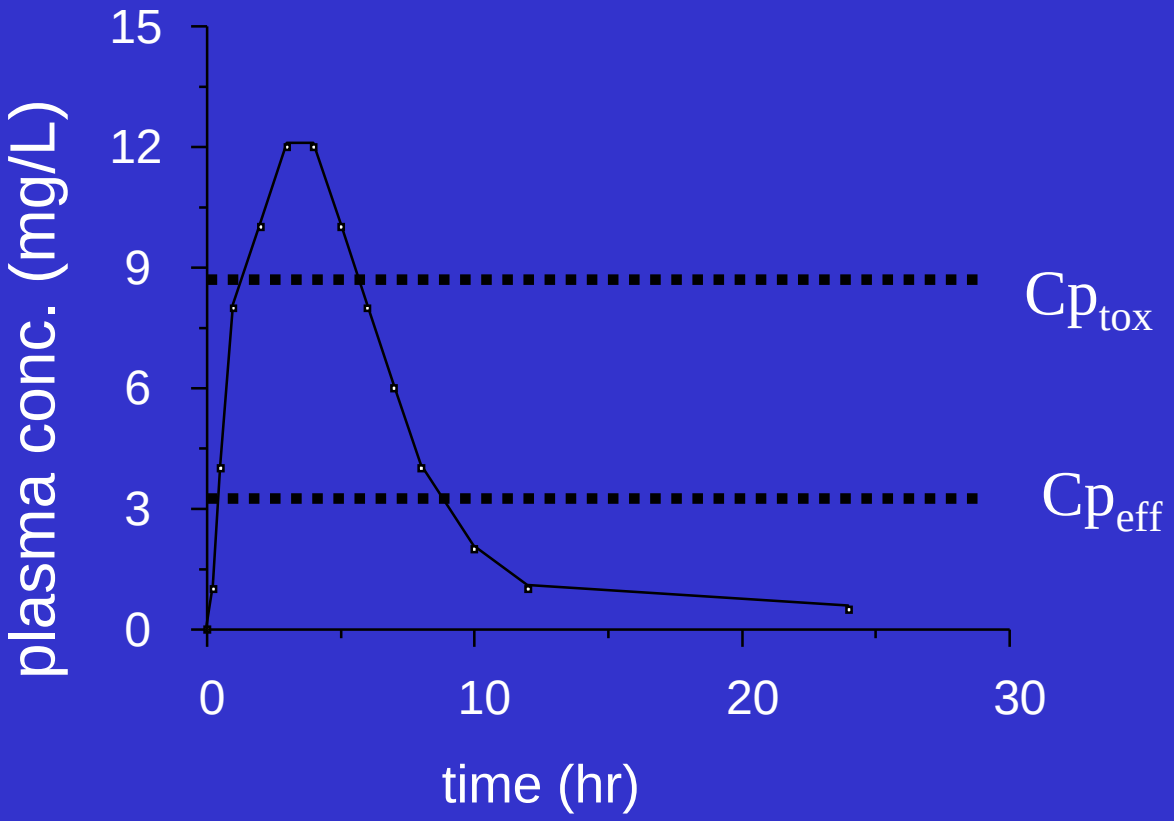
or

- why do I have to learn this stuff?

drug dosing calculations

Concepts: *target plasma concentration*

therapeutic window



- Therapeutic window: Difference between the minimum effective concentrations (MEC) required for a desired response and one that produces an adverse effect.
- For some drugs it is small (only two- to three-fold difference)
- E.g. digoxin, theophylline, lidocaine, aminoglycosides, cyclosporine, anticonvulsants.

Loading Dose (DL) = a *dose* of drug sufficient to produce a plasma concentration of drug that would fall within the therapeutic window after only one or very few doses over a very short interval.

Information needed to calculate a DL

- Volume of distribution, usually in L or L/Kg - from literature -
- Desired concentration - from literature

CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: INTRODUCTION TO V_D

By DEFINITION: $V_D = D/[C]_P$

Rearranging: $D = V_D \times [C]_P$

Suppose you want a certain desirable $[C]_p$, call it $[C]_{P(target)}$

Substituting $[C]_{P(target)}$ for $[C]_P$: $D_{target} = V_D \times [C]_{P(target)}$

Where D_{target} is the amount of drug in body required to achieve a given $[C]_{P(target)}$

CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: INTRODUCTION TO V_D

If patient has no drug in body to begin with, then can administer an amount (called "Loading Dose") to achieve a given D_{target} and $[C]_{P(target)}$

For the *oral* loading dose we have to take the *fraction bioavailable* into account (0-1)

$$L = C_p . V_d / F$$

Loading dose

- LD = target C_p V_d/ F

e.g. lidocaine t1/2 = 1-2 h

Post MI arrhythmias – life threatening – can't wait 4-8 h – LD is used

- Another example: Digoxin for heart failure
- If only maintenance dose is given it takes 10 days t1/2 = 61 h

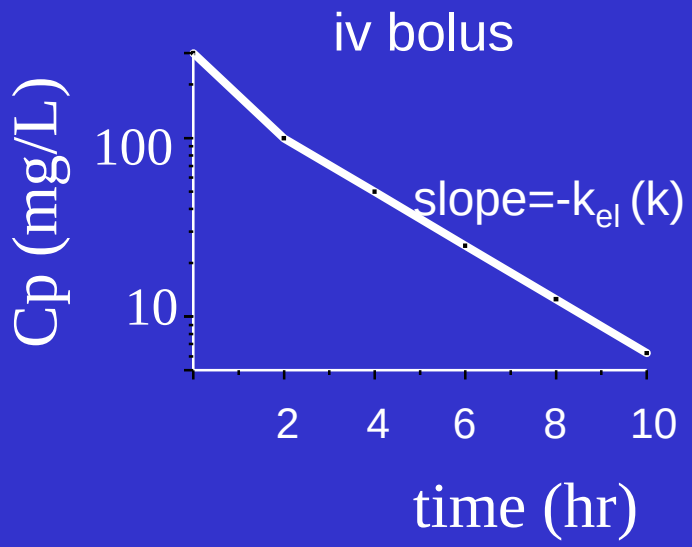
DL = 1.5 ng/ml x 580 / 0.7 = 1243 micg ~ 1 mg

