Pharmacokinetics IV: Kinetics of Elimination

PHC 721

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In dental practice, you will be using for the most part medication that's in already established dosage, forms doses, and their treatment measurements, so you don't need to know kinetics of elimination for this type of treatment. But from time to time, you may encounter the situation that **you will have to calculate how long the drug for the given patient,** for the given situation, stay in the body. This is all about **effectiveness of your time and also preventing toxicity**.

Kinetics of Elimination

The basis for rational dosage regimens to achieve therapeutic results with minimal drug toxicity.

Fundamental Pharmacokinetic Parameters:

- Bioavailability (F) √
- Volume of Distribution (V_d) √
- Clearance (CL) & Plasma Half-Life ($t_{1/2}$)

DRUG ELIMINATION = Metabolic Inactivation + Excretion

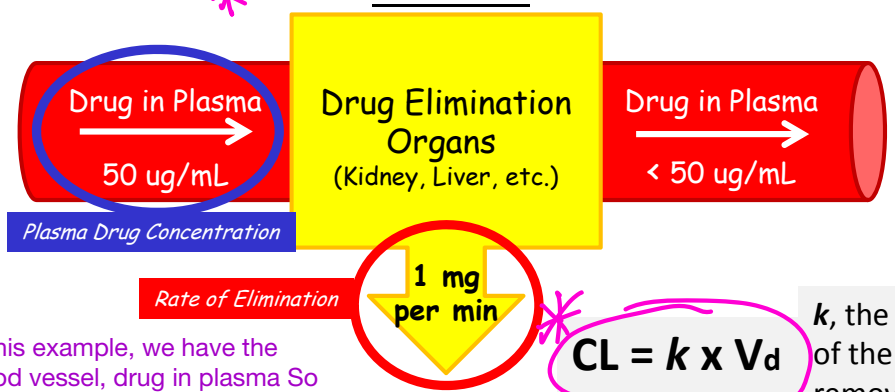
Drug is eliminated only from Blood, which is in equilibrium with the Site of Action & Reservoirs.

CLEARANCE (CL)

The theoretical volume of plasma which is completely 'cleared' of a drug in a unit of time:

Clearance = Rate of Elimination / Plasma Drug Concentration

EXAMPLE:



$$CL = \frac{1000\ ug/min}{50\ ug/mL} = 20\ mL/min$$

It requires 20 mL of plasma to account for the amount of drug being eliminated every minute: clearance is 20 mL/min

In this example, we have the blood vessel, drug in plasma So but start again only drug from circulation can be eliminated

$$CL = k \times V_d$$

k, the elimination rate constant (i.e., the fraction of the total amount of drug in the body which is removed per unit of time).

Clearance = elimination rate constant x volume of distribution

Kinetics of Elimination … & Absorption Distribution

First-Order (Exponential) Kinetics

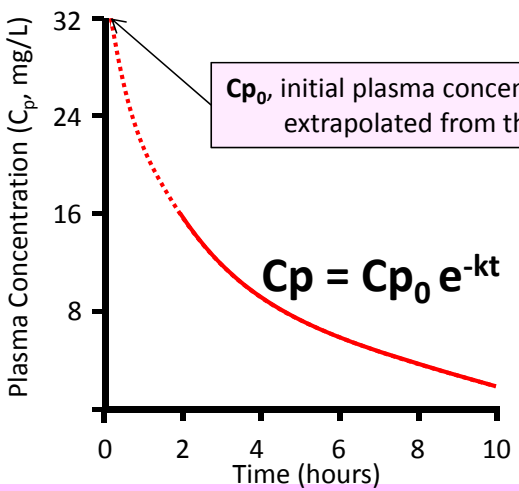
For majority of drugs, the processes involved in elimination are not saturated (no ceiling) over the clinically obtained concentrations; they follow first-order kinetics:

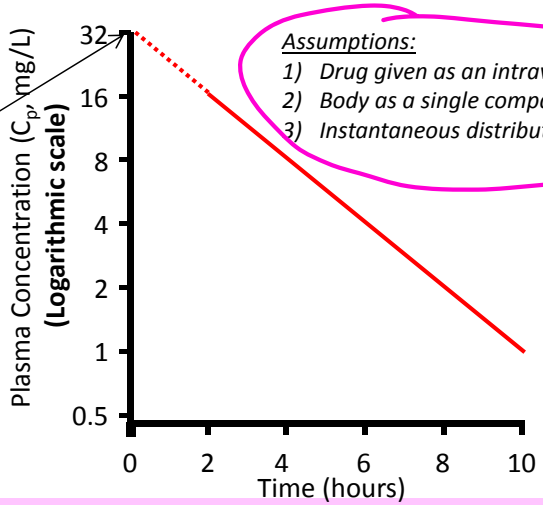
✳ A constant ***fraction*** of drug present in the body is eliminated in a unit of time;

⇒ *the rate of elimination is directly proportional to drug concentration.*

$$dC/dt = k\,C_p$$

***dC/dt**, the rate of change in drug concentration; **k**, elimination rate constant; **C_p**, plasma drug concentration*





Rate of Elimination / **Plasma Drug Concentration** = **Clearance**

✳ *Clearance remains constant* ✳

(a constant ***fraction*** of drug is eliminated ⇒ a constant fraction of plasma volume is cleared)

LEFT graph: this is the exponential kinetics. The graph starts at 2 hours because we are talking about drug being injected to the circulation. It's impossible to measure the actual concentration in the plasma immediately because you need to give time for the drug to be distributed in that entire circulation, not entire body entire. Circulatory system obviously you don't need two hours as you know cardiac output determines that within a minute you have the entire blood turned around in the body. But passengers presented this way after two hours, we have the a certain amount of drug measured. In this case, the 16 mg/L would be the drug concentration and we can extrapolate.

RIGHT graph: you would like to use a logarithmic scale, we will get linear relationship and we can easily extrapolate the values on those graphs you get now 32 mg/L.

The assumption: the drug is given intravenously, so you are injecting the drug to the circulation. (You will see later we'll have a draft showing the time course of plasma concentration. With oral already applied drugs, you first have the increase in concentration, and then slow decline due to elimination or distribution outside of the circulation.) So with injection you get the maximal concentration at time zero. Again, it's impossible to measure at time zero because you need to allow for the time for the drug to distribute and across the circulation. This is why you need the extrapolation there.

Another assumption is that the body is a single compartment. So one compartment where the drug can be distributed evenly. That distribution is instantaneous. This is for the graphical representation of the exponential kinetics.

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This is the MOST important concept. **EXAM**: you will be ask about the half life, given some original concentration and you will be able to tell the final amount of the drug at whatever time you are asked, how long the drug will stay in the body.

Most drugs are within the clinical range of concentrations are eliminated by first order kinetics and the half life remains the same. If you are given plasma drug concentration, and you are asked how long will it take for the drug to get eliminated. If you are given half-life, you can very easily calculate the time. Or if you are given time, you can then figure out what was the plasma concentration at a given time. If you are given the half life and the time, you want to know what's the level of the drug remaining, etc.

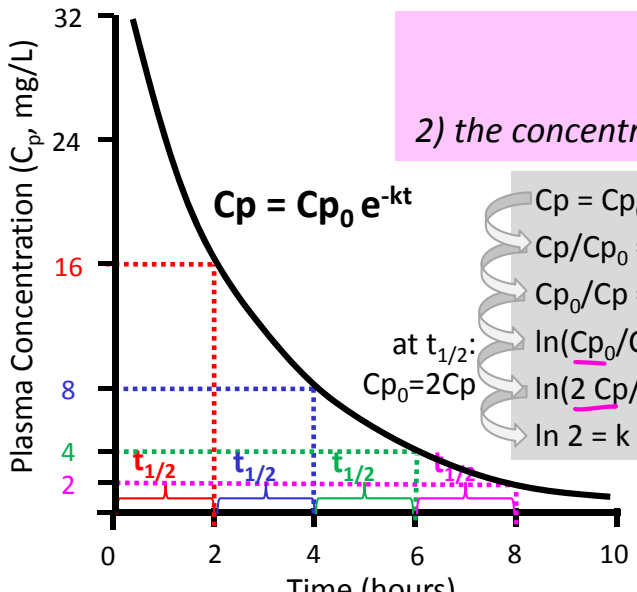
First order kinetics, the rate of elimination is proportional to the drug concentration. This is because the mechanisms of elimination are not saturated, so you add more drugs, the rate of elimination increases the amount of the drug process per unit of time.

