**IV Infusion**

**Outline**
- Infusion plasma C vs. T
- The plateau value
- Approaching plateau
- Time to reach plateau
- Post infusion
- Change infusion rate
- Bolus and infusion
- Calculate PK parameters from infusion data
  - During infusion
  - Post infusion
  - Post infusion before Css has been reached

**Constant-Rate Regimens**
- IV infusion
  - Maintain constant plasma or tissue concentration
  - Infusion pump or drip
  - Mainly in hospital setting
- Controlled release device achieve the same purpose
- Transdermal delivery
- Implants

**IV Infusion**

\[ \text{R0} \]

\[ \text{C, V} \]

\[ \text{Elimination} \]

- \( \text{R0} = \text{amount} / \text{time} \)
1. Infusion Plasma C – T Relationship

2. The Plateau Value

2. The Plateau Value

1. Infusion Plasma Concentration C vs. T

- Time 0: amount of drug in the body is zero, no elimination
- Time 0-t: amount of drug in the body increase
- Plateau:
  - rate of infusion = rate of elimination
  - Plasma C reaches steady state (plateau)
  - Rate of change is zero

- Rate change in the body = rate of infusion – rate of elimination
  - Ro: constant rate of infusion
  - K.A: rate of elimination

\[
\frac{dA}{dt} = Ro - k \cdot A \\
V \cdot \frac{dC}{dt} = Ro - CL \cdot C
\]
2. The Plateau Value

- Amount of drug in the body at steady state is determined by
  - Infusion rate
  - Elimination constant
- Steady state plasma concentration is determined by
  - Infusion rate
  - Clearance
- All drug infused at the same rate and have the same CL reach the same plateau concentration
  - The amount of drugs in the body vary with volume of distribution.
- All drugs infused with same rate and having the same half life accumulate same amount of drugs at the plateau

2. The Plateau Value: Example

- Theophyline
  - CL = 4 L/h
  - Infusion rate = 60 mg/h
  - K = 0.14 hr⁻¹
  - V = 29 L
  - Desired Plasma Css = 15 mg/L
- How much drug in the body at steady state
  - Ass = Ro/k = 60 /0.14 = 428 mg
  - Ass = Css . V = 15 x 29 = 435 mg
- If you find plasma C (15 mg/L) is too high, you need to decrease the desired plasma C to 10 mg/L in another patient (assume the drug’s PK is the same). What infusion rate you need to adjust?

3. Approaching Plateau

\[ \frac{dA}{dt} = R_0 - k \cdot A \]

Integrate both sides

\[ A = \frac{R_0}{k} (1 - e^{-kt}) = A_{ss} (1 - e^{-kt}) \]

Divided both sides by V

\[ C = C_{ss} (1 - e^{-kt}) \]

3. Approaching Plateau: Loading dose analogy
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- To reach certain desired plasma level $C_{ss}$
  - Loading dose by IV bolus: $D = Ass = \frac{R_0}{k}$
- The plasma level $C_{ss}$ can be maintained by infusion $(R_0)$ thereafter.
- The amount of drug eliminated from IV bolus dose at any given time

$$A_{\text{remaining from bolus dose}} = A_{ss} \cdot e^{-kt}$$

4. Time to Reach Plateau

<table>
<thead>
<tr>
<th>Time (in half lives)</th>
<th>Percent of plateau (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>29</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>87.5</td>
</tr>
<tr>
<td>3.3</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>93.75</td>
</tr>
<tr>
<td>5</td>
<td>97</td>
</tr>
</tbody>
</table>

3. Approaching Plateau: Loading dose analogy

- The drug loss from IV bolus will be exactly matched from IV infusion to maintain the plateau $(Ass)$

$$A_{\text{inf}} = A_{ss} - A_{ss} \cdot e^{-kt}$$

Divide both side by $V$

$$C_{\text{inf}} = C_{ss} (1 - e^{-kt})$$
4. Time to Reach Plateau

- Half life is the only factor to control the time to reach plateau
  - The shorter of half life, the sooner is the plateau reached
- The time is independent of infusion rate and plateau concentration
  - Although infusion rate and the plateau concentration will be different

Example

- The recombinant tissue-type plasminogen activator (t-PA): a drug with a short t½ (5 min) would reach a plateau after a short infusion (~17.5 minutes)
- A drug with a long t½, like phenobarbital (t½ =100 hr) would not reach steady-state for a really long time (~15 days).
- This becomes important to clinicians when they try to attain therapeutic results over a long period of time and avoid toxicity