Can be given iv divided – 0.5 mg, aft 6-8 h 0.25 mg, aft 6h 0.125 mg and then 0.125 mg (to avoid over digitalization and toxicity)

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

time interval after which the concentration is half that at the beginning of the time interval

has real-life meaning ***only*** in first-order kinetics!



half life ($t^{1/}2$)

the *time* taken for the C_p to fall by half

$t^{1/}2 = 0.693/k$

where k is the rate constant (in hrs^{-1})

most drugs follow first order kinetics:

rate of change of drug in the body = $-k_{el}$.Amount of Drug in the body

where k_{el} (k) is the *rate constant* of elimination

a few drugs (e.g. ethanol) follow 0 order kinetics:

rate of change = k

a few drugs (e.g. phenytoin) follow 1st order kinetics:

at low conc. and 0 order at high conc.

zero-order

constant ***amount*** of drug eliminated per unit of time

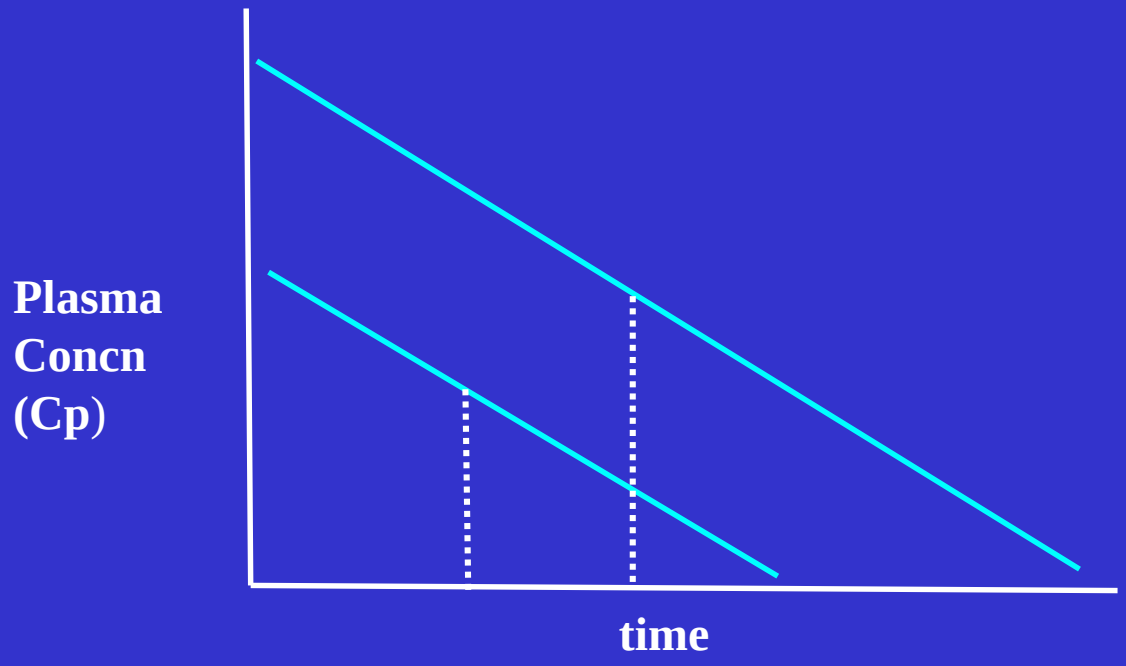
elimination rate constant has units of weight/time:

K_e = 50 mg/h, for example

typical drug: ethanol

Zero order elimination

Half life varies with concentration



Designing a Dosage Regimen

Capacity-Limited Metabolism
(Also called "Zero Order Kinetics")

- An infrequent, but important phenomenon

- Clearance is not constant with respect to C_P because metabolizing enzymes are saturated at "therapeutic concentrations"

- Rate of drug elimination is fixed and cannot use clearance to calculate dosage regimen

- For such drugs, daily dose should not exceed fixed rate of elimination

Designing a Dosage Regimen

Ethanol is Eliminated by "Zero Order Kinetics"

- For average adult, rate of metabolism is 10 g/hr
- 45 ml of whiskey contains 14 g of ethanol
- If drink 45 ml of whiskey every hr, will accumulate 4 g ethanol/hr and develop coma in 48 hr
- However, can drink 30 ml whiskey (9 g ethanol) every hr with impunity

first-order

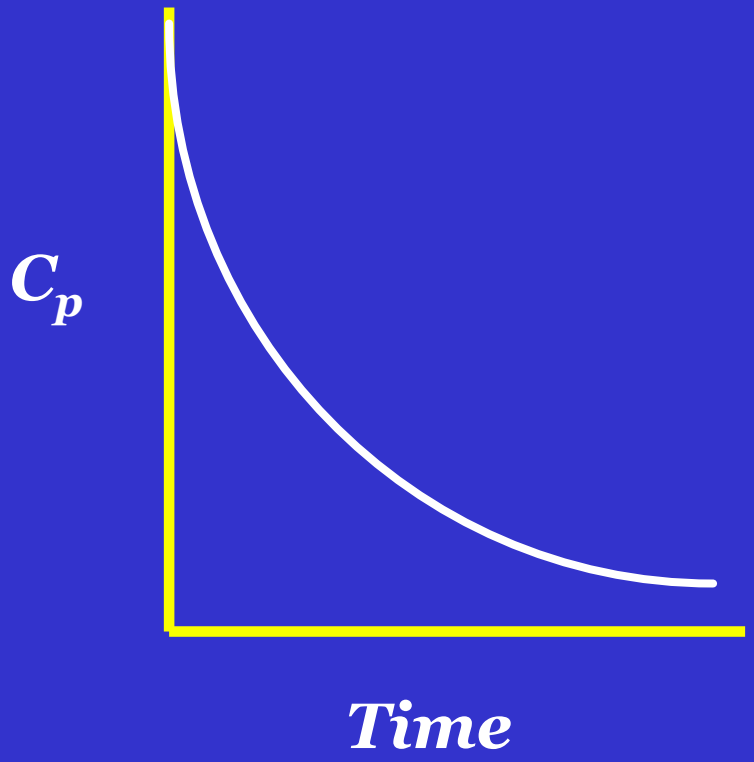
constant ***fraction or percent*** of drug eliminated per unit of time