Kinetics of Elimination

First-Order (Exponential) Kinetics

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

The plasma half-life of a drug is the time taken for its plasma concentration to be reduced to one half of its original value.



*The **half-life** is useful in determining:*
1) the rate of drug disappearance,
2) the concentration of drug remaining after a given period of time.

$Cp = Cp_0 e^{-kt}$

$Cp/Cp_0 = 1/e^{kt}$

$Cp_0/Cp = e^{kt}$

at $t_{1/2}$: $Cp_0 = 2Cp$

$\ln(Cp_0/Cp) = k\,t$

$\ln(2\,Cp/Cp) = k\,t_{1/2}$

$\ln 2 = k\,t_{1/2}$

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

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

$CL = k \times V_d$

For drugs eliminated by first-order kinetics, $t_{1/2}$ remains constant
(V_d and CL do not change with dose)

- **1 $t_{1/2}$ – 50%** drug is eliminated
- **2 $t_{1/2}$ – 75%** (50% + 25%) drug is eliminated
- **3 $t_{1/2}$ – 87.5%** (50% +25% + 12.5%) drug is eliminated
- 4 $t_{1/2}$ – 93.75% (50% + 25% + 12.5% + 6.25%) drug is eliminated

Nearly complete drug elimination in 4-5 half-lives

nearly complete drug elimination in 4-5 half lives, you can figure out how much you will have to add for the five, you would have half of the amount left and the left is 6.25 so you divide 6.25.

5 t1/2 — 96.875% (50% + 25% + 12.5% + 6.25%) drug is eliminated

Kinetics of Elimination

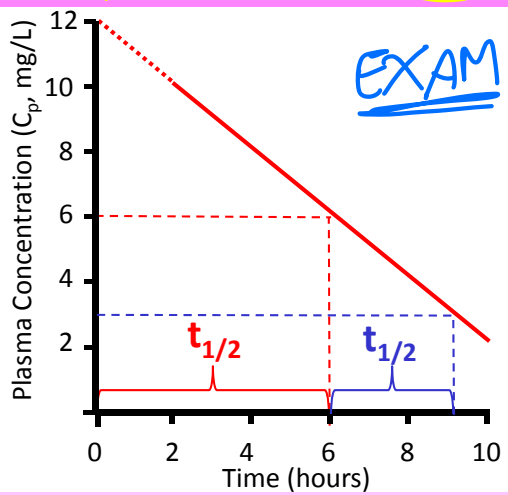
Zero-Order (Linear) Kinetics

When mechanisms of elimination are **saturated** drugs are handled by zero-order kinetics:
A constant ***amount*** of drug is eliminated in a unit of time
⇒ *the rate of elimination remains constant, independent of drug concentration.*

$$dC/dt = k_0$$

***dC/dt**, the rate of change in drug concentration; **k_0**, elimination constant in units of drug amount per time*

IMPORTANT EXAMPLES: **Aspirin**, Ethanol, Phenytoin; Drug Overdose (Poisoning)



EXAM

For drugs eliminated by zero-order kinetics,
$t_{1/2}$ increases with dose
(CL progressively decreases as dose is increased)

Capacity-Limited Metabolism (First-Order → Zero-Order Kinetics)

The elimination of some drugs
(e.g., Phenytoin, Warfarin)
approaches saturation over the therapeutic range ⇒
the kinetics change from first-order to zero-order
as the drug dose increases ⇒ plasma drug concentration
increases disproportionately with increase in dose.

