Plasma Half Life

Dr Asma Inam

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

$$CL = \frac{\text{Rate of Elimination (mg/hr)}}{\text{Concentration (mg/L)}} = \text{vol/time}$$

Plasma Half -Life

- **“ The time it takes for the plasma concentration of a drug to be reduced by 50%”.**

For Example:

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 1 hour.

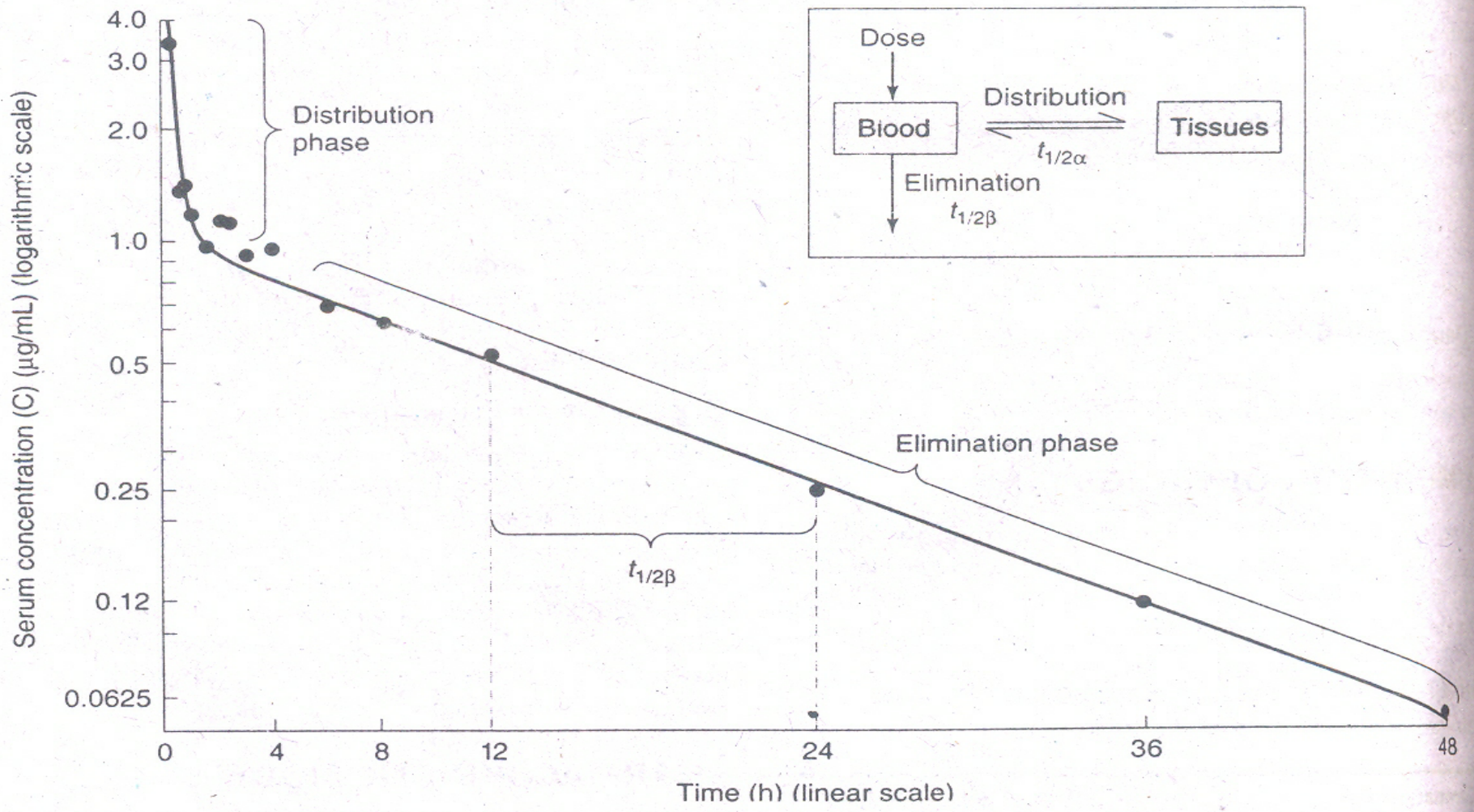


Figure 1–3. Serum concentration-time curve after administration of chlordiazepoxide as an intravenous bolus. The experimental data are plotted on a semilogarithmic scale as filled circles. This drug follows first-order kinetics and appears to occupy 2 compartments. The initial curvilinear portion of the data represents the distribution phase, with drug equilibrating between the blood compartment and the tissue compartment. The linear portion of the curve represents drug elimination. The elimination half-life ($t_{1/2\beta}$) can be extracted graphically as shown by measuring the time between any 2 plasma concentration points on the elimination phase that differ by twofold. (See Chapter 3 for additional details.) (Modified and reproduced, with permission, from Greenblatt DJ, Koch-Weser J: Drug therapy: Clinical pharmacokinetics. N Engl J Med 1975;293:702.)

