Steady State Drug Levels

DR. A. P. BEDSE
K. K. WAGH COLLEGE OF PHARMACY, NASHIK

Contents

- Steady state drug levels
- Calculation of loading dose
- Calculation of maintenance dose

Learning Objective

- To understand the concept and significance of Steady state level of drug.
- To learn calculation of Loading dose and maintenance dose.

Learning Outcomes

At the end of this session students should be able to explain

- Need to achieve steady state level.
- Importance of loading and maintenance dose to achieve steady state within short period of time.
- Various factors influencing the loading and maintenance dose.

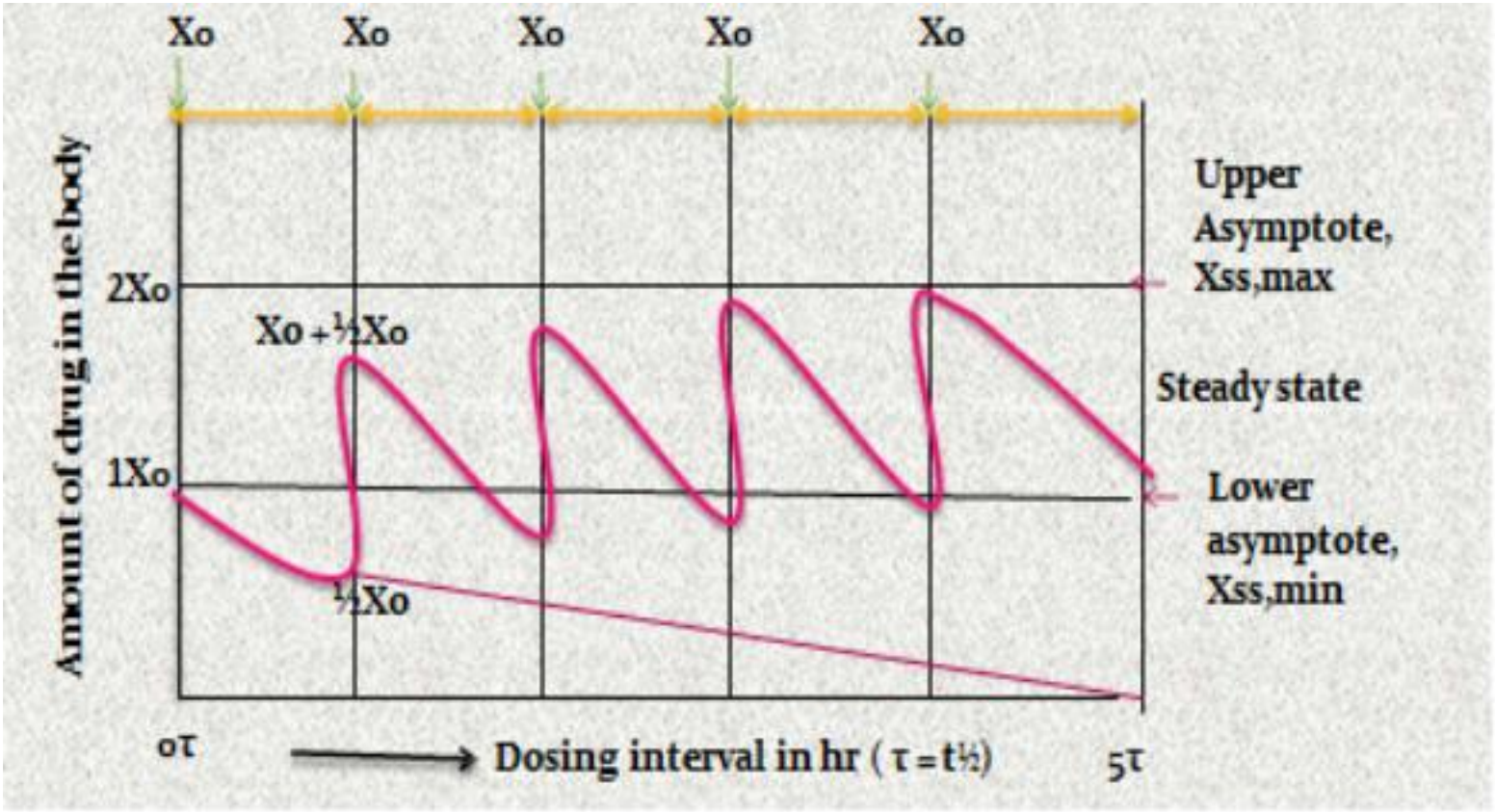
What is Dosage Regimen?

Discuss reason behind administration of multiple dosage regimen is administered.

Steady state levels of drugs

Steady state is an important term in pharmacokinetics.