Rate of Elimination / **Plasma Drug Concentration** = **Clearance**

Clearance decreases with increase in drug concentration

(a constant ***amount*** of drug is eliminated ⇒ a smaller plasma volume can be cleared of the drug)

E.g., *Ethanol* – 6g/hr; a first-order elimination rate only at "asymptomatic" concentrations.

Zero order kinetics, the situation is different. The mechanisms of elimination are saturated. They're already at the maximum, so you add more drug, you increase the drug concentration, but the system is already at the maximum performance. So, the **rate of elimination remains the same. Constant amount of drug is eliminated in a unit of time, so the rate is the same, independent of drug concentration.**

Aspirin is a non-steroidal anti-inflammatory drugs.
Ethanol is not really drug, but it is very important example, often comes up on EXAMS as an example of the agent that's processed with zero order kinetics.
Phenytoin is an antiepileptic drug.
Drug overdose is also considered as zero order because overdose meaning the drug that nobody will be applied at much lower dose. That still fulfills the requirements of the first order kinetics. When it's overdosed, the system is already saturated.

GRAPH: the plasma concentration overtime in this case is a linear relationship. We don't need to use logarithmic scale to get the linear straight line. At 0, this will be the concentration at the time when the drug was applied to the system, now let's briefly look at the half lives here. After first half life, half of the drug gets eliminated from 12 to 6. This takes six hours.

Look what happens for the next half life. When you go from 6 to 3, the half life is much shorter. Why is that? Because now we have lower drug concentration to begin with, it takes less time to eliminate half of the drug. The system is saturated, but you have less drug to process.

With the first order kinetics, the half-life increases with the dose. Higher dose, longer half-life. Smaller dose, shorter half-life. About the clearance when we talked about first order kinetics, rate of elimination is the same and plasma concentration would change. The clearance decreases with increasing drug concentration because the numerator stays the same, rate of elimination. The nominator increases, the clearance goes down.

Capacity-Limited Metabolism: Some **drugs go from first order to zero order kinetics.** The main important examples, phenytoin is one of them. When you use services about the clinical range of drugs, when you use the lower drug doses, it's processed according to the first order, increase the drug dose, then it goes to zero. Or they're basically saturate the system.

Kinetics of Elimination

Approximate Half-Lives (hrs) of Some Drugs Used in Dentistry

Don't memorize numbers.
Notes:

Aspirin: there is wider range of half lives between 3 and 20 (capacity limited metabolism). Basically when you apply at low dose such as for antiplatelet effects to prevent a blood clots forming, protecting patients from heart attacks or ischemic strokes. At low doses aspirin is processed through first order kinetics because the system it's not saturated yet. But when you increase the dose, it goes from first to zero order kinetics. With zero order kinetics, with a saturated system, when you increase the dose, the half life of the drug increases, it takes much longer to eliminate the drug.

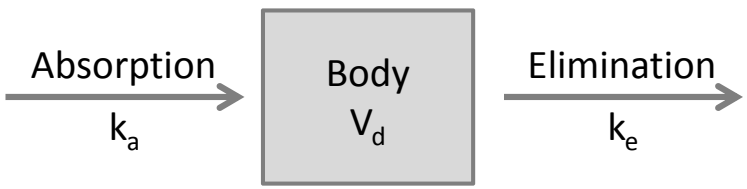
Converted to active metabolite: diazepam~ 45 hours half life. This basically includes the diazepam and its metabolite. For some drugs, you have several metabolites and then some of them have very long half lives. So we consider the action of the original drug and the metabolites.

