GEORGIA CAMPUS
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PHAR 227G Pharmacokinetics:

Intravenous infusion

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Learning objectives

After completing this lecture, students should be able to:

1. Explain steady state during intravenous continuous infusion.
2. Describe how half-life affects the time required to reach steady state.
3. Describe the situations where continuous IV infusion stops before or after the steady state is reached.
4. Calculate plasma concentration of a drug following continuous IV infusion before or after the steady state is reached.
5. Explain the reason why a loading dose is required right before continuous IV infusion.
6. Solve problems related to the calculation of a loading dose and plasma concentration of a drug at any time after a loading dose and immediate IV infusion.

Intravenous infusion

Intravenous infusion

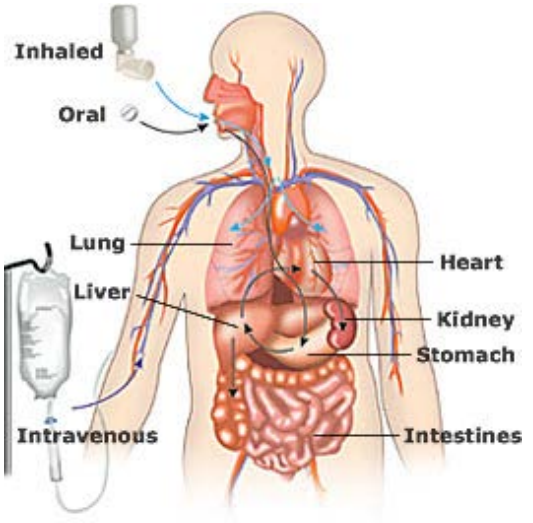
Introduction:

Drug administration route:

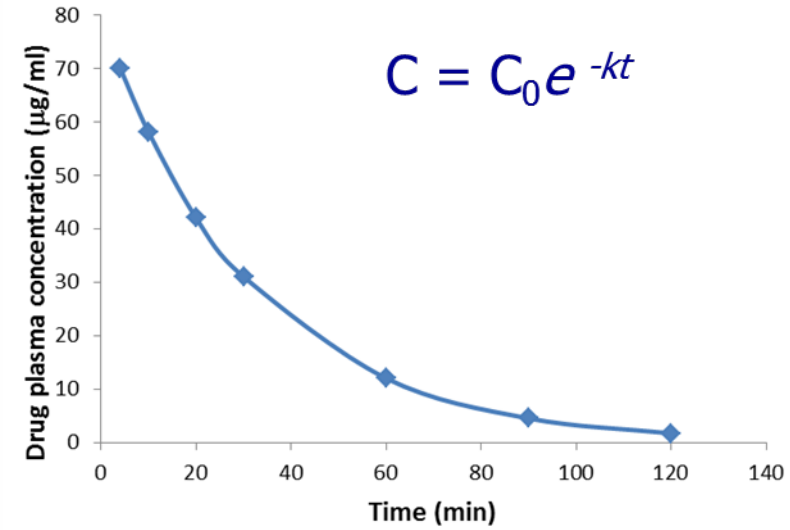
--- oral, topical, or parenteral

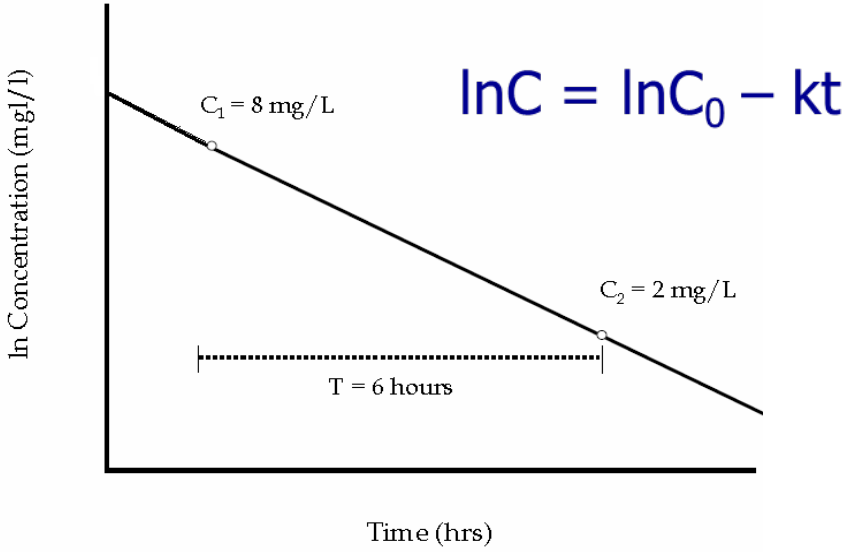
--- parenteral: intravenous, subcutaneous, and intramuscular

--- intravenous: intravenous bolus and intravenous infusion



Intravenous Bolus Dosing:



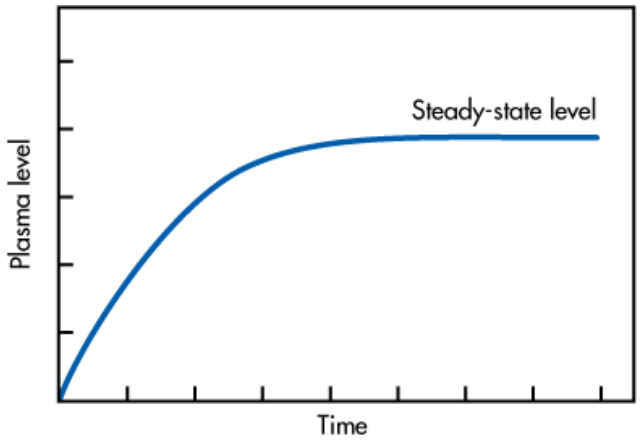


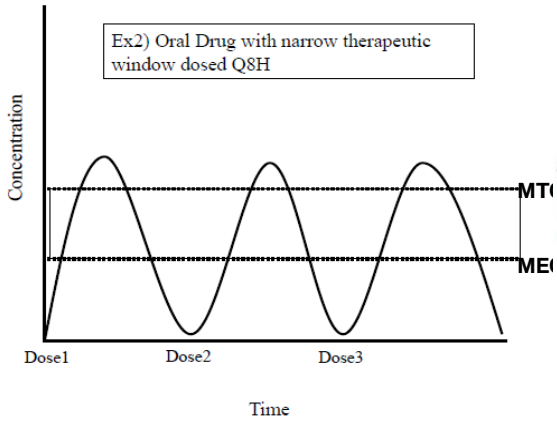
Intravenous infusion

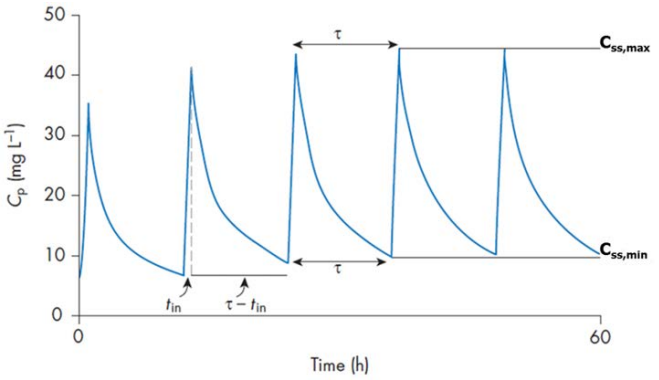
Introduction:

Intravenous infusion:

--- Drug is infused slowly through a vein into the plasma at a constant rate.
--- It allows precise control of C_p to match the individual needs of the patient.
--- It maintains an effective constant C_p for drugs with a narrow therapeutic window.
--- Continuous IV infusion avoids wide fluctuation between C_{max} and C_{min}.
--- It allows co-administration of drugs (antibiotics) with IV fluids (electrolytes and nutrients).
--- It allows easy control of maintenance or termination of drug therapy.







Intravenous infusion

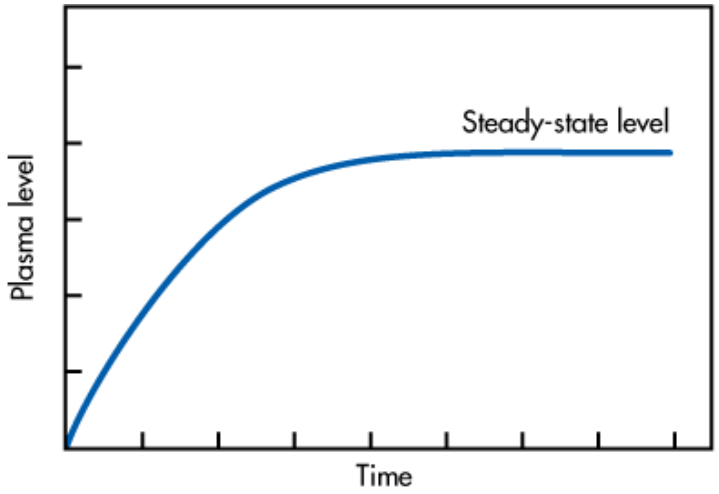
Continuous IV infusion:

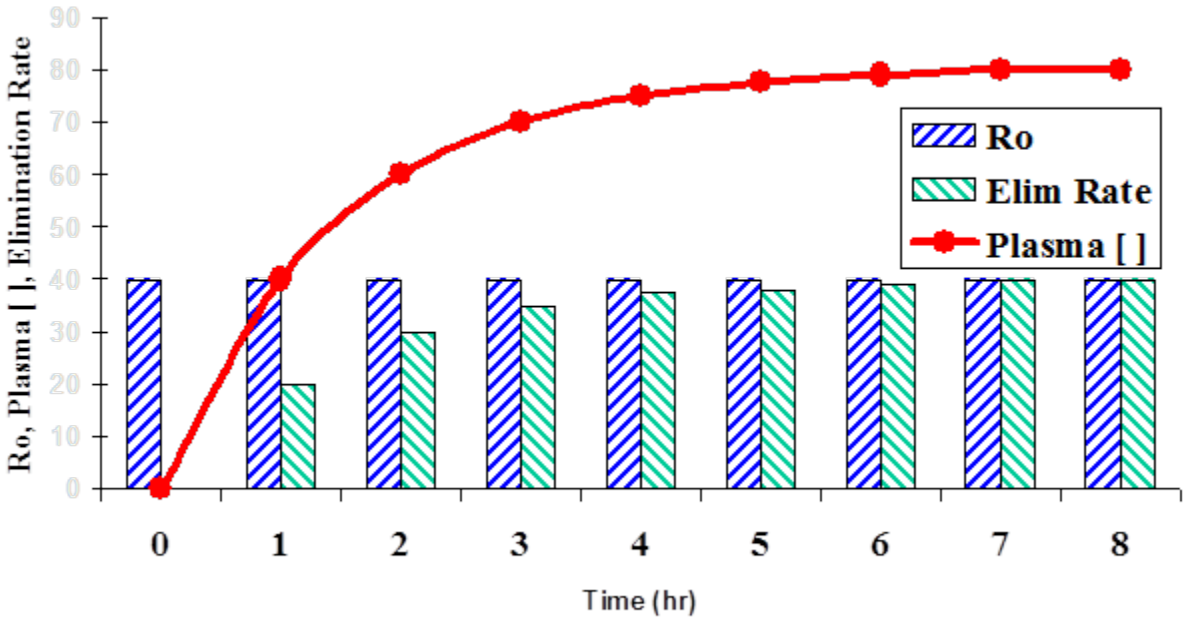
--- At time zero, $C_p = 0$

--- At steady state,

Rate of drug input (infusion rate) =

Rate of drug output (elimination rate)