The graph shows two phases:

- Initial rapidly declining (α) phase ------ $t_{½\alpha}$.

This phase is due to distribution of drug.

- Later linear (β) phase ------ $t_{½\beta}$.

This phase is due to elimination of drug .

Generally **plasma half life ($t_{½}$) considered is** the $t_{½\beta}$

Formula

- **Half Life = $\frac{0.693(0.7) \times Vd}{Cl}$**
- **$t_{1/2} \propto Vd$**
- **$t_{1/2} \propto 1/Cl$**

Examples of Half Lives of Different Drugs

- **Digoxin : 36 Hours**
- **Warfarin: 44 Hours**
- **Diazepam: 30 Hours**
- **Tolbutamide: 6 Hours**
- **Benzyl Penicillin: 1/2 Hours**

Factors Affecting Half Life

- 1. Vd --including All factors affecting Vd
- 2. Cl-- including all factors affecting renal clearance
- 3. Plasma Protein Binding-drugs that are highly plasma protein bound have longer half lives. Why?

Importance of Plasma Half Life

- 1. Indicates how quickly a drug is removed from the plasma
- 2. Indicates duration of action of a drug

- 3. It determines the frequency of dosing for a drug i.e. a drug that a short half life will have to be given more frequently than that drug that has a longer half lives

- **4. Knowledge of t1/2 of different drugs helps us to choose between different drugs of a same group according to the requirement of duration of action. For example different Benzodiazepines have different half lives and we can chose according to requirement of duration of sedation**

- 5. Knowledge of Half-life prevents excess administration causing toxicity or inadequate administration causing decline in effect of the drug

- **6. Half life of a drug gives indication of time required to reach *steady state concentration*.**
- **A drug will reach steady state concentration in approximately 4-5 half lives**

Plasma half-life

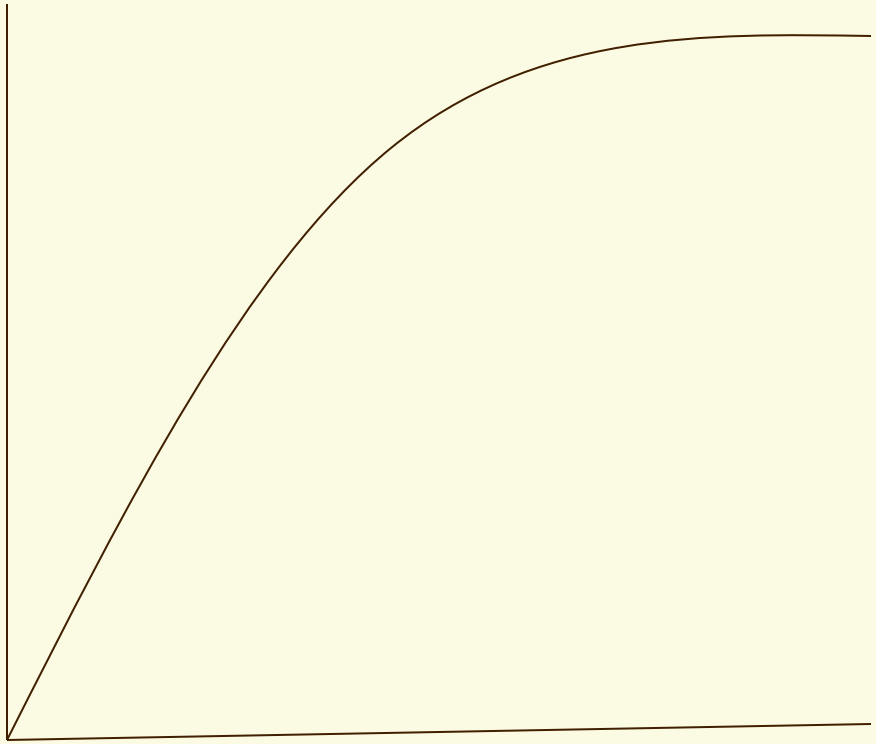
- A drug's half-life (measured in time) determines how often it must be taken and how long it takes for the drug to leave one's system.