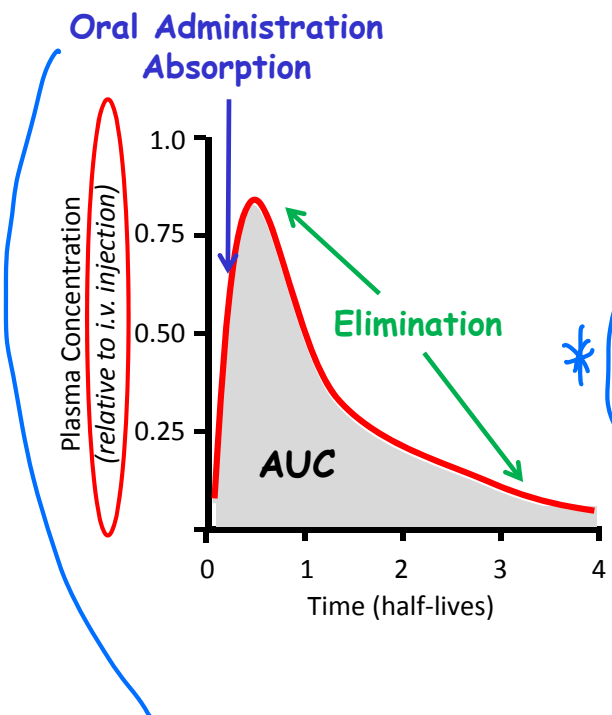
Analgesics:	
Acetaminophen	3
Aspirin (as Salicylate)	3-20 *(Capacity-limited metabolism)*
Codeine	3 *(Converted to active metabolite)*
Meperidine	3
Morphine	2 *(Converted to active metabolite)*
Local Anesthetics:	
Articaine	0.4
Bupivacaine	2.4
Lidocaine	1.8 *(Converted to active metabolite)*
Procaine	0.01
Sedatives:	
Ethyl Alcohol	1.4-20 *(Capacity-limited metabolism)*
Diazepam	45 *(Converted to active metabolite)*
Pentobarbital	30
Triazolam	3
Antibiotics:	
Amoxicillin	1.7
Clindamycin	3
Erythromycin	1.5
Penicillin G	0.5
Tetracycline	10

Kinetics of Elimination

Plasma Concentration: Single Dose

In dentistry, therapeutics are often administered as single doses
(e.g. **Lidocaine**-local anesthesia, **Atropine**-control of salivation, **Triazolam**-preoperative sedation)





- For first-order kinetics (i.e., unlimited capacity in absorption, binding, metabolism and excretion), the **plasma drug concentration is at all times directly proportional to the dose**.

Meaning the entire curve will be shifted UP

$$Cp = \frac{Dose}{V_d}$$

$$dC/dt = k\,C_p$$

- As long as absorption is several times faster than elimination, changes in the rate of drug uptake have little effect, except for altering the peak concentration.

- Area Under the Curve (AUC) is an important pharmacologic measure of clinical activity of a drug: it is used to compare the influence of various factors on the magnitude of drug effect.

Oral administration absorption (Blue arrow on graph): The phase of the first is the rise in the plasma concentration. What responsible for the rise is the absorption of the drug. More drug gets absorbed, the plasma concentration increases and reaches a peak. Note: the peak is less than 1 because the absorption happens first. There is limited by your availability, so not all drug gets absorbed. Actually, as soon as the drug gets observed, the elimination process starts. So you are not reaching the peak because it takes time to actually get most drug to the circulation. Unlike the IV injection, as we discussed in the those models for the first zero order kinetics, you actually start with 1, meaning with the whole dose. The concentration coming from the whole dose that was applied.

Then, we have the decline in the plasma concentration. This is elimination (green on graph) of the drug. With time, the drug gets eliminated from the body, so the plasma concentration drops.

We always want the absorption to be as fast as possible. You don't reach the maximum with oral administration because the absorption is slow enough to already have the processes of elimination going on as soon as the drug gets to the circulation. But, if absorption is several times faster than elimination, the changes in how fast the drug is actually taken to the circulation have very little effect, except for altering the peak concentration. If you increase the absorption rate, that gets faster, you will get closer to 1 with the peak concentration.