Intravenous infusion

Continuous IV infusion: one compartment model drugs

--- dD/dt: The change in the amount of drug in the body at any time

--- dD/dt = rate of input – rate of output

--- Differential equation: $dD/dt = R_a - k_eD$

D: the amount of drug in the body

R_a: the infusion rate (zero order)

k_e: the elimination rate constant (first order)

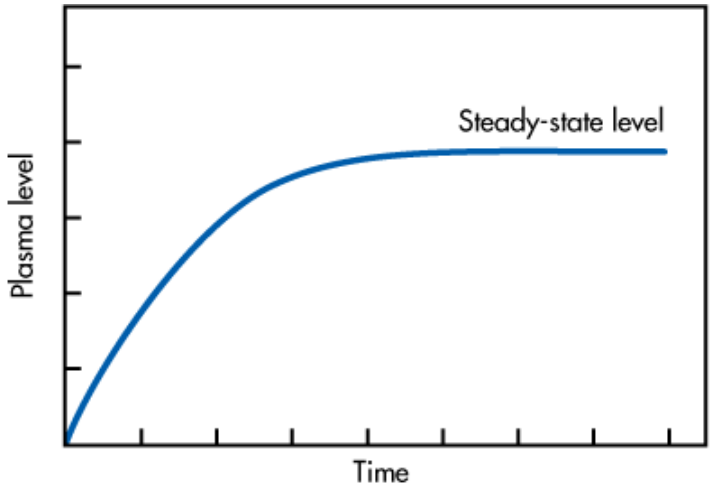
--- Integrated equation with substitution of $D = C_p \cdot V_d$:

$$C_p = \frac{S \cdot F \cdot R_a}{k_e \cdot V_d}(1 - e^{-k_e \cdot t})$$

Intravenous infusion

Continuous IV infusion: one compartment model drugs

$$C_p = \frac{S \cdot F \cdot R_a}{k_e \cdot V_d}(1 - e^{-k_e \cdot t})$$



At infinite time ($t = \infty$), $e^{-k_e t}$ approaches zero and $1 - e^{-k_e t} = 1$.

C_p is drug plasma concentration at steady state C_{ss}.

$$C_{ss} = \frac{S \cdot F \cdot R_a}{k_e \cdot V_d} \Rightarrow C_{ss} = \frac{S \cdot F \cdot R_a}{Cl}$$

Intravenous infusion

Continuous IV infusion: one compartment model drugs

$$C_{ss} = \frac{S \cdot F \cdot R_a}{Cl}$$

$$R_a = \frac{Dose}{\tau}$$

$$\Rightarrow \quad C_{ss} = \frac{S \cdot F \cdot Dose/\tau}{Cl}$$

Clearance:

--- proportionality constant relates steady state drug plasma concentration to rate of drug administration.

$S \cdot F \cdot R_a = \mathbf{Cl} \cdot C_{ss}$

$$Cl = \frac{S \cdot F \cdot Dose/\tau}{C_{ss}}$$

Intravenous infusion

Continuous IV infusion: one compartment model drugs

1) A.J. is a 65 kg patient with asthma. What would be an appropriate infusion rate of drug A if the target steady-state concentration were 12 mg/L? Given that V_d = 0.50 L/Kg and $t_{1/2}$ = 8.0 hour for drug A.

2) B.M. is a 76 kg patient with asthma receiving 40 mg/hr of drug X. A steady-state plasma level was 16.9 mg/L. What would be an appropriate infusion rate for B.M. if the target steady-state plasma level were 12 mg/L?

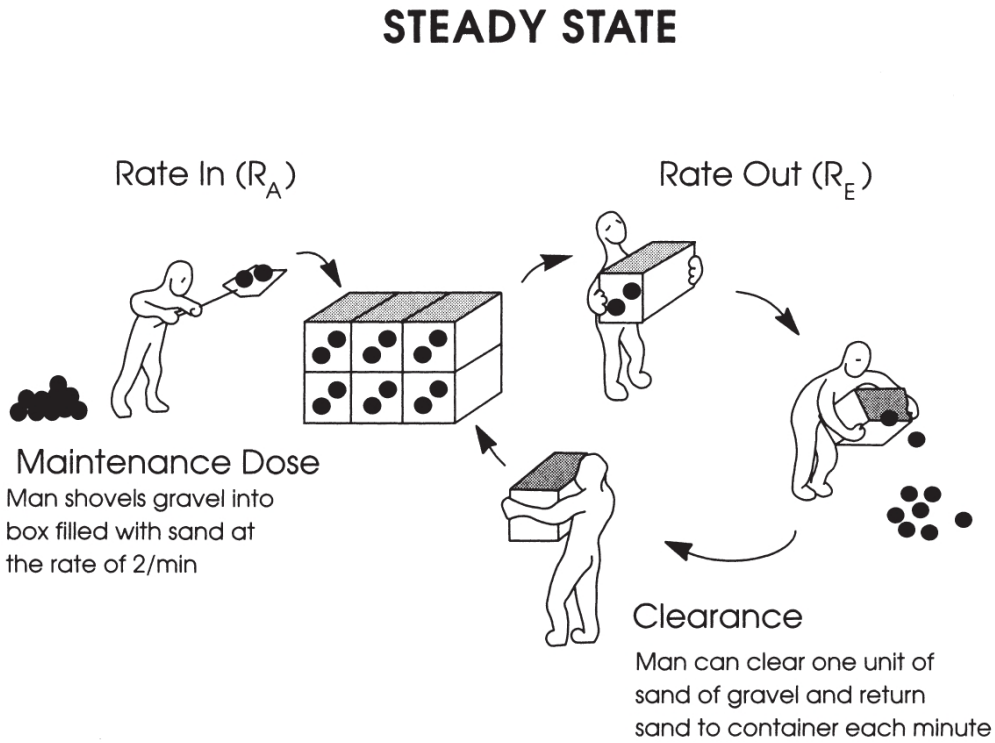
Intravenous infusion

Continuous IV infusion: one compartment model drugs

Steady-state drug concentration (C_{ss}):

--- C_p where the rate of drug leaving the body equal to the rate of drug entering the body (No net change in the amount of drug in the body).