When the rate of drug input is equal to the rate of drug elimination, steady state has been achieved.



Rate of input $= \frac{F \times Dose}{\tau}$, where τ is the dosing interval

Rate of elimination $= CL \times C_p$

At Steady state, Rate of input= Rate of elimination

$$\frac{F \times Dose}{\tau} = CL \times C_p$$

By solving for C_p, you get the following:

$$C_p = C_{ss} = \frac{F \times Dose}{\tau \times CL}$$

As a further simplification, we know that there is a relationship between dose, clearance, and bioavailability shown by the following equation:

$$CL = \frac{F \times Dose}{AUC}$$

$$CL = \frac{F \times Dose}{AUC}$$

By rearranging terms we can get the following:

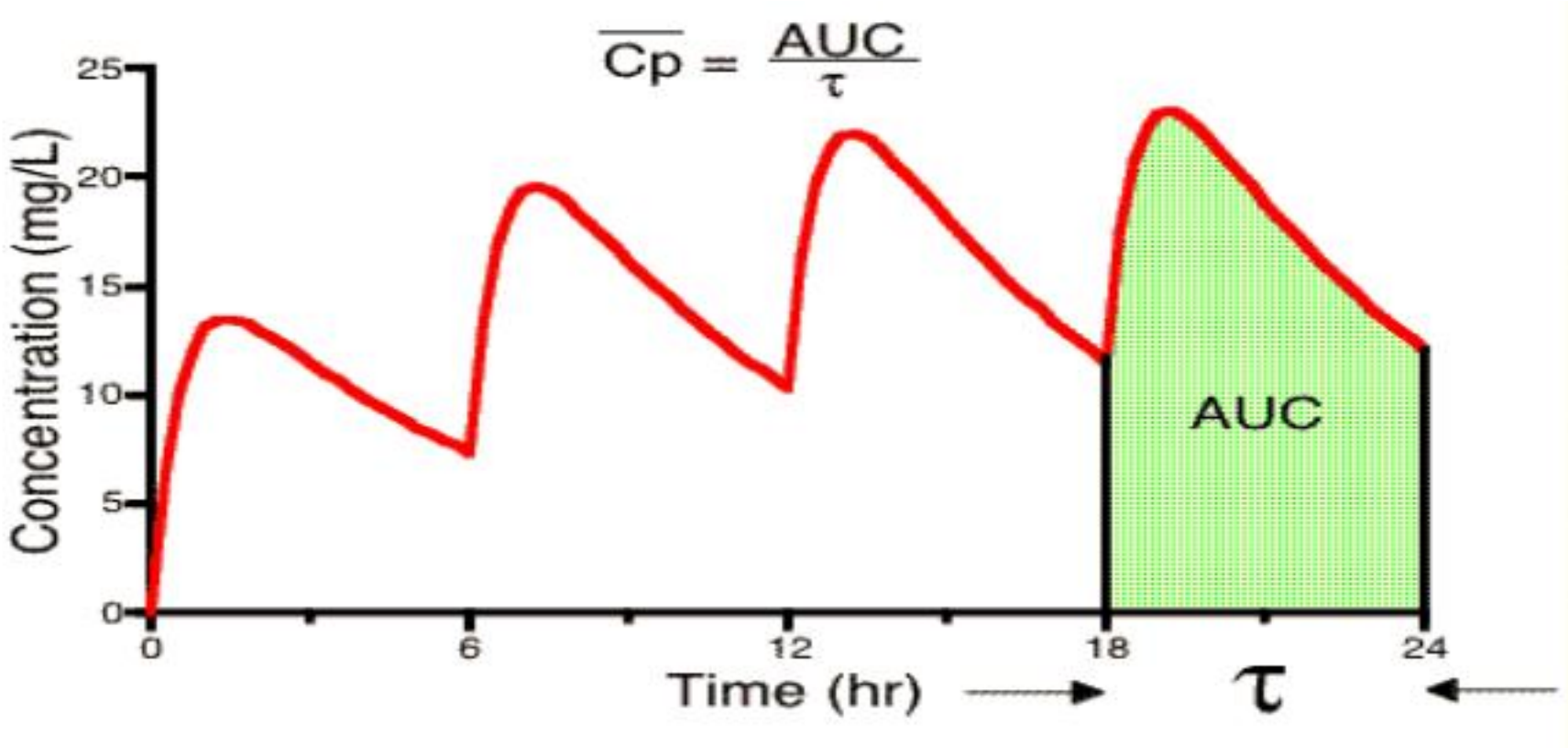
$$AUC = \frac{F \times Dose}{CL}$$

$$C_{ss} = \frac{F \times Dose}{\tau \times CL}$$

$$C_{ss} = \frac{AUC}{\tau}$$

Thus, the average concentration at steady state is simply the total exposure over single dosing interval divided by the time of the dosing interval.