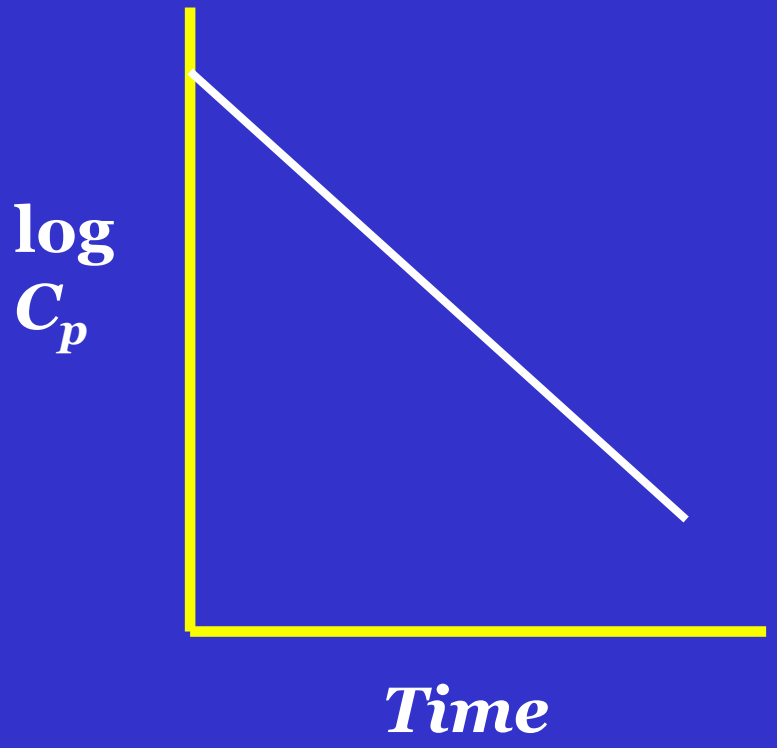
elimination rate constant has units of weight/time:

K_e = 0.25/h or 0.25 h^{-1} , for example.

typical drug: theophylline, most other drugs

first-order elimination following single IV bolus dose





Special properties of first-order kinetics

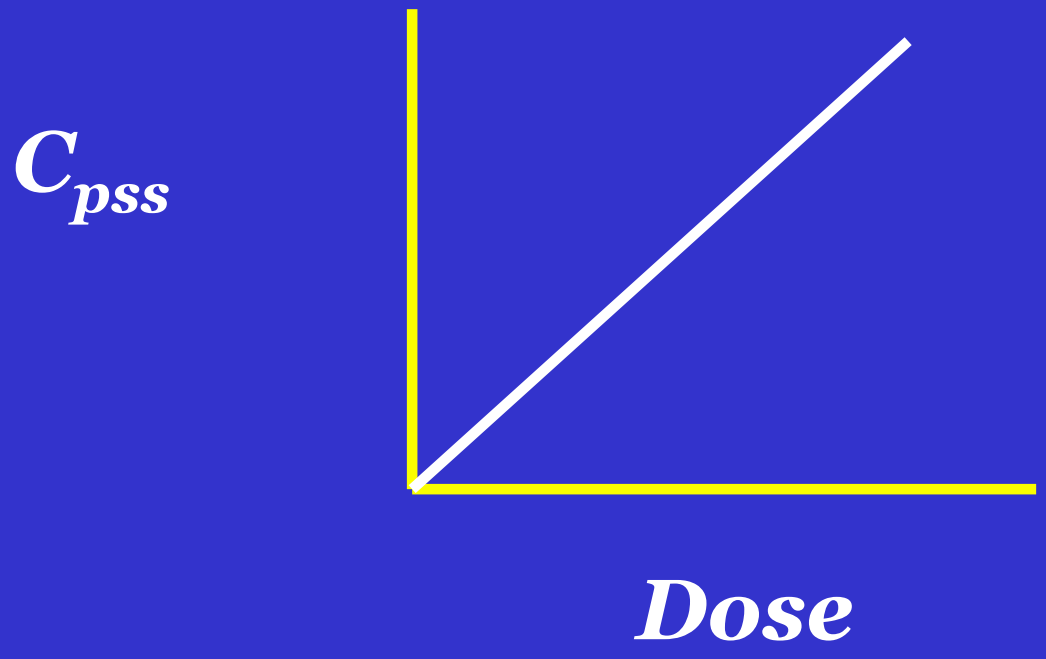
C_p is 90% of the way to new steady-state level after change of dose in 3 $t_{1/2}$,
96% in 5 $t_{1/2}$

this is true regardless of
- initial concentration
- final concentration
- dose

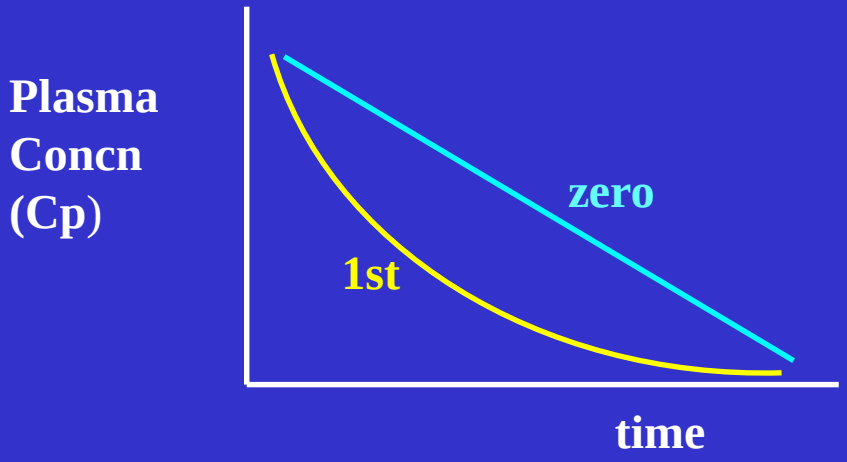
*but **only** for first-order kinetics !*

First-order is also known as *linear kinetics*:

there is a linear relationship between dose and steady-state concentration



Revision of pharmacokinetic terms



1st order elimination

rate of elimination depends on plasma concentration

$C = C_0 e^{-kt}$ (k= rate constant of elimination)