5. Infusion Rate and Infusion Time

- Infusion rate (dose) is based on CL and desired Css
  - Css is determined by infusion rate and clearance
- Infusion time is based on $T_{1/2}$
  - Time to reach Css is only determined by $T_{1/2}$

6. Post-Infusion

- Postinfusion after steady state
  - Amount of drug in the body Ass
  - Steady state concentration Css
  - The decline of A or C follow the IV bolus kinetics from Ass or Css
- Postinfusion before steady state
  - Amount of drug in the body $A_{inf}$
  - Steady state concentration $C_{inf}$
  - The decline of A or C follow the IV bolus kinetics from $A_{inf}$ or $C_{inf}$
7. Changing Infusion Rate

- If first infusion reaches plateau ($C_{ss1}$), new infusion rate needs to be adjusted to reach $C_{ss2}$.
  - Since $C_{ss} = R_0 / CL$
    - To double $C_{ss}$, double $R_0$
    - To halve $C_{ss}$, halve $R_0$
  - The time to reach new $C_{ss2}$ from $C_{ss1}$ is solely depends on the $T_{1/2}$.

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7. Changing Infusion Rate

- If first infusion has not reach plateau ($C_{inf}$), new infusion rate needs to be adjusted to reach new plateau ($C_{ss2}$).
  - The time to reach new $C_{ss2}$ from $C_{inf}$ is solely depends on the $T_{1/2}$.

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7. Changing Infusion Rate: Example 1

- Theophylline
  - Original infusion rate = ($C_{ss1}$ x CL) = 30 mg/min
  - $C_{ss1}$ = 7.5 mg/L
  - New target conc $C_{ss2}$ = 15 mg/L
  - New infusion rate = $C_{ss2}$ x CL = 60 mg/min
  - Time to reach new plateau is dependent on $T_{1/2}$.
7. Changing Infusion Rate: Example 2

- **T-PA**
  - IV bolus 10 mg
  - C = 350 IU/ml
  - IV infusion rate = 1.6 mg/min for 60 min
  - C<sub>s1</sub> = 550 IU/min
  - IV infusion rate drop to 0.3 mg/min
  - C<sub>s2</sub> = ~103 UI/ml
  - Time to reach is dependent on T<sub>1/2</sub> (but since there was a first infusion, the time to reach plateau may be longer than that of only one infusion)

8. Bolus and Infusion

- **Loading dose**
  - IV bolus
  - C<sub>s</sub> can reach rapidly due to clinical demand
  - Dose = V . Css
  - Ass = R<sub>0</sub>/K
    - When Dose = Ass, maintain Css at time 0
    - When Dose > Ass, C will gradually decrease to Css
    - When Dose < Ass, C will gradually increase toCss

- **Maintenance dose**
  - Infusion to maintain Css
  - Infusion dose
    - Infusion rate R<sub>0</sub> = Css . CL

**8. Bolus and Infusion: Example**

- **Drug X**
  - IV bolus, Initial C(0) = 500 ug/L
  - IV infusion, Css = 100 ug/L
  - Desired C = 110 ug/L
  - How long the desired C (110 ug/L) can be reached?
8. Bolus and Infusion: Example

\[ C = C(0) \cdot e^{-kt} + C_{ss} \cdot (1 - e^{-kt}) \]

\[ C = C(0) \cdot e^{-kt} + C_{ss} - C_{ss} \cdot e^{-kt} \]

\[ (C_{ss} - C(0)) \cdot e^{-kt} = C_{ss} - C \]

\[ e^{-kt} = \frac{C_{ss} - C}{C_{ss} - C(0)} \]

9. Calculate PK Parameters From IV Infusion Plasma Data (Example)

- Drug Y
- Infusion rate = 40 mg/hr
- Css = 9.5 mg/L
- Calculate
  - CL
  - V
  - T_{1/2}

8. Bolus and Infusion: Example

\[ n = \frac{t}{t_{1/2}} \quad k = \frac{\ln 2}{t_{1/2}} \quad e^{-kt} = (\frac{1}{2})^n \]

\[ e^{-kt} = \frac{C_{ss} - C}{C_{ss} - C(0)} = (\frac{1}{2})^n \]