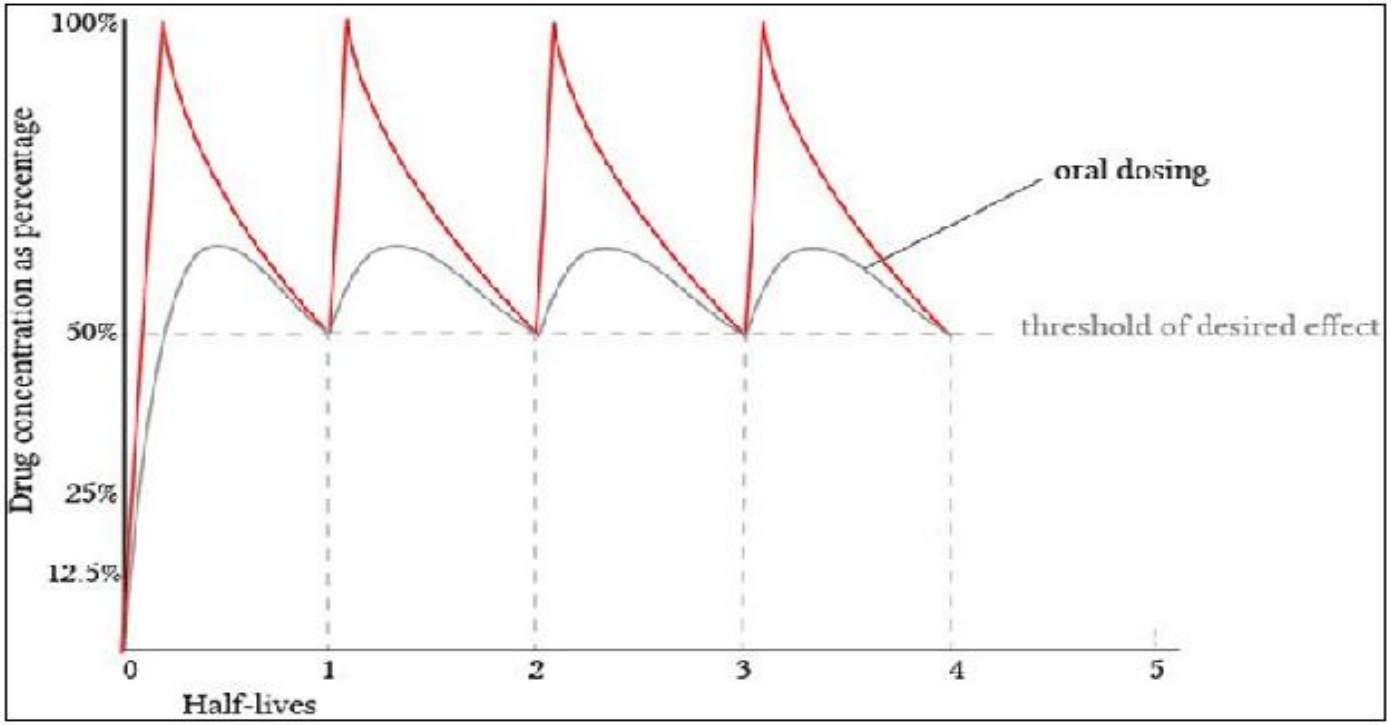
So while concentrations rise and fall during a dosing interval at steady state, the average concentration does not change. Furthermore, the only factors that control C_{ss} are the dose, the dosing interval, and the clearance.



Assuming clearance cannot be altered by a clinician, the steady state levels of drug can be modulated using the dose and the dosing interval.

$$C_{ss} = \frac{F \times Dose}{\tau \times CL}$$

Lower doses and longer intervals will result in lower C_{ss} values, while higher doses and shorter intervals will give higher C_{ss} values.



The situation is even simpler for intravenously administered drugs where you can directly calculate the C_{ss} using the following equation:

$$C_{ss} = \frac{R_0}{CL}$$

where R_0 is the rate of drug input.

The C_{ss} is proportional to the infusion rate directly.