--- C_{ss} remains constant at steady state.

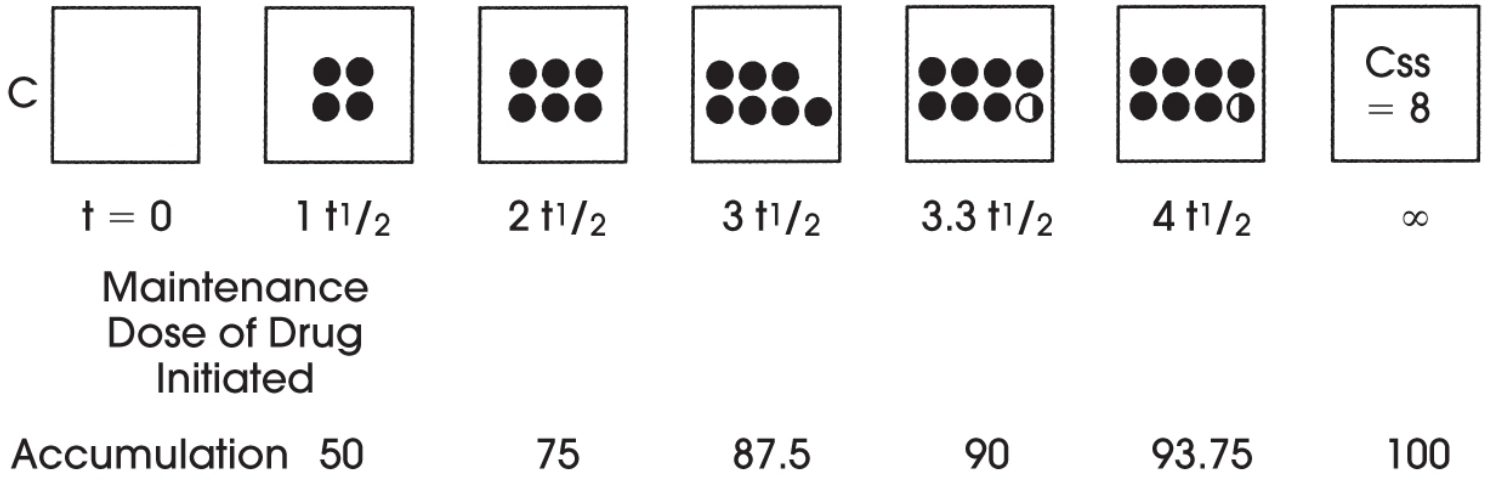


Intravenous infusion

Continuous IV infusion: one compartment model drugs

Time required to reach C_{ss}:

--- Depending on the elimination half-life of the drug.



Percent of C_{ss} Reached	Number of Half-Lives
90	3.32
95	4.32
99	6.65

Intravenous infusion

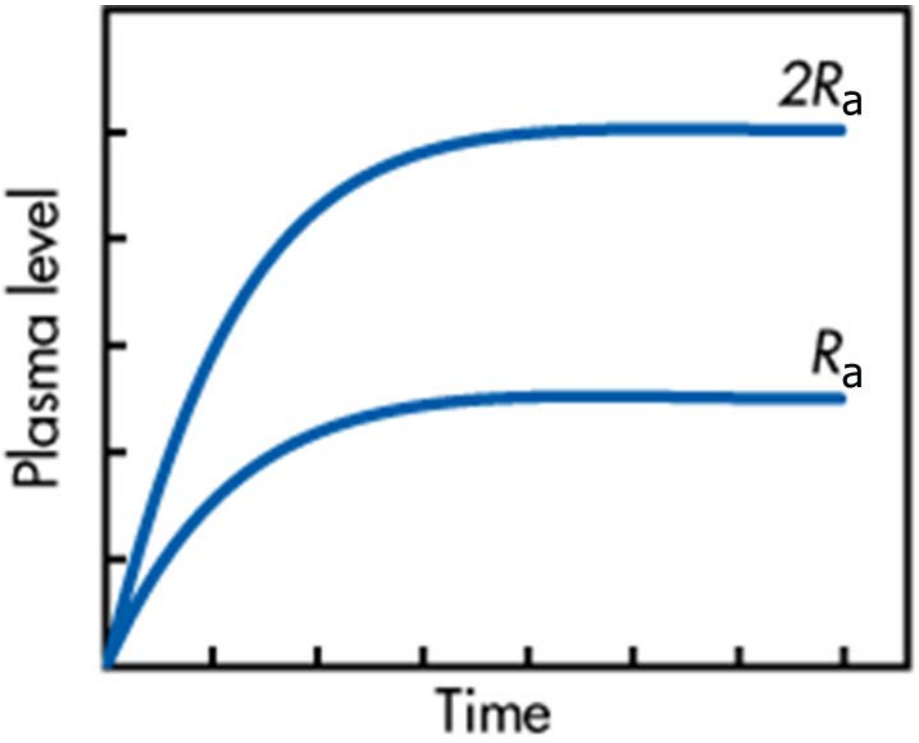
Continuous IV infusion: one compartment model drugs

Effect of R_a on C_{ss}:

--- Increase in R increase C_{ss}.