Half life ($t_{1/2}$)

time for plasma concentration to fall by 50%

Zero order elimination

rate of elimination is constant and independent of plasma concentration

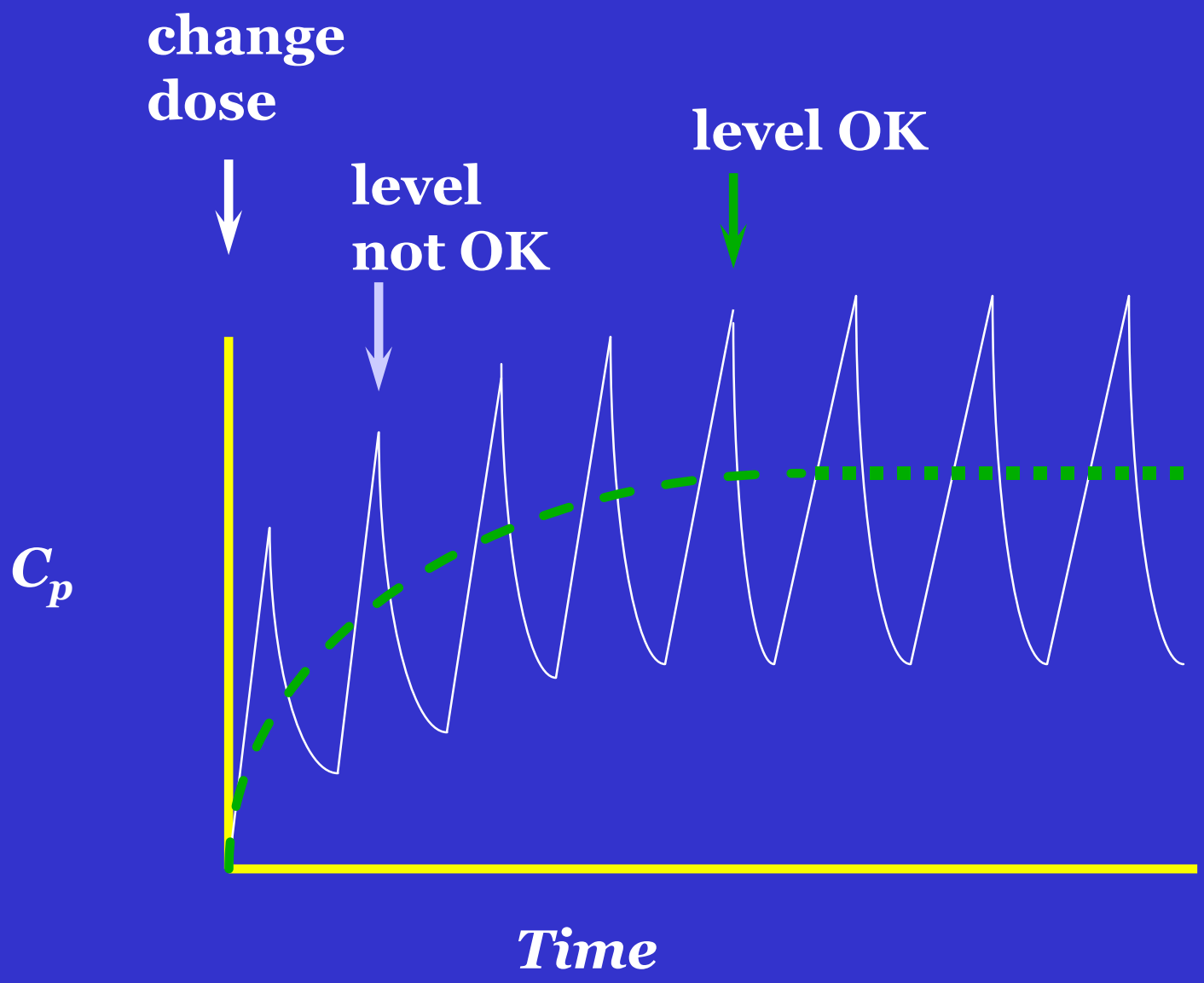
A patient's peak serum phenobarbital level is 12.0 ug/mL at steady state on a dose of 60 mg/day. If we want a level of 20 ug/mL, what new dose should we order if we know that phenobarbital has linear kinetics?

$$\frac{12.0 \text{ ug/mL}}{20 \text{ ug/mL}} = \frac{60 \text{ mg/day}}{X}$$

$$X = 100 \text{ mg/day}$$

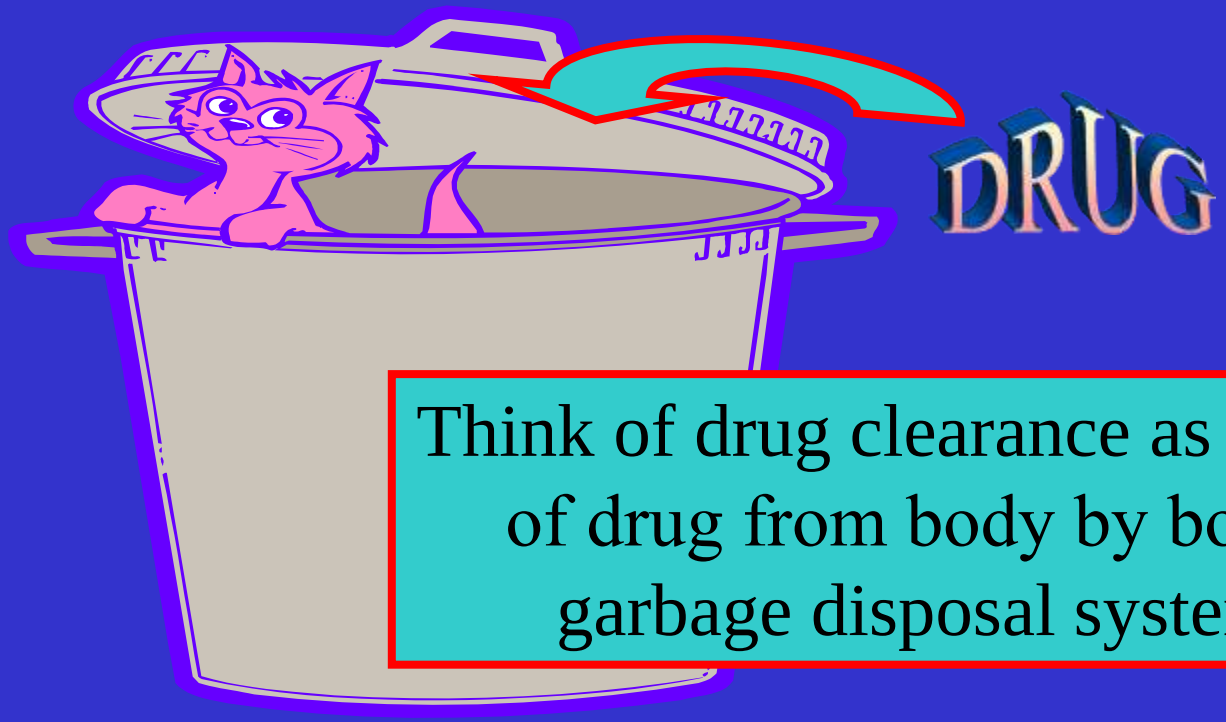
If we change the dose to 90 mg/day, when can we get another plasma level to check our calculations?