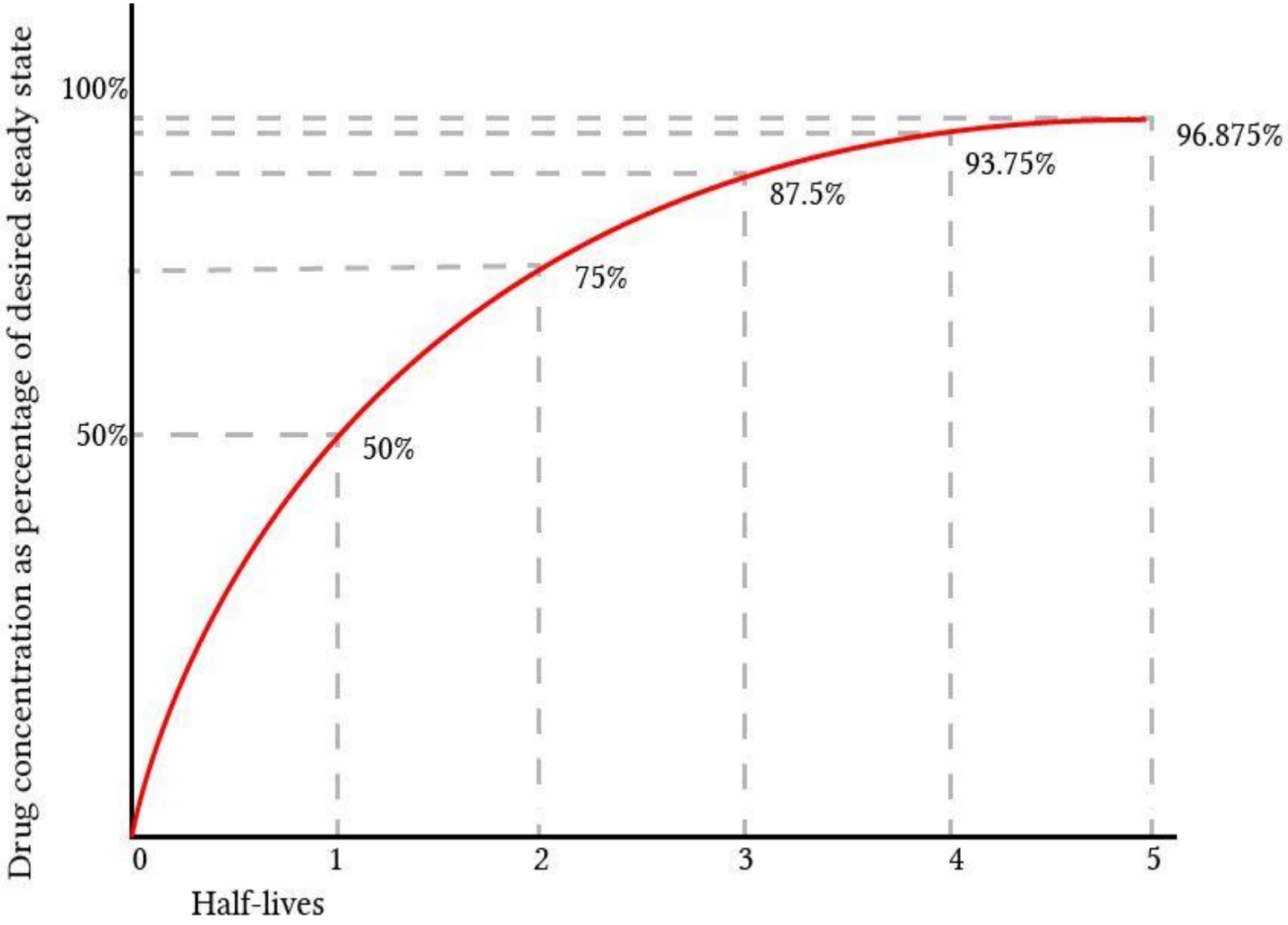
Time to reach steady state

The time to reach steady state is defined by the elimination half-life of the drug.

After 1 half-life, you will have reached 50% of steady state.

After 2 half-lives, you will have reached 75% of steady state, and after 3 half-lives you will have reached 87.5% of steady state.

The rule of thumb is that steady state will be achieved after 5 half-lives (97% of steady state achieved).


Drug concentration as percentage of desired steady state
100%
50%
50%
75%
87.5%
93.75%
96.875%
0
1
2
3
4
5
Half-lives

Loading dose

To achieve steady-state, you need approximately 5-7 half-lives of the drug.

For drugs with rapid elimination and short half-life values, this is not a problem; however drugs with slow elimination could require days or weeks to achieve steady-state.

If therapeutic effects are needed quickly, and the drug has a long half-life, one can use a loading dose to achieve therapeutic levels on the first dose.

The loading dose rapidly achieves the therapeutic response and subsequent doses maintain the response.

Drugs which may be started with an initial loading dose include digoxin, teicoplanin, voriconazole, procainamide and fulvestrant.

For an example, one might consider the hypothetical drug *foosporin*.