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GRAPH: The drug will be applied here once every half life. There's assumption that the absorption rate is 10 times higher than the elimination rate. Just talking about the single doses, the first little effect on changes in plasma concentration of the drug, absorption rate is significantly higher than elimination rate.

At time 0, their rise begins and then reaches ~.8 and then starts to decline. Then at one half life, you have the next dose that you add. Because there is still significant level of the drug left, you see that the entire curve rises. There is accumulation of the drug in the body, although you see it starts to plateau around 5 or so half lives.

Let's compare this before we get to this plateau phase, compare it with continuous intravenous infusion. Now we are applying as continuous infusion, the drug of the equivalent dosage meaning of time the same amount of drug is applied to the body as you would apply with those repeated applications.

What's the most characteristic feature of the red curve? Is the **fluctuation**. You don't have a smooth line that you would actually like to have for your patient that continuous constant level of the drug. So as far as the red graph and the fluctuations, we can characterize them by describing the minimum the maximum. Then, the distance between them would be the amplitude. We also have the average value. The average is very close to the what we get with the intravenous infusion because the average concentration of the drug applied. But those was the same, so the average concentration is expected to be the same.

What about this **amplitude**? Meaning of fluctuations after repeated dose. So we would like to have this amplitude to be as small as possible, so the patient doesn't experience the higher levels of the lower levels. They're as close to continuous infusion as possible.
There are two major factors that affect the amplitude: (1) the fluctuations can be decreased by decreasing the rate of absorption. When you decrease the rate of absorption, you basically spread out the absorption over a longer time. So there is less drug absorbed in a smaller unit of time, so it will smooth out the curve. (2) the other way to decrease the amplitude is to decrease the dosage interval. So rather than giving certain dose at once every one half life, you could give half of the dose every half life.

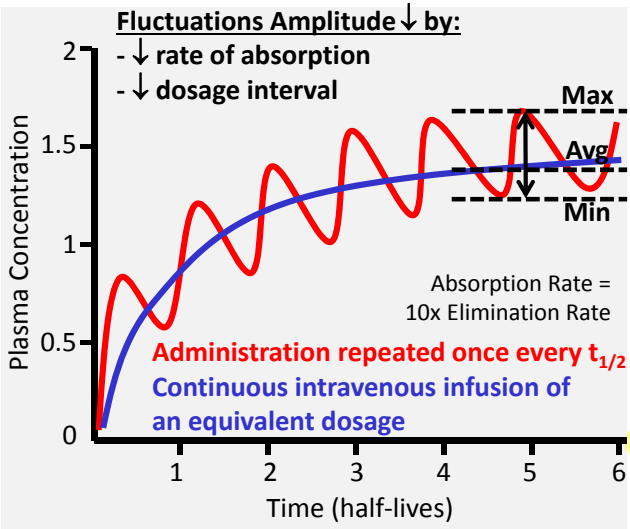
Kinetics of Elimination

Plasma Concentration: Repeated Doses

Whenever a drug is administered **more than once every four half-lives**, **accumulation** of the compound occurs within the body.

Assuming First-Order Elimination Kinetics and No Change in the Dosing Rate:

1. A constant dose repeated before the expiry of 4 $t_{1/2}$ ⇒ ↑ peak plasma drug concentration
2. ↑ plasma drug concentration ⇒ ↑ rate of elimination ⇒ Input ↔ Elimination Balance
3. **A plateau** (steady-state) **average plasma drug concentration** (Cp_{ss}) is reached in **4-5 half-lives** (50%, 75%, 87.5% of steady-state in 1, 2, 3 half-lives, respectively), unless dose interval >> $t_{1/2;}$ **regardless of dosage.**



If the data on therapeutic plasma concentration & clearance are available, the dose rate needed to achieve the target Cp_{ss} can be determined.

$$Cp_{ss} = \frac{\text{Dose Rate}}{CL}$$

$$\text{Dose Rate} = \text{target } Cp_{ss} \times CL$$

*After oral administration, often only a **fraction (F)** of the dose reaches systemic circulation in the active form (limited bioavailability).*

$$\text{Dose Rate} = \frac{\text{target } Cp_{ss} \times CL}{F}$$

So now we are assuming that the drug is eliminated according to the first order kinetics and that we are not changing the dose. We are applying the drug at the same rate, e.g. once every half life.