--- increase in R does NOT shorten the time to reach C_{ss}.

$$C_{ss} = \frac{S \cdot F \cdot R_a}{Cl}$$

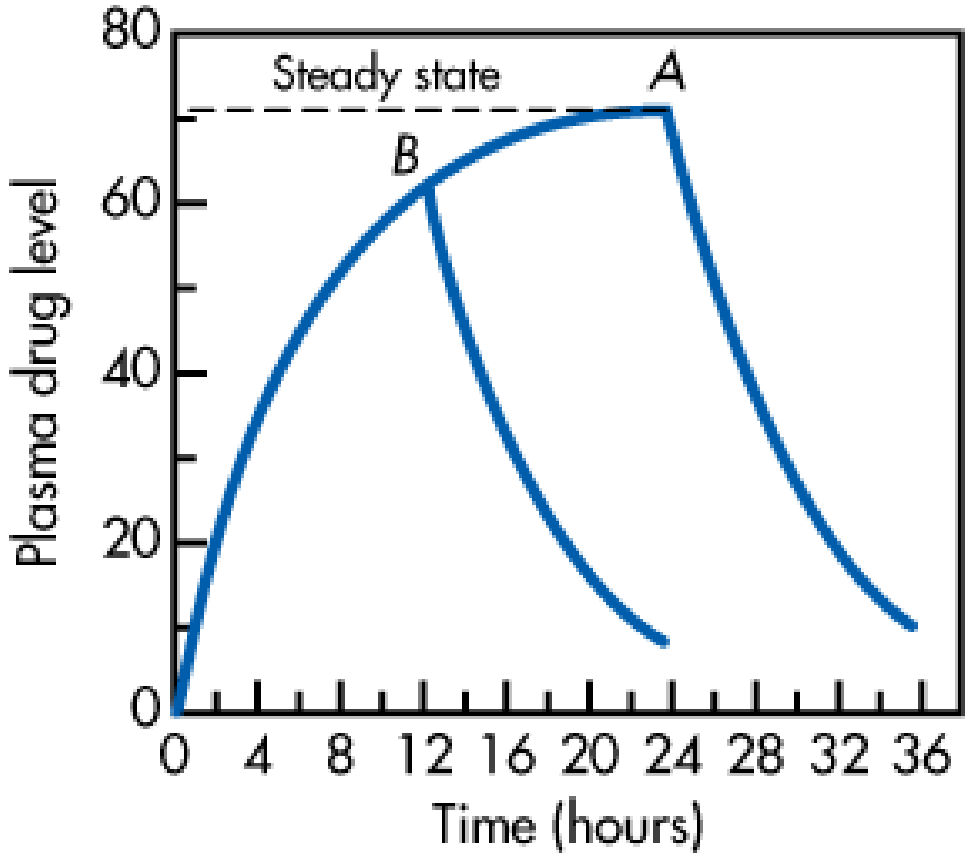


Intravenous infusion

Continuous IV infusion: one compartment model drugs

CASE 1: Infusion stopped prior to steady state

CASE 2: Infusion stopped after steady state is reached



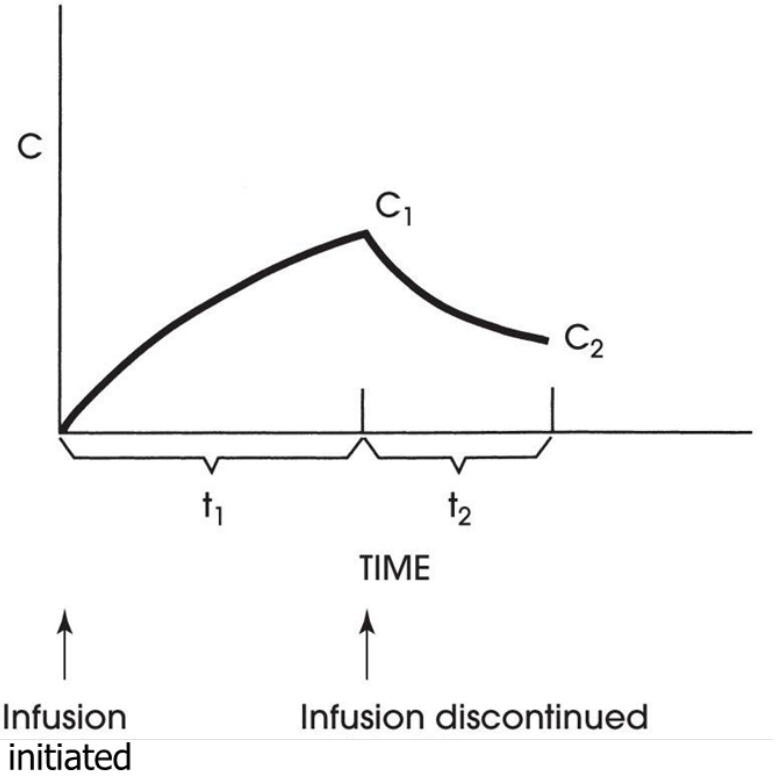
Intravenous infusion

Continuous IV infusion: one compartment model drugs

CASE 1: Infusion stopped prior to steady state

$$C_1 = \frac{S \cdot F \cdot R_a}{Cl}\left(1 - e^{-k_e \cdot t_1}\right)$$

$$C_2 = \frac{S \cdot F \cdot R_a}{Cl}\left(1 - e^{-k_e \cdot t_1}\right) \cdot e^{-k_e \cdot t_2}$$