Suppose it has a long lifetime in the body, and only ten percent of it is cleared from the blood each day by the liver and kidneys. Suppose also that the drug works best when the total amount in the body is exactly one gram. So, the maintenance dose of *foosporin* is 100 milligrams (100 mg) per day—just enough to offset the amount cleared.

Suppose a patient just started taking 100 mg of *foosporin* every day.

On the first day, they'd have 100 mg in their system; their body would clear 10 mg, leaving 90 mg.

On the second day, the patient would have 190 mg in total; their body would clear 19 mg, leaving 171 mg.

On the third day, they'd be up to 271 mg total; their body would clear 27 mg, leaving 244 mg.

As one can see, it would take many days for the total amount of drug within the body to come close to 1 gram (1000 mg) and achieve its full therapeutic effect.

For a drug such as this, a doctor might prescribe a loading dose of *one gram* to be taken on the first day.

That immediately gets the drug's concentration in the body up to the therapeutically-useful level.

First day: 1000 mg; the body clears 100 mg, leaving 900 mg.

On the second day, the patient takes 100 mg, bringing the level back to 1000 mg; the body clears 100 mg overnight, still leaving 900 mg, and so forth.

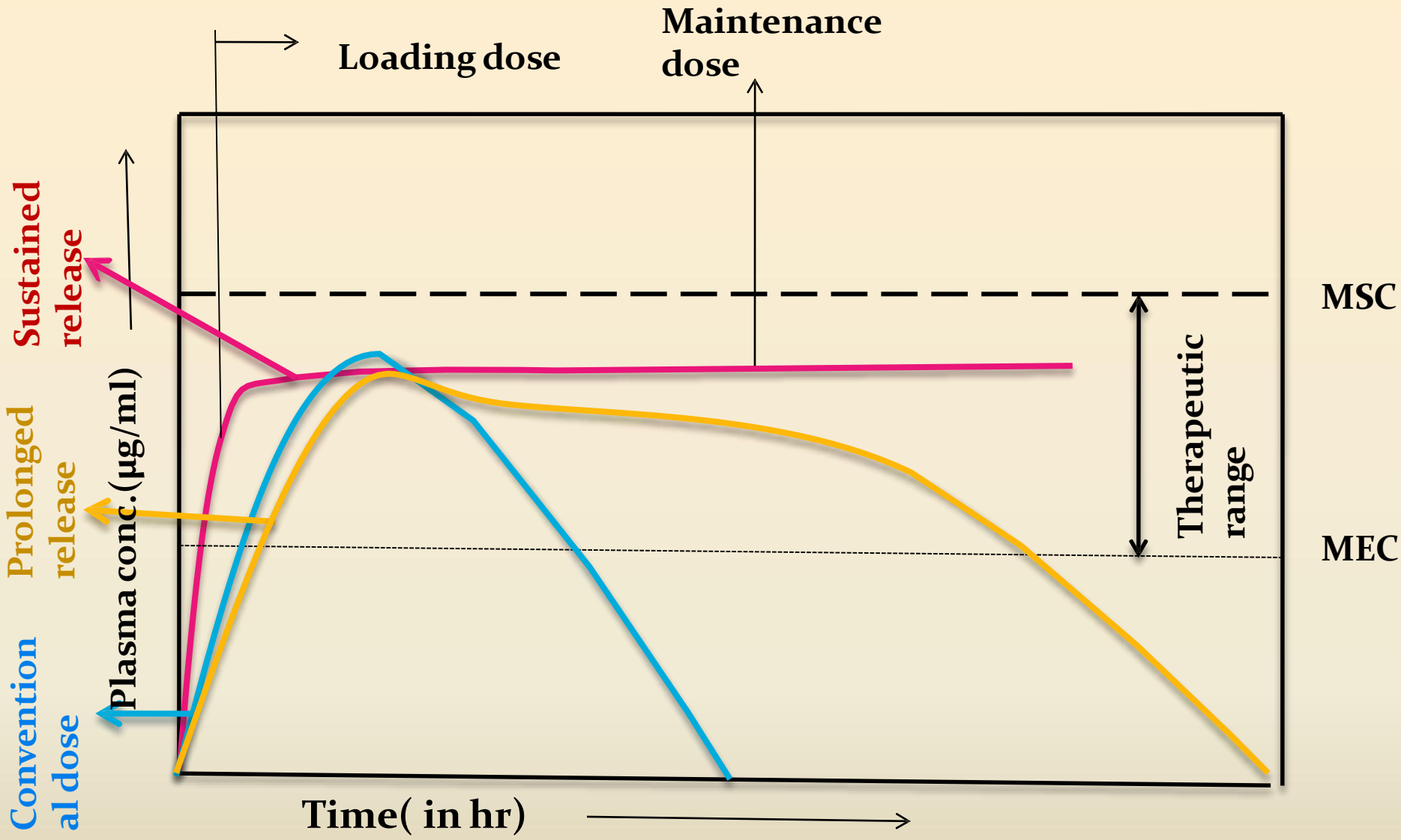
The loading dose can be determined using the following equation:

$$Loading\ Dose = \frac{Maintainance\ Dose}{1 - e^{-k\tau}}$$

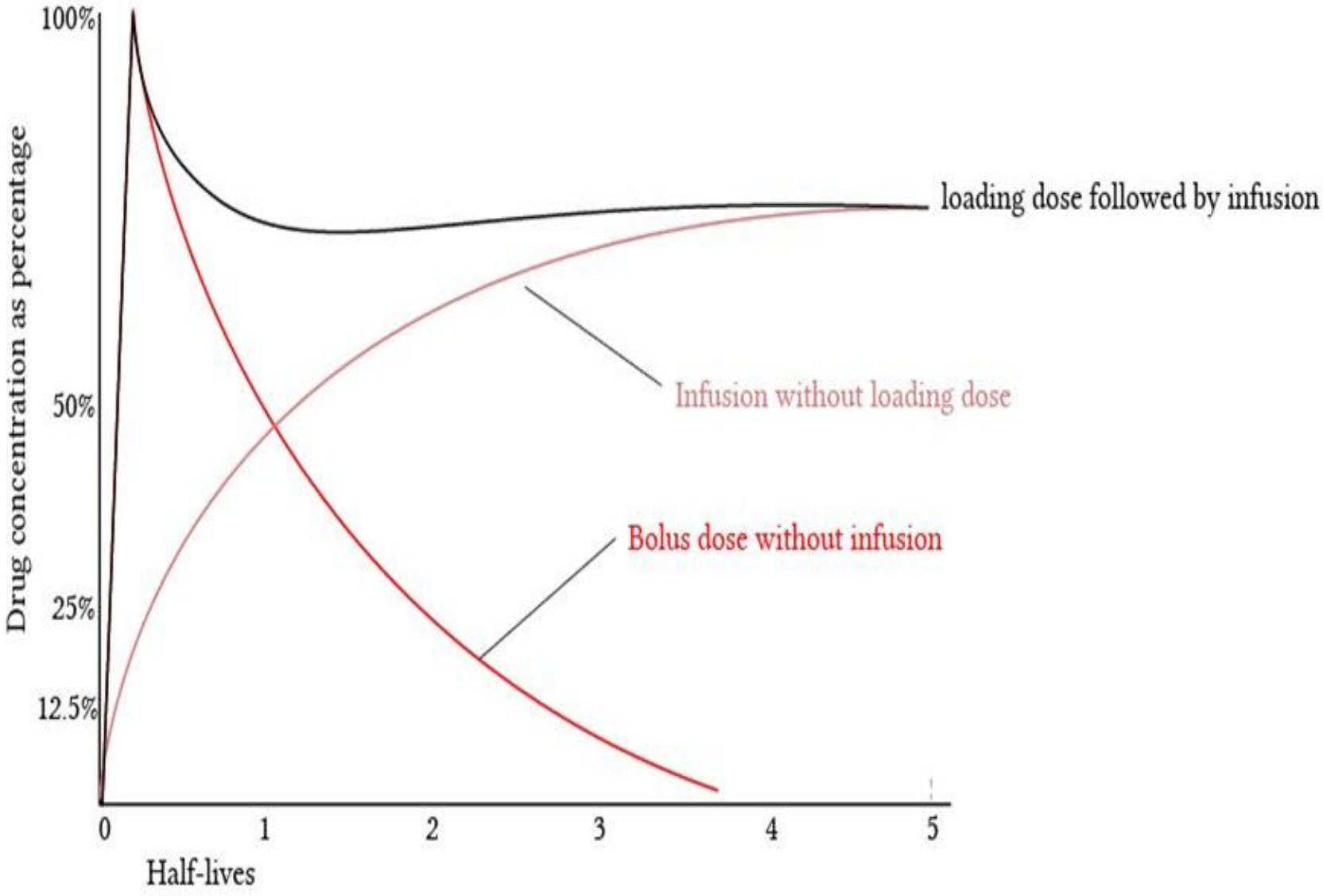
Where τ is dosing interval for the maintenance dose, and k is the terminal elimination rate constant.

Loading dose

= desired peak concentration (mg/L) × volume of distribution(L)/F =Cp × Vd/F



Plot showing the effect of loading dose and maintenance dose.