In adults, the half-life averages 100 hours. In 3 half-lives (300 h, or 12.5 days) we will be 90% of the way from 12.2 ug/mL to the new steady-state level (we hope it's 20 ug/mL). This is close enough to get a level. Reschedule the patient to come back in 2 weeks for this level.


change
dose
level
not OK
level OK
C_p
Time

MAJOR CONCEPT #2

CONCEPT OF DRUG CLEARANCE (Cl)



Think of drug clearance as removal of drug from body by body's garbage disposal systems!

clearance

defined as the volume of blood from which drug is irreversibly removed per unit time.

ml/min

can calculate: UV/P = excretion rate/plasma concentration

at *steady state*: rate of excretion = rate in (the dose, M)

M = rate of excretion = Cl_{drug}. Cp

Clearance

- **Clearance is the VOLUME of plasma that can be freed of drug per unit time**, i.e., gives estimate of function of organs of elimination and rate of removal of drug from the body
- $$CL = \frac{\text{Rate of Elimination (mg/hr)}}{\text{Concentration (mg/L)}} = \text{vol/time}$$

CONCEPT OF DRUG CLEARANCE (Cl): DEFINITION OF Cl

By Definition:

$$Cl = \frac{\text{Rate of Drug Elimination}}{[C]_P}$$

Units of Cl:

$$\frac{\text{Amount/Time}}{\text{Amount/Volume}} = \frac{\text{Volume}}{\text{Time}}$$

CONCEPT OF DRUG CLEARANCE: DEFINITION OF Cl

Example:

Rate of Drug Elimination = 10 mg/hr

$[D]_P = 4$ mg/L

$$Cl = \frac{10 \text{ mg/hr}}{4 \text{ mg/L}} = 2.5 \text{ L/hr}$$

the maintenance dose

- **Maintenance Dose (DM)** = The dose needed to maintain the concentration within the therapeutic window when given repeatedly at a constant interval

$$M = Cl_{drug}.Cp$$

for oral dosing

$$M = Cl_{drug}.Cp/F$$

Why clearance and Vd?

- clearance and volume of distribution are independent variables.
- they determine the half-life (Cl = k*Vd)

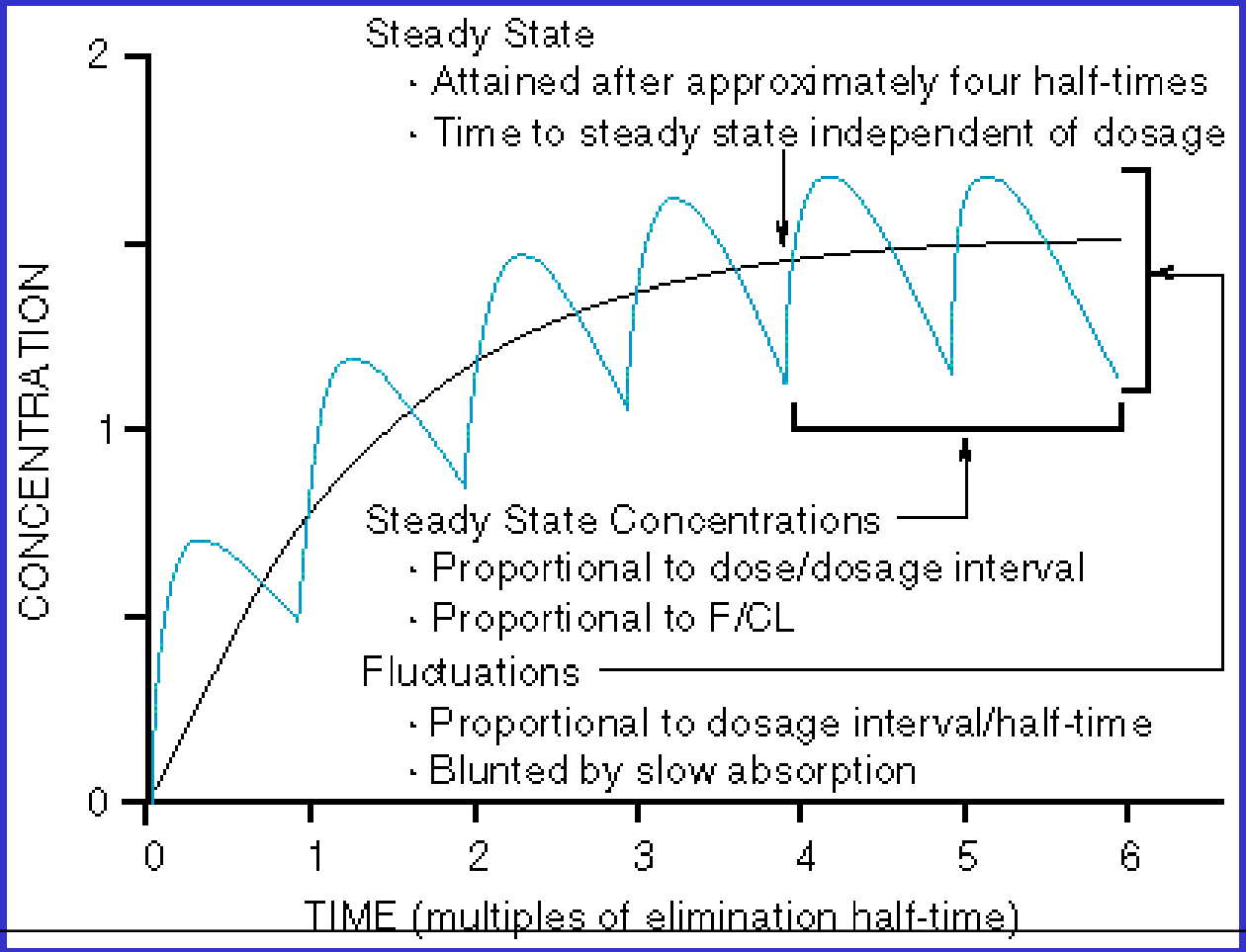
$$t_{1/2} = \frac{0.693}{k}$$

or

$$k = \frac{0.693}{t_{1/2}}$$

$$t_{1/2} = \frac{0.693\ Vd}{Cl}$$

oral dosing



the time taken to reach steady state depends only on $t^{1/2}$

(= 4-5 x $t^{1/2}$)