# of Half-lives	Percent eliminated
0	0
1	50
2	75
3	87.5
4	93.8
5	96.9
6	98.4

- This assumes normal liver and kidney function. Older, younger, or sick people may clear drugs more slowly.

- **Most of a drug is eliminated after 4-5 Half lives**
- **If we administer again and again before this time, the plasma levels will start to rise until a steady state concentration is achieved**

Steady State Conc.



Steady State concentration

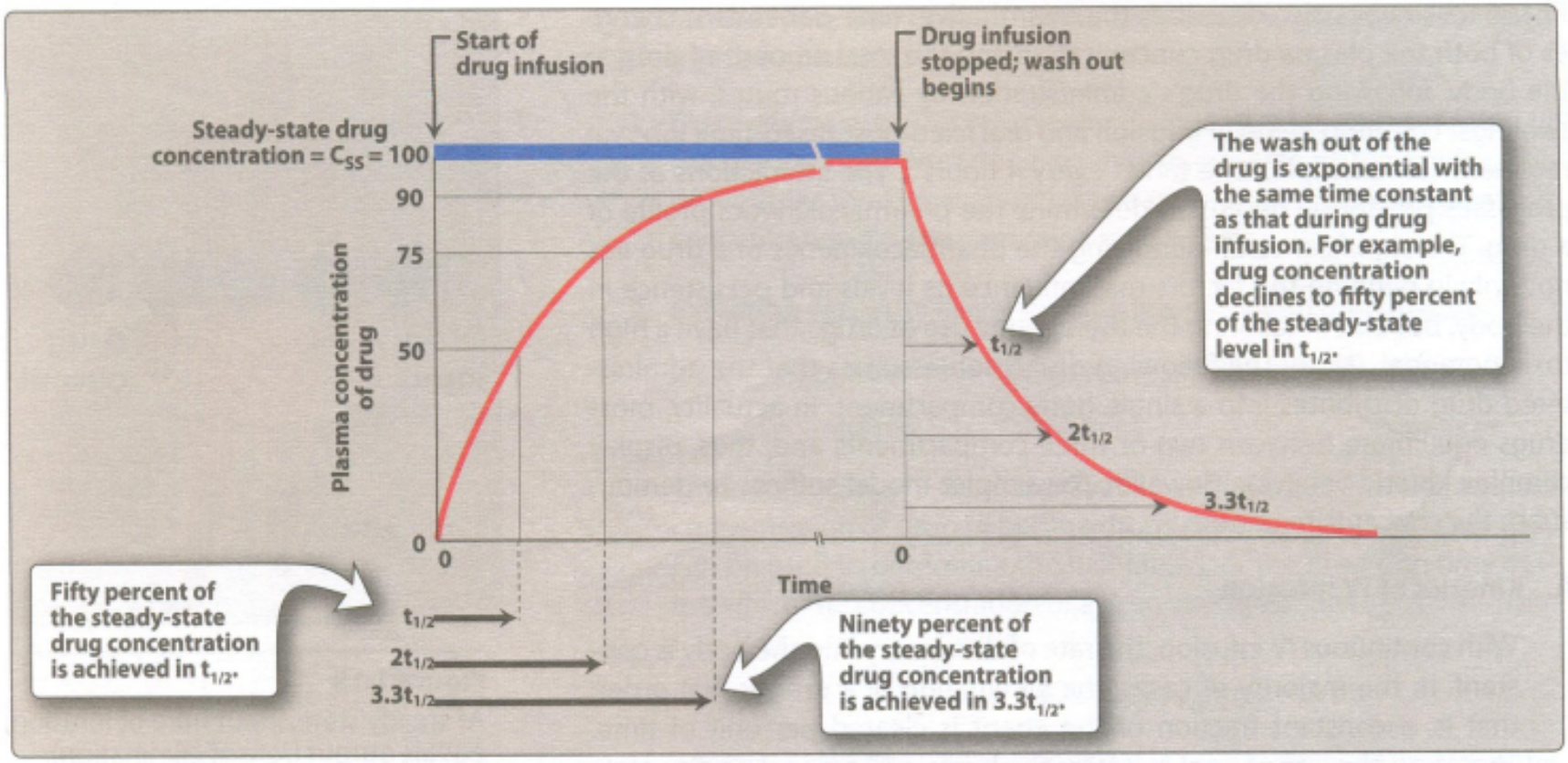


Figure 1.21
Rate of attainment of steady-state concentration of a drug in the plasma.

- 50% of SS reaches in one $t_{1/2}$

Steady state (SS):

- In pharmacokinetics the steady state is a condition in which the average total amount of the drug in the plasma does not change over multiple dosing cycles. (i.e the condition in which the Rate of elimination equals the Rate of drug administration).