Plot showing the effect of loading dose and maintenance dose

In pharmacokinetics, a **maintenance dose** is the maintenance rate [mg/h] of drug administration equal to the rate of elimination at steady state.

This is not to be confused with dose regimen, which is a type of drug therapy in which the dose [mg] of a drug is given at a regular dosing interval on a repetitive basis.

Continuing the maintenance dose for about 4 to 5 half lives ($t_{½}$) of the drug will approximate the steady state level.

One or more doses higher than the maintenance dose can be given together at the beginning of therapy with a loading dose.

A loading dose is most useful for drugs that are eliminated from the body relatively slowly.

Such drugs need only a low maintenance dose in order to keep the amount of the drug in the body at the appropriate level, but this also means that, without an initial higher dose, it would take a long time for the amount of the drug in the body to reach that level.

Calculating the maintenance dose

The required maintenance dose may be calculated as:

$$\text{Maintenance Dose (mg/h)} = \frac{C_p CL}{F}$$

Cp= desired peak concentration of drug(mg/L)

CL= Clearance of drug in body (L/h)

F= Bioavailability

For an intravenously administered drug, the bioavailability *F* will equal 1, since the drug is directly introduced to the bloodstream.

If the patient requires an oral dose, bioavailability will be less than 1 (depending upon absorption, first pass metabolism etc.), requiring a larger loading dose.

For IV drugs given by infusion,

Dose rate (mg/hr)

= dose (mg) divided by dosing interval(hrs)

=X/ τ

Maintenance dose rate (mg/hr)

= desired peak concentration (mg/L) × clearance (L/hr)

= Cp × CL

Loading dose

= desired peak concentration (mg/L) × volume of distribution(L)

= Cp × Vd

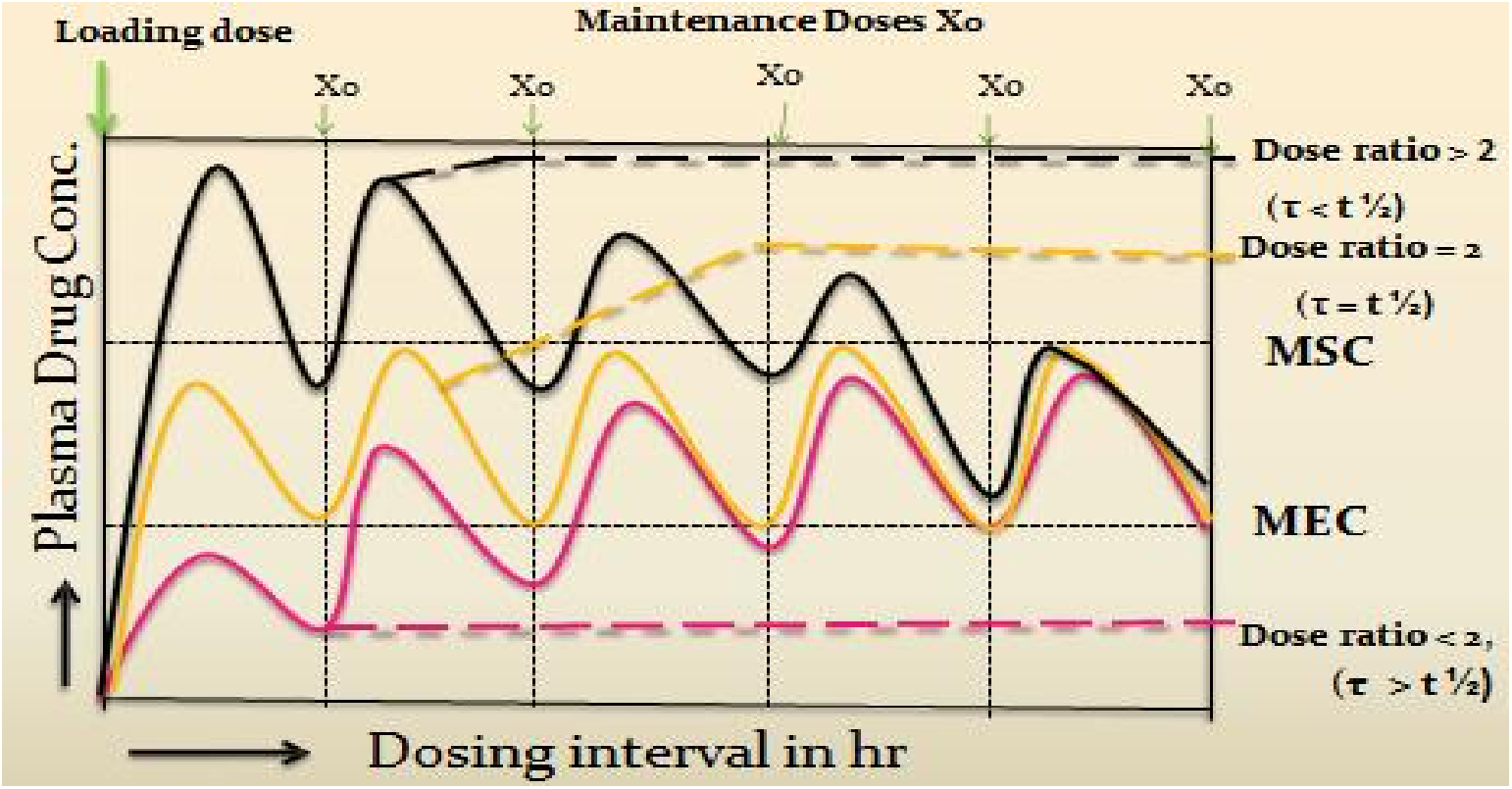
For drugs **not** given IV, these doses need to be divided by the bioavailability.