Intravenous infusion

Continuous IV infusion: one compartment model drugs

CASE 1: Infusion stopped prior to steady state

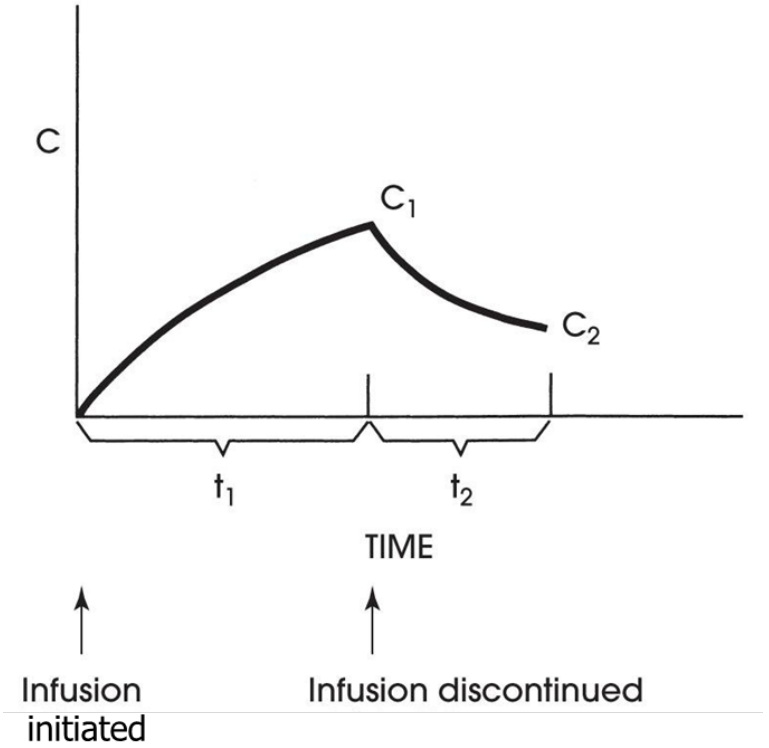
$$C_1 = \frac{S \cdot F \cdot R_a}{Cl}(1 - e^{-k_e \cdot t_1}) \qquad C_{ss} = \frac{S \cdot F \cdot R_a}{Cl}$$

Fraction of steady state achieved at time t_1:

$$(1 - e^{-k_e \cdot t_1})$$

$$C_2 = \frac{S \cdot F \cdot R_a}{Cl}(1 - e^{-k_e \cdot t_1}) \cdot e^{-k_e \cdot t_2} \qquad C_2 = C_1 \cdot e^{-k_e \cdot t_2}$$

Fraction of drug remaining at t_2 : $e^{-k_e \cdot t_2}$



Intravenous infusion

Continuous IV infusion: one compartment model drugs

CASE 1: Infusion stopped prior to steady state

Example: A drug was administered at a rate of 500 mg/hr by iv infusion (S=1). This drug has a clearance of 5.0 L/hr and an elimination half life of 5 hr.

a) Estimate the drug plasma concentration 10 hr after the initiation of the infusion.

b) If the drug was infused for 10 hr, estimate the drug plasma concentration 15 hr after the initiation of the infusion.

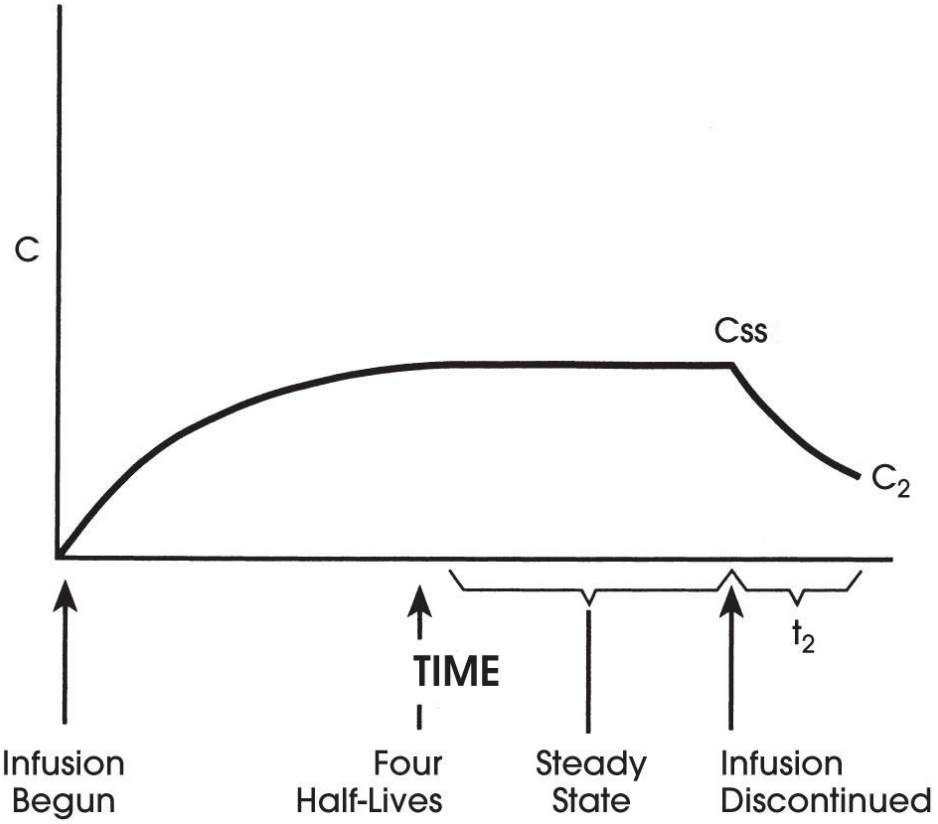
Intravenous infusion

Continuous IV infusion: one compartment model drugs

CASE 2: Infusion stopped after steady state is reached

$$C_1 = C_{ss} = \frac{S \cdot F \cdot R_a}{Cl}$$

$$C_2 = C_{ss} \cdot e^{-k_e \cdot t_2}$$



Intravenous infusion

Continuous IV infusion: one compartment model drugs

CASE 2: Infusion stopped after steady state is reached

Example: An Aminophylline (ethylene diamine salt of theophylline) infusion was administered at a rate of 100 mg/hr to a patient (S=0.8). This patient has a theophylline clearance of 2.8 L/hr and an elimination half life of 3 hr.

a) Estimate the expected steady-state plasma concentration of theophylline after the initiation of the infusion.

b) If the drug was infused for 20 hr, estimate the drug plasma concentration 25 hr after the initiation of the infusion.