$$Cpss = \frac{F.dose}{CL.T}$$

M (*average* Cp) = Cl.Cp/F

for drugs with short $t^{1/2}$, must dose frequently

Time to steady-state or elimination is independent of dosage

Time required to reach steady state

- Depends on elimination rate
- Requires 5 elimination half-lives to reach 97% of steady state
- Requires 5 elimination half-lives to eliminate 97% of drug

number of half-lives	Drug	remaining
0	100	500
1	50	250
2	25	125
3	12.5	62.5
4	6.25	31.25
5	3.125	15.625

summary

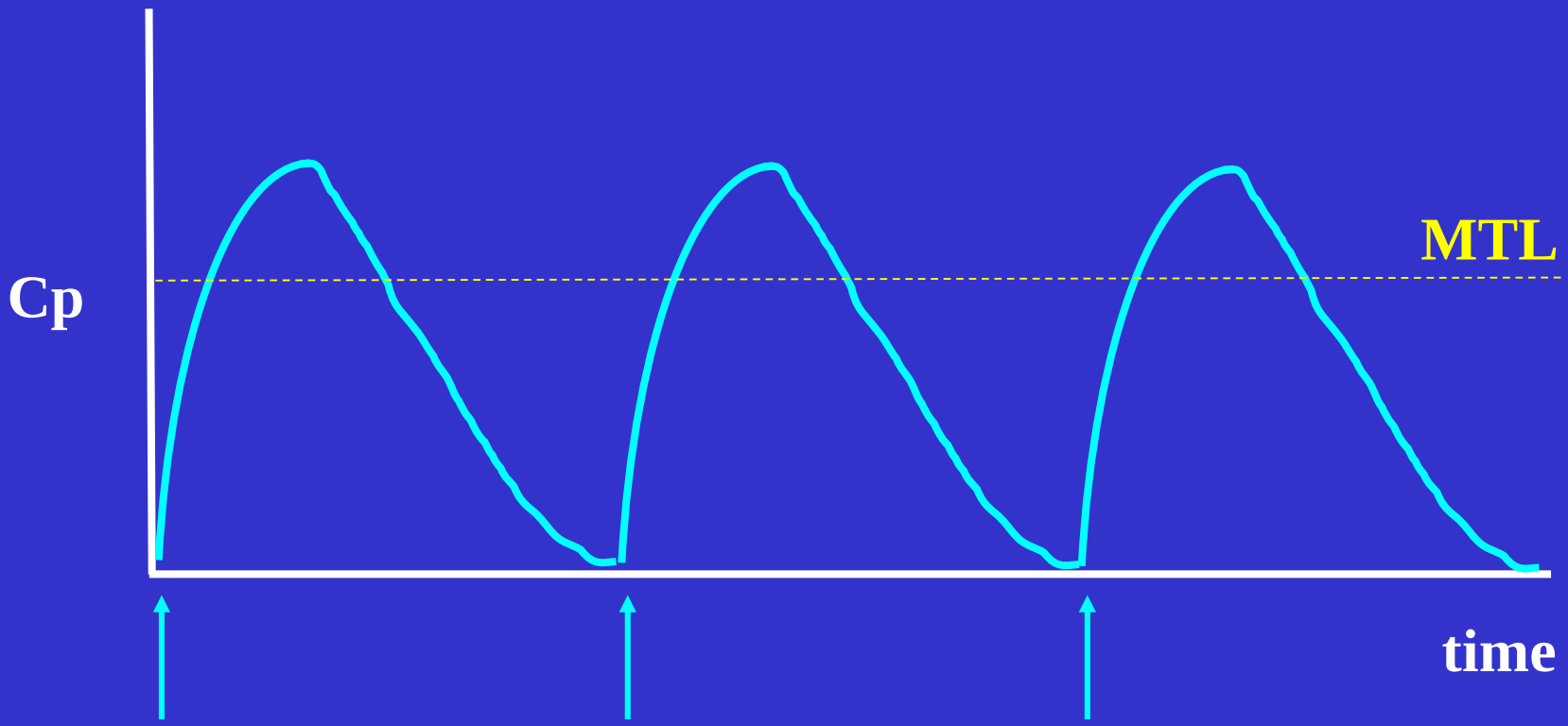
- drug dosing should aim for the *target plasma concentration*.
- the *volume of distribution* is useful in calculating the *loading dose*
- the *clearance* is useful in calculating the *maintenance dose*
- the time to reach steady state depends only on the *half life*