Factors which influence the dosing interval

Elimination half-life

Therapeutic index

Convenience



Factors which influence maintenance dose and loading dose

Factor involved	Effects of critical illness	Impact on loading dose and maintenance dose
Volume of distribution	Increased Vd (due to fluid overload)	Increased loading dose and maintenance dose or dose rate
	Decreased Vd (due to hypovolemic)	Decreased loading dose and maintenance dose or dose rate

Hypovolemia, also known as volume depletion or volume contraction, is a state of decreased intravascular volume. This may be due to either a loss of both salt and water or a decrease in blood volume.

Hypovolemia refers to the loss of extracellular fluid and should not be confused with dehydration.

Factors which influence maintenance dose and loading dose

Factor involved	Effects of critical illness	Impact on loading dose and maintenance dose
Clearance	**Decreased renal clearance** (due to decreased renal blood flow or renal parenchymal damage)	Decreased maintenance dose or dose rate; also possibly increased dosing interval. Loading dose could remain unchanged.
	Increased renal clearance (hyperdynamic states, eg. early sepsis)	Increased maintenance dose or dose rate; also possibly decreased dosing interval. Loading dose could remain unchanged.
	Decreased hepatic clearance (decreased hepatic blood flow or inhibited liver enzyme function)	Decreased maintenance dose or dose rate; also possibly increased dosing interval. IV loading dose could remain unchanged; Oral loading dose would need to be decreased to accommodate for the decreased first pass metabolism.
	Increased hepatic clearance (increased hepatic blood flow or hepatic parenchymal clearance)	Increased maintenance dose or dose rate; also possibly decreased dosing interval. IV loading dose could remain unchanged Oral loading dose would need to be increased to accommodate for the increased first pass metabolism.

Factors which influence maintenance dose and loading dose

Factor involved	Effects of critical illness	Impact on loading dose and maintenance dose
Bioavailability	**Decreased protein binding** (due to lower levels of protein)	Increased free unbound fraction of the drug, which gives rise to increased clearance and increased drug effect.
	Decreased gut absorption (due to decreased splanchnic blood flow and/or decreased peristalsis)	Variable and inconsistent absorption of an otherwise correctly calculated oral loading dose
	Competition for protein binding (eg. where bilirubin competes for albumin binding sites)	Increased free unbound fraction of the drug

Factors which influence maintenance dose and loading dose

Theophylline: a drug which is dosed every half-life (300mg every 8 hours), which is equivalent to a dose rate of 37.5mg/hr, which is in turn equivalent to an infusion rate of 37.5mg/hr (Dosing Interval).

Phenobarbitone: a drug with a vast volume of distribution, where the loading dose would be massive and toxic (volume of distribution).

Factors which influence maintenance dose and loading dose

Morphine: a drug which is poorly orally bioavailable; an example of how the oral loading dose is affected by bioavailability (Bioavailability).

Phenytoin: a drug which is highly protein-bound, and which is highly affected by the low plasma albumin associated with critical illness (thus, with low total drug levels the levels of free unbound drug may still be therapeutic)(Protein binding).

Factors which influence maintenance dose and loading dose

Gentamicin: a drug which is cleared rapidly by the kidneys, a clearance which is significantly affected by poor renal function.

It is an example of how the loading or maintenance dose should remain unchanged; instead the dosing interval should be extended (Increased renal clearance& Dosing Interval).

Vancomycin and β-lactams: examples of drugs which are subject to increased renal clearance in the context of hyperdynamic circulatory states, for example in early sepsis (Increased renal clearance).

THANK YOU