Intravenous infusion

Continuous IV infusion: one compartment model drugs

Continuous IV infusion + Loading dose:

Reason:

--- It usually takes 4 to 5 half-lives for a drug to reach steady state concentration after continuous IV infusion.

--- An immediate therapeutic effect of the drug is desired.

Limitation:

--- Drugs with substantial side effect at large doses.

--- Drugs preferred to be accumulated slowly rather than achieving therapeutic concentrations immediately.

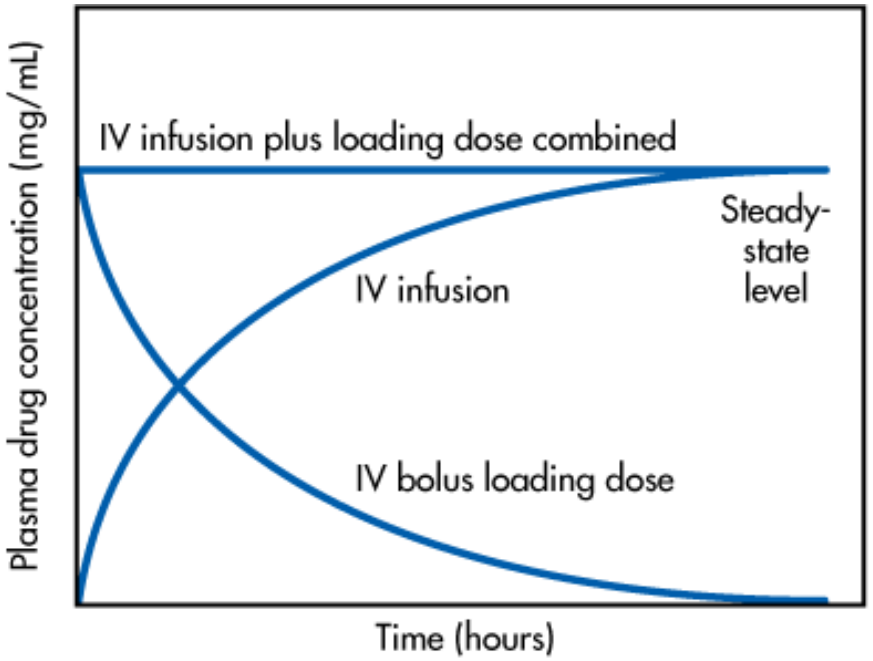
Intravenous infusion

Continuous IV infusion: one compartment model drugs

Continuous IV infusion + Loading dose (IV bolus):

C_p from loading dose (LD) only:

$$C_p = C_0 \cdot e^{-k_e \cdot t} = \frac{S \cdot F \cdot LD}{V_d} \cdot e^{-k_e \cdot t}$$



C_p from IV infusion only:

$$C_p = \frac{S \cdot F \cdot R_a}{k_e \cdot V_d}(1 - e^{-k_e \cdot t})$$

C_p from combined IV bolus of a LD and IV infusion given at the same time:

$$C_p = \frac{S \cdot F \cdot LD}{V_d} \cdot e^{-k_e \cdot t} + \frac{S \cdot F \cdot R_a}{k_e \cdot V_d}(1 - e^{-k_e \cdot t})$$

Intravenous infusion

Continuous IV infusion: one compartment model drugs

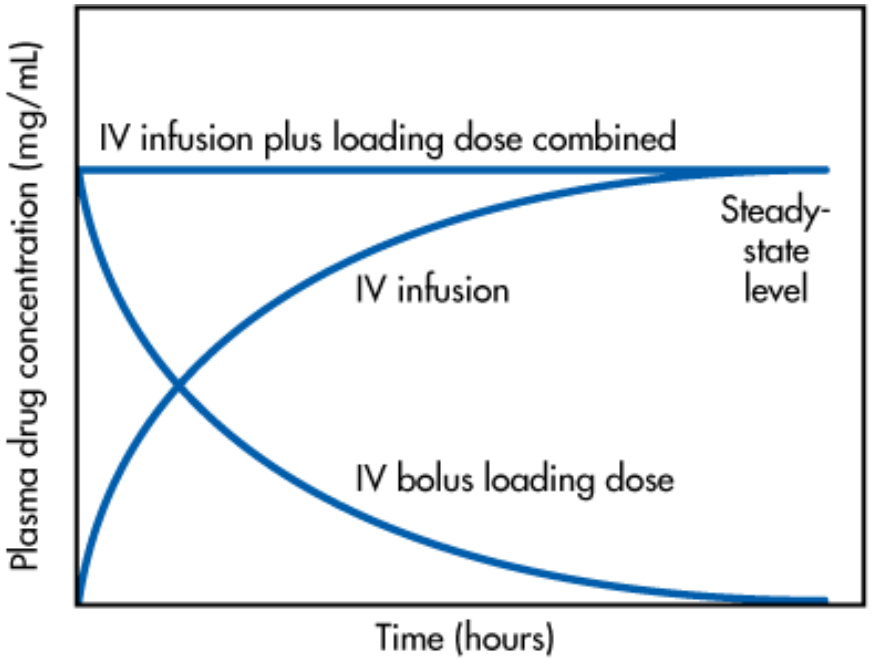
Continuous IV infusion + Loading dose (IV bolus):