- Time to reach SS --4-5 $t_{½}$.
- 50% of SS reaches in one $t_{½}$

- After 1 t1/2, Conc. = 100/2 = 50%
- After 2 t1/2, Conc. = 50+ 50/2 = 75%
- After 3 t1/2, Conc. = 75 + 25/2 = 87.5%
- After 4 t1/2, Conc. = 87.5 + 12.5/2 = 93.75%
- After 5 t1/2, Conc.= 93.75 +6.25/2 = 96.88%
- **So drug reaches steady state conc. After 4-5 half lives**

- **Css =Steady state Concentration**
- **Css = Ro/Cl**
- **Css ∝ Ro (Rate of Infusion)**
- **Steady state conc. is inversely ∝ Clearance**

- **7. Thus Half life may be used to predict the manner in which plasma concentration alters in response to altering (increasing or decreasing or stopping) drug administration.**

- **For example, when the rate of administration is altered to cause increase in plasma concentration , a new steady state concentration is achieved and it will take 5 half lives of that drug to reach a new steady state concentration**

- **Similarly, if we stop administration of the drug, we can predict the rate and extent of decline in plasma concentration.**
- **(After 1 half life conc. Falls to 50%, after 2 half lives conc. of drug falls to 25% and so on.)**

- 8. **This rule of half life only applies to drugs undergoing First Order Kinetics and does NOT apply to drugs undergoing Zero Order Kinetics (To be discussed)**

First Order Kinetics

- **In most cases, the rate at which the processes of pharmacokinetics occurs is directly proportional to the concentration of the drug.**

- **E.g. Elimination $\propto$ Conc. Of Drug**

- This is according to the “law of mass action” :
- The rate of reaction is directly proportional to the active masses of reacting substances

- Higher the concentration → more the opportunity for interaction

- **Processes for which rate is directly proportional to the concentration are called 1st order Order Processes I.e. A constant FRACTION of a drug is absorbed, distributed, metabolized and excreted per unit time or the drug is undergoing First Order Kinetics**

- Thus Most drugs given in therapeutic doses follow first order kinetics
- But if the dose is high they may may start undergoing Zero Order Kinetics
- There are a few drugs that even if given in therapeutic doses obey

Zero Order Kinetics

- **As we further increase the concentration of the drug, the kinetic processes become full or saturated, e.g. maybe the carriers or enzymes involved may become saturated**
- **So the rate of kinetic processes reaches a maximum, the rate of kinetic processes will not increase with increase in conc.**

- This Zero Order Kinetics is also known as:
- Rate Limited Kinetics
- Dose Dependent Kinetics
- Saturation Kinetics
- Zero Order Processes are taking place

Example Kinetics of Metabolism

- **thus the rate of metabolism remains constant over time and a constant AMOUNT of drug is metabolized per unit time**

Constant Fraction Vs Constant Amount

Time (Hours)	Plasma Concentration of Drug	
	Drug X	Drug Y
0	1200	1200
8	600	1000
16	300	800
24	150	600
32	75	400
40	38	200

- As we can see from the above table the half life of a drug undergoing Zero order kinetics is not constant and keeps on changing
- The biological half-life is affected by the dose
- And the drug does not reach steady state concentration in 4-5 half lives

- Three drugs follow zero order kinetics even if given within therapeutic doses:
- Phenytoin, Aspirin and Alcohol
- But many drugs show zero order kinetics if given in toxic doses
- thus distinction is very important: at what concentration a drug starts exhibiting Zero Order kinetics to avoid drug toxicity

- Alcohol follows first order at plasma conc. 10mg/dl
- Above this concentration it follows Zero Order kinetics
- the main metabolic enzyme (alcohol dehydrogenase) becomes saturated and the conversion of alcohol into acetaldehyde will not occur as fast as increase in alcohol conc.

- **So the rule of half life does not apply to drugs that exhibit Zero Order kinetics because then the rate of Elimination is NOT proportional to the concentration of rug in the plasma and it will keep on changing so t1/2 will also keep on changing and will not be constant.**

Maintenance Dosage:

Dosing rate = $\frac{\text{CL x Desired plasma conc.}}{\text{Bioavailability (F)}}$

Loading Dosage:

Initial large dose given for drug with large Vd

i.e. Digoxin, chloroquine.

Or to achieve higher conc. in certain diseases, when half life is longer

Loading dose= $\frac{\text{Vd x Desired plasma conc.}}{\text{Bioavailability (F)}}$