#1 is directly related to what you have written on top about accumulation. If you apply new dose before they expire of 4 half lives of the drug, you expect increase in the peak plasma concentration. This is because of the accumulation.

#2 because it's the 1st order kinetics, elimination and the rate of elimination is directly proportional to the plasma drug concentration. When you increase the plasma drug concentration, you increase rate of elimination. Basically there is input elimination balance~ same propulsion goes in and goes out

#3 thanks to the balance, we are able to reach a plateau (steady-state). This is what we are seeing here on the graph around 4 or 5 half lives. The plateau is reached in ~five half lives. Here I also listed what percentage of the steady state is reached after those shorter periods of time. This is with the assumption that the dosage interval is shorter or around the half life of the drug. If you have the dosage interval significantly longer than half life, you will not be able to reach the plateau. You will not be able to get the drug accumulation.

All of this is regardless of the dose. **Regardless of the dose, you are reaching the plateau after four to five half-lives**. This is the reverse of what we talked about the half lives at the drug elimination.

For plasma concentration of the drug, the steady state plasma concentration is directly proportional to the dose rate and then inversely proportional to the cleaners.

The clinical application of all this is that clearance for drugs is available. If you have your target plasma concentration, the steady state plasma concentration, you can calculate what's the dose rate that you actually need to apply in order to achieve the steady state plasma concentration.

If we're talking about application of this or any application other than pretty much IV application, we need to consider the bioavailability, so that only a fraction of the drug would be actually absorbed. You need to correct it for the fraction. This is pretty much all so again the practical application. Knowing those equations, you are able to figure out dose rate for a drug when you have your target plasma concentration in math.

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What **Therapeutic Target Level Strategy** can we use to make sure that the level of the drug is as close to the therapeutic level as possible? What are the situations that actually necessitate such approach?

#1 is **when we are dealing with the drugs with a small safety margin**. Drugs with a low therapeutic index, in this case, when you exceed the plasma concentration of the drug, this can be dangerous for the patient. There is also another possibility on the other end. When you are dealing with emergency situation, you are applying a drug. You want to make sure that actually the drug reaches that theraputed concentration in plasma, so the aim in those situations is to achieve that therapeutic plasma concentration.

Here are three scenarios:

1. The first scenario of is based on what we've just talked about. If you have a drug with short half life, gets eliminated pretty quickly. But you administer it at conventional intervals, 6-12 hours for drug that has two to three hour half-life. What do you expect after 8 hours? You already have 4 half lives and the drug is pretty much gone from the body before you apply the next dose, you have huge fluctuations in the drug level.
2. The second scenario is when the drug has significantly longer half-life, and then it's similar levels to the interval. You are basically applying the drug once, maybe every half life, or once every two half lives, so we get drug accumulation.
3. This is not so good if you want to achieve your therapeutic level quickly. In this scenario, the dose is not high enough to achieve the target level until the steady state. You wouldn't be applying the drug according to the first scenario if you want the effect of the drug really quick.

A couple of more equations for you to remember because in this scenario, if you want to apply the drug quickly, the immediate pharmacological fact you need to be able to calculate the loading dose. You would apply the loading those to load the body with the proper amount of the drug.

Here is the formula for the **loading dose**. You know the target plasma concentration. Loading dose is dependent on volume of distribution of the drug and F, which is the bioavailability that you need to consider. If the drug has low bioavailability, you need to significantly increase the the loading dose.

Maintenance doses (MD) Is to replace eliminate a drug and the maintenance dose is not dependent on volume of distribution, but it's dependent on clearance. Clearance is tells you how much of drug is eliminated from the body in a certain amount of time.