Drug dosing

Important factors

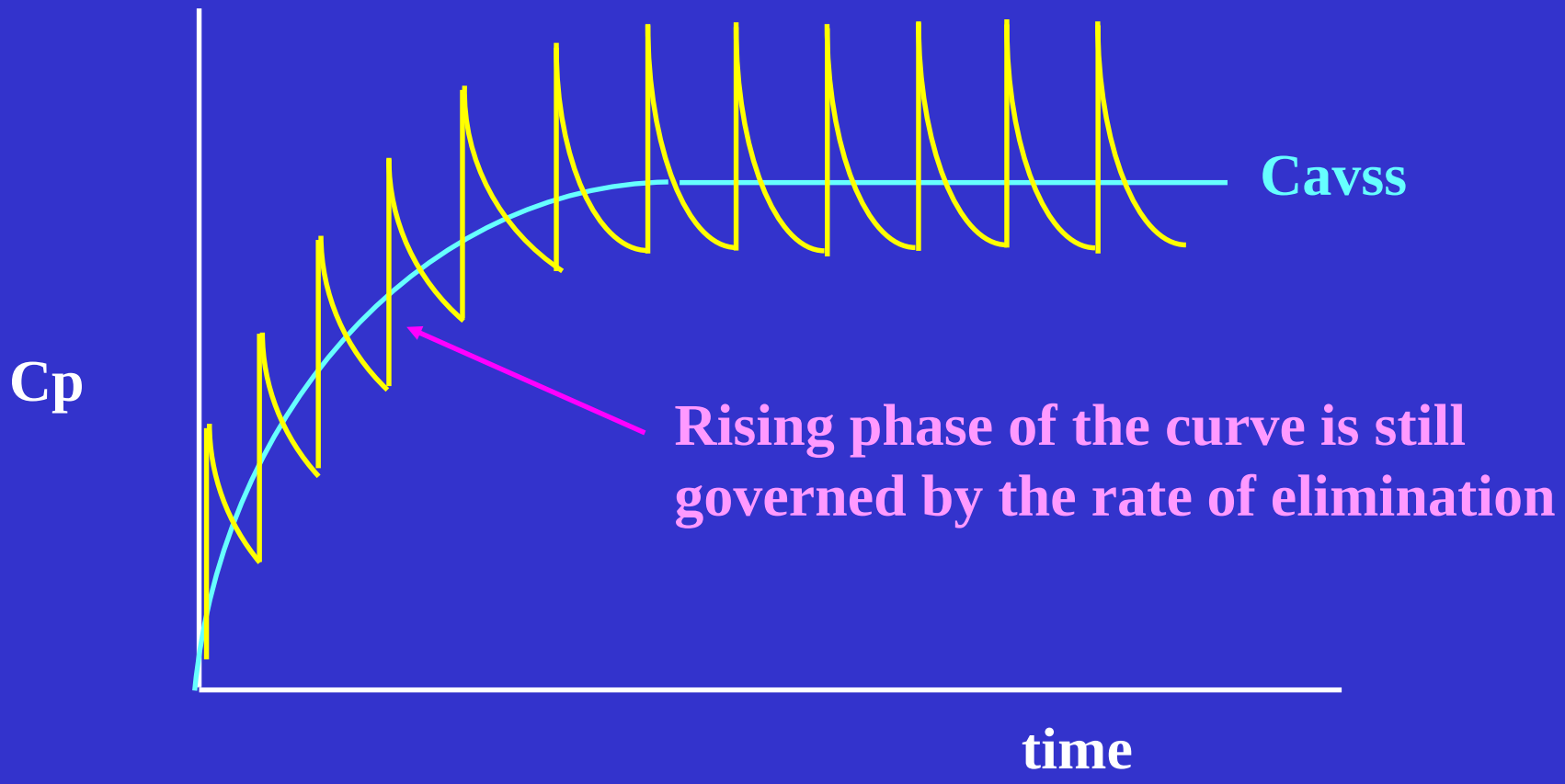
- **concentration of drug in plasma**
- **rate of drug elimination**
- **rate of drug absorption**

Dosing interval



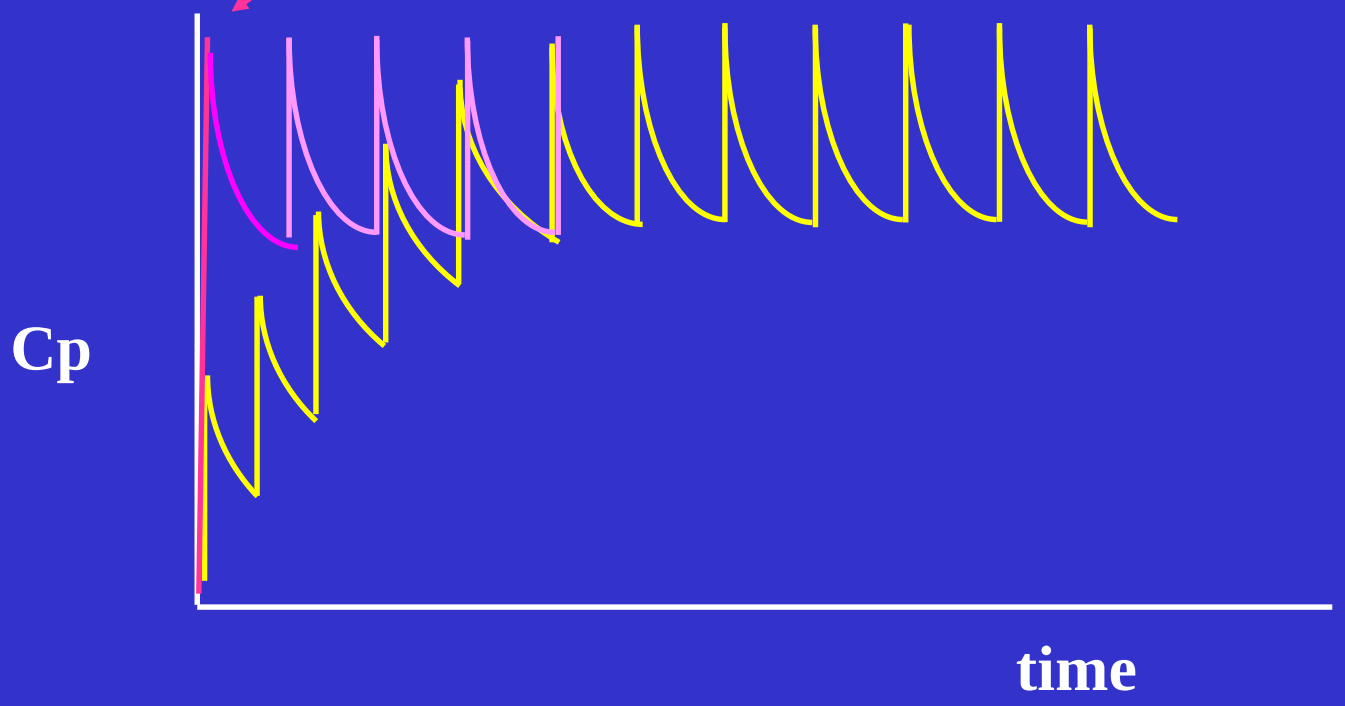
Multiple dosing

At Steady State
amount administered = amount eliminated between doses



Loading dose(s)