- Css = 100 ug/L
- C= 110 ug/L
- C(0) = 500 ug/L
- n = 5.5 half lives

9.1. Plasma C vs. T During and After IV Infusion

<table>
<thead>
<tr>
<th>Time, hr</th>
<th>C, mg/L</th>
<th>C_{ss} - C</th>
<th>ln(C_{ss} - C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>During Infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4.1</td>
<td>3.3</td>
<td>6.2</td>
</tr>
<tr>
<td>2</td>
<td>5.4</td>
<td>4.1</td>
<td>7.6</td>
</tr>
<tr>
<td>4</td>
<td>7.6</td>
<td>1.9</td>
<td>8.7</td>
</tr>
<tr>
<td>6</td>
<td>8.7</td>
<td>0.8</td>
<td>9.3</td>
</tr>
<tr>
<td>8</td>
<td>8.7</td>
<td>0.8</td>
<td>9.3</td>
</tr>
<tr>
<td>10</td>
<td>9.6</td>
<td>1.41</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>9.5</td>
<td>2.25</td>
<td></td>
</tr>
<tr>
<td>Post Infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.5</td>
<td>2.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.59</td>
<td></td>
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<tr>
<td>8</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>-1.97</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
9.1. Plasma C vs. T During and After IV Infusion

![Plasma Drug Concentration Graph]

9.2. Calculate CL

- \( CL = R_0 / C_{ss} = (40 \, \text{mg/hr}) / (9.5 \, \text{mg/L}) = 4.2 \, \text{L/hr} \)
  - Best way to calculate CL

9.3. Calculate K (or T1/2) (Method 1: During Infusion)

\[
C_{\text{inf}} = C_{ss} \left(1 - e^{-kt}\right)
\]
\[
C_{ss} - C_{\text{inf}} = C_{ss} \cdot e^{-kt}
\]
\[
\ln(C_{ss} - C_{\text{inf}}) = \ln C_{ss} - kt
\]

- Plot \( \ln(C_{ss} - C_{\text{inf}}) \) vs. t
  - Slope = \( k \)
  - \( T_{1/2} = \frac{0.693}{k} = 1.7 \text{hr} \)
- \( V = CL / k = CL \cdot T_{1/2} / 0.693 = 10 \, \text{L} \)
# 9.4. Calculate K (or T1/2)

Method 2: based on postinfusion data afterCss has been reached

<table>
<thead>
<tr>
<th>Time, hr Post-infusion</th>
<th>C, mg/L</th>
<th>ln(C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9.5</td>
<td>2.25</td>
</tr>
<tr>
<td>2</td>
<td>4.1</td>
<td>1.41</td>
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<tr>
<td>8</td>
<td>0.33</td>
<td>-1.11</td>
</tr>
<tr>
<td>10</td>
<td>0.14</td>
<td>-1.97</td>
</tr>
</tbody>
</table>

$$C = C_{ss} \cdot e^{-kt}$$

- Identical to IV bolus
  - When dose = Ass
  - C(0) = Css = 9.5 mg/L
- Slope = K
- $T_{1/2} = 0.693/K$
- What is the concentration two hour post-infusion (after Css) (mg/L)

$$C = 9.5 \cdot e^{-2k}$$

# 9.5. Post Infusion Before Css Has Been Achieved: Example

- A drug is administered by constant-rate intravenous infusion at a rate of 40 mg/hr for 6 hrs. Plasma levels are collected during and post the infusion and listed below.
- Estimate $t_{1/2}$, Css, and drug concentration at 5 hr post-infusion.

\[ C_1 = C_{ss} \left(1 - e^{-kt_1}\right) \]

\[ C_2 = C_1 \cdot e^{-kt_2} \]
Plasma C vs. t during and post infusion before C curves has been reached

<table>
<thead>
<tr>
<th>Time, hr (t1)</th>
<th>Time, hr (t2)</th>
<th>C, mg/L</th>
<th>ln(C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>During infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>3.3</td>
<td>1.17</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>5.4</td>
<td>1.66</td>
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<td>3</td>
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<td>4</td>
<td>4</td>
<td>7.6</td>
<td>1.97</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>8.7</td>
<td>2.12</td>
</tr>
<tr>
<td>Post infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>5.5</td>
<td>1.71</td>
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<tr>
<td>14</td>
<td>8</td>
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<td>-1.44</td>
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</tbody>
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