How to calculate loading dose (LD):

$$LD = \frac{C_{ss} \cdot V_d}{S \cdot F}$$

Recall equation for C_{ss}:

$$C_{ss} = \frac{S \cdot F \cdot R_a}{k_e \cdot V_d} \Rightarrow \frac{C_{ss} \cdot V_d}{S \cdot F} = \frac{R_a}{k_e}$$



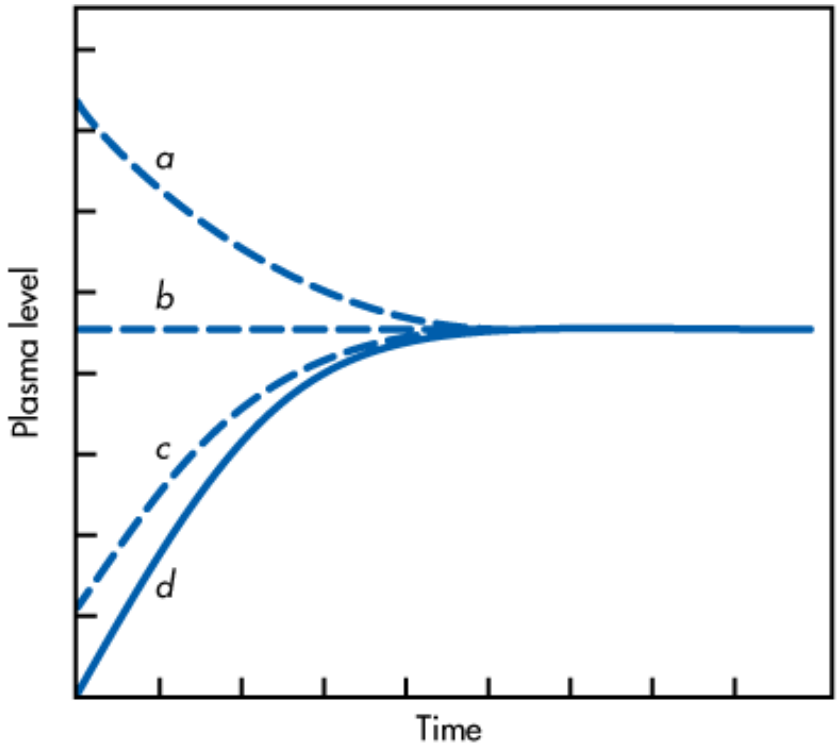
Equation for LD:

$$LD = \frac{R_a}{k_e}$$

Intravenous infusion

Continuous IV infusion: one compartment model drugs

Continuous IV infusion + Loading dose (IV bolus):



Intravenous infusion with loading doses a ($>R_a/k_e$), b ($=R_a/k_e$), and c ($<R_a/k_e$). Curve d represents an IV infusion without loading dose.

Intravenous infusion

Continuous IV infusion: one compartment model drugs

Continuous IV infusion + Loading dose (IV bolus): practice problems

1) A physician wants to administer an anesthetic agent at a rate of 2 mg/hr by IV infusion. The elimination rate constant is 0.1 hr^{-1} and the volume of distribution (one compartment) is 10 L. What loading dose should be recommended if the doctor wants the drug level to reach 2 μg/mL immediately?

2) What is the concentration of a drug 6 hours after administration of a loading dose (IV bolus) of 10 mg and simultaneous infusion at 2 mg/hr (the drug has a $t_{1/2}$ of 3 hours and a volume of distribution of 10 L)?

Intravenous infusion

Continuous IV infusion: one compartment model drugs

fast IV infusion (Loading dose) followed by slow IV infusion:

For example,
A patient needs to receive drug T ($k = 0.17\ hr^{-1}$; $V_d = 25$ L) with a required $C_p = 14.1$ mg/L. If we wish to give a loading dose in the form of a fast infusion over 30 minutes we need to give the infusion at a rate which will produce $C_p = 14.1$ mg/L at 30 minutes. Therefore, $C_{p(30\ min)} = 14.1$ mg/L. Calculate the fast infusion rate R_a.

Intravenous infusion

Continuous IV infusion: one compartment model drugs

loading dose + multiple continuous IV infusion:

A male patient (70 kg) is given drug X by continuous IV infusion. The following dosage regimen is provided:

a) A loading dose of 550 mg drug X was given by IV bolus followed immediately by IV infusion;
b) 1st continuous IV infusion of 60 mg/hr is administered for 30 hrs and then stopped for 12 hr;
c) 2nd continuous IV infusion of 50 mg/hr is administered for 15 hrs and then stopped for 2 hr.

What is the concentration of drug X at this time?

Assume V_d = 0.48 L/kg and Cl = 3.6 L/hr.

Intravenous infusion

Continuous IV infusion: two compartment model drugs

--- Many drugs given by IV infusion follow 2-compartment kinetics.
examples: theophylline and lidocaine

--- C_{ss} is achieved after a distribution equilibrium is reached between central and tissue compartment.

--- Constant C_{ss} results in constant drug concentrations in the tissue.

--- At steady state, C_{plasma} does not equal to C_{tissue}.

--- Continuous IV infusion + Loading dose (IV bolus):

Note: It is not possible to maintain an instantaneous, stable steady-state blood level for a two-compartment model drug with a zero-order rate of infusion.

Reference

1. Winter's Basic Clinical Pharmacokinetics, 6th Edition (2018), Beringer, PM.

2. Concepts in Clinical Pharmacokinetics, 6th Edition (2014), DiPiro, JT, *et al*.

3. Applied Biopharmaceutics and Pharmacokinetics, 7th Edition (2016), Shargel, L, *et al*.

The End

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