Loading dose = Cpeak . Volume of distribution



Therapeutic Drug Monitoring

Onset, Peak, and Duration of Action

Onset

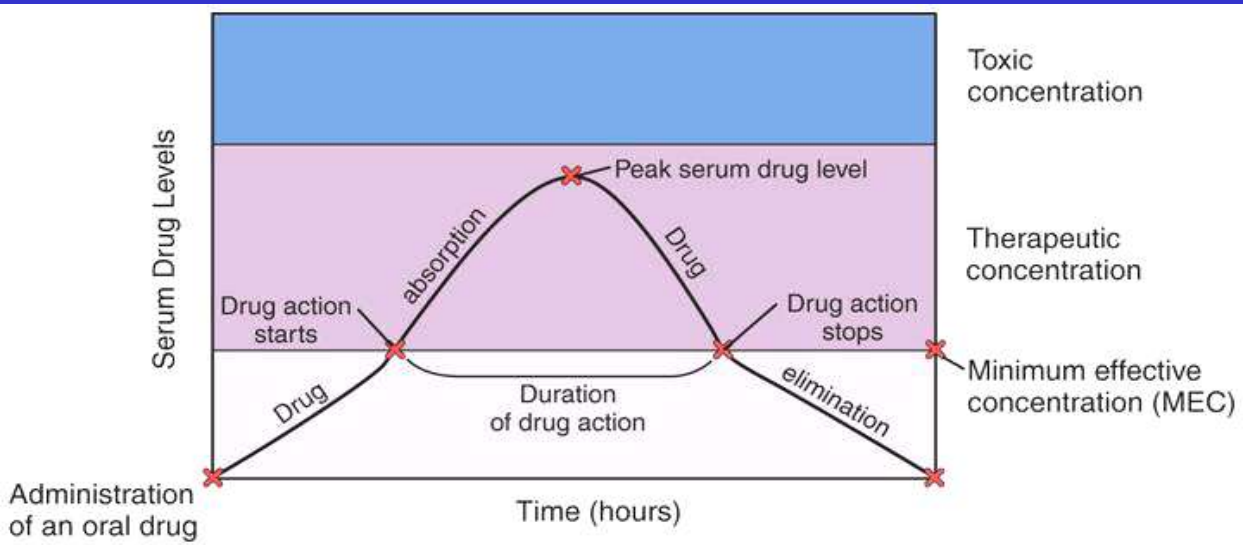
- The time it takes for the drug to elicit a therapeutic response

Peak

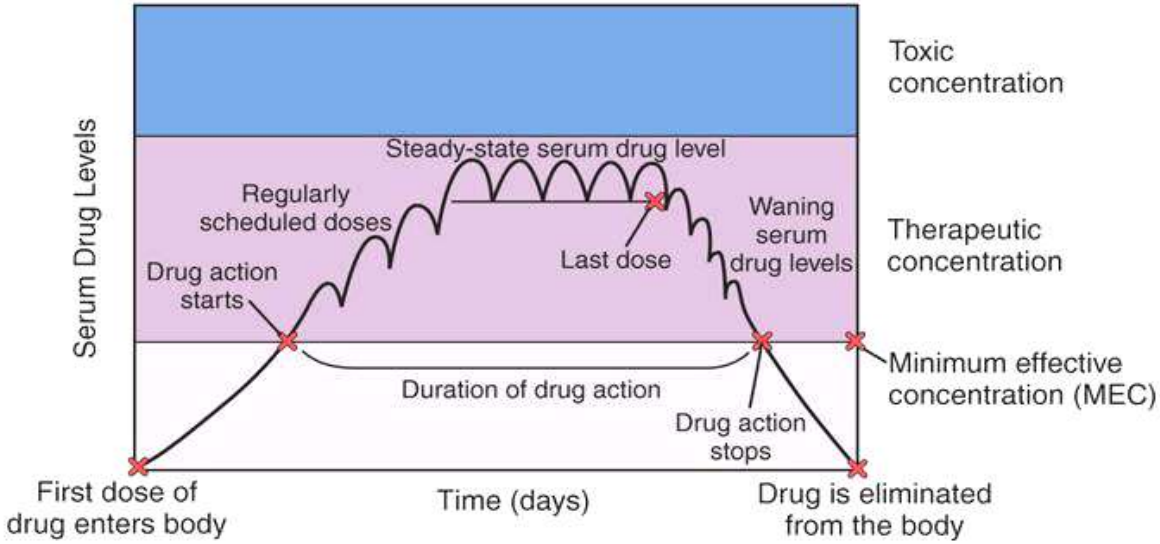
- The time it takes for a drug to reach its maximum therapeutic response

Duration

- The time a drug concentration is sufficient to elicit a therapeutic response



Drug action in relation to serum drug levels and time after a single dose.



Drug action in relation to serum drug levels with repeated doses.

Therapeutic Drug Monitoring

Peak level

- Highest blood level

Trough level

- Lowest blood level

Drug plasma concentration monitoring is helpful for drugs

- that have a low therapeutic index
- that are not metabolized to active metabolites
- whose concentration is not predictable from the dose
- whose concentration relates well to either the therapeutic effect or the toxic effect, and preferably both
- that are often taken in overdose

For which specific drugs is drug concentration monitoring helpful?

The important drugs are:

- aminoglycoside antibiotics (plasma or serum)
- cyclosporine (whole blood)
- digoxin and digitoxin (plasma or serum)
- lithium (serum)
- phenytoin (plasma or serum)
- theophylline (plasma or serum)
- paracetamol and salicylate (overdose) (plasma or serum).

Other drugs are sometimes measured:

- anticonvulsants other than phenytoin (eg carbamazepine, valproate)
- tricyclic antidepressants (especially nortriptyline)
- anti-arrhythmic drugs (eg amiodarone).

The uses of monitoring are

- to assess adherence to therapy
- to individualize therapy
- to diagnose toxicity
- to guide withdrawal of therapy
- to determine whether a patient is already taking a drug before starting therapy (eg theophylline in an unconscious patient with asthma)
- in research (eg to monitor for drug interactions in post-marketing surveillance using population pharmacokinetics).

Altered pharmacokinetic profile

- **liver metabolism**
  - **Disease**
  - **Pharmacogenetics (cytochrome P450 polymorphisms)**

- **renal impairment**
  - **Disease**
  - **Elderly**