Kinetics of Elimination

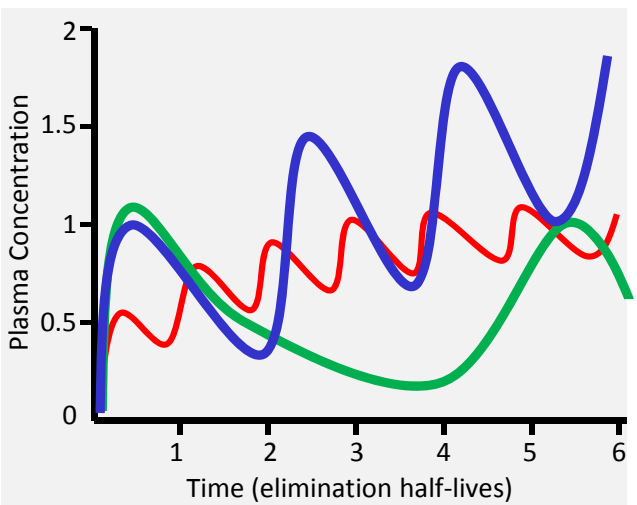
Therapeutic Target Level Strategy

For drugs with a small safety margin (e.g., anticonvulsants, antidepressants, some antimicrobials) and for preventing an event, it is best to **aim at achieving a therapeutic plasma concentration**.

Scenario 1: Drugs with short $t_{1/2}$ (up to 2-3 hrs) administered at conventional intervals (6-12 hrs) achieve the therapeutic target levels intermittently; large fluctuations in plasma drug levels.
Examples: Penicillin, Ampicillin, Chloramphenicol, Erythromycin, Propranolol.

Scenario 2: Drugs with longer $t_{1/2}$ (>3 hrs) administered at conventional intervals (6-12 hrs) accumulate according to 'plateau principle', and later on produce toxicity if a single dose is already sufficient to attain the therapeutic target level.

Scenario 3: If dosing does not achieve target level until steady-state, the therapeutic effect is delayed.



If an immediate pharmacologic effect is needed, a loading dose (LD) of the drug must be administered.

Note: Frequently applied to Chloroquine, Doxycycline, etc.

$$\text{Loading Dose} = \frac{\text{target } Cp \times V_d}{F}$$

Note: Loading Dose is governed by V_d, but not by CL or $t_{1/2}$.

Maintenance doses (MD) replace eliminated drug.

$$\text{Maintenance Dose Rate} = \frac{\text{target } Cp_{ss} \times CL}{F}$$

Note: For a drug given once each $t_{1/2}$, **LD = approx. 2x MD**.

Now approximately, if you give the drug once every half life, you can assume that loading those will be approximately twice

as high as the maintenance doses.

Prolongation of Drug Action* very important

BENEFITS:

1. ↓ frequency of administration (⇒ more convenient for the patient/caregiver).
2. Improved patient compliance (e.g., one dose per day is less likely to be forgotten).
3. ↓ fluctuations in plasma concentration (⇒ ↓ side-effects related to high peak plasma drug levels).
4. Preservation of drug effect overnight without disturbing sleep.

1. Prolonging Absorption from Site of Administration.

A. Oral: controlled/sustained release tablets or capsules (prolong action by 4-6 hrs).

B. Parenteral (prolong action by days, months, or even years):

(a) s.c. and i.m. injections of drug in insoluble form or as oily solution

EXAMPLES: Benzathine Penicillin, Long-Acting Insulin Analogues

(b) pellet implantation (sialistic and biodegradable implants)

(c) transdermal drug delivery systems (adhesive patches, ointments on skin)

(d) inclusion of a vasoconstrictor

EXAMPLE: Epinephrine with Local Anesthetics

2. Increasing Plasma Protein Binding.

Drug congeners highly bound to plasma protein for slow release in a free active form.

3. Retarding Rate of Metabolism.

Minor chemical modifications to the drug

4. Retarding Renal Excretion.

EXAMPLE: Probenecid inhibits tubular secretion (⇒ prolongs action) of Penicillin & Ampicillin.