Dosing Regimen Design
Multiple Dosing

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Objectives

Through the preparation for and participation in this lecture, a successful student should be able to:

- Use the Multiple Dosing Function to convert a single dose equation to a multiple dose equation.
- Use the accumulation index to convert a single dose equation to a steady-state equation and predict the extent of drug accumulation for a given dosage regimen.
- List the factors that determine if a drug concentration will stay within a given therapeutic target window.
- Develop and alter a dosage regimen under given conditions.
Multiple Dosing

Most drugs are given more than once. ∴ we need to be able to understand and predict what will happen when a dose of drug is given repeatedly at constant intervals.
Bolus Dosing
Principle of Superposition

Log Plasma Drug Conc

Cmax₁

Cmin₁

Cmax₂

Cmin₂

Cmax₁

Cmax₂

Etc for “n” doses
Recall,

\[ C_{\text{max}2} = C_{\text{max}1} + C_{\text{min}1} \]
\[ C_{\text{min}1} = C_{\text{max}1} e^{-k\tau} \]
\[ C_{\text{max}2} = C_{\text{max}1} + C_{\text{max}1} e^{-k\tau} \]
\[ C_{\text{max}2} = C_{\text{max}1} (1 + e^{-k\tau}) \]

etc...
Before Steady State: Multiple Dosing Function (MDF)

MDF is used to convert a single dose equation to a multiple dose equation

\[
MDF = \frac{1 - e^{-n \cdot k \cdot \tau}}{1 - e^{-k \cdot \tau}}
\]
Bolus Dosing
Using MDF

- Fast Forward from first dose to any dose after that
  - Concentration after single dose $\times$ MDF = Concentration at that time at “n” doses
  - Equation for single dose $\times$ MDF = Equation at “n” doses
Recall

- \( e^{-kt} \) = fraction of drug remaining at time “t”
- \( \therefore e^{-k\tau} \) = fraction of drug remaining at the end of the dosing interval
- \( 1-e^{-kt} \) = fraction of drug removed at time “t”
- \( \therefore 1-e^{-k\tau} \) = fraction of drug removed at the end of the dosing interval
Review: $C_p = C_0 e^{-kt}$

- $b = y$-intercept
- $m = \text{slope}$
- $m = \frac{\Delta Y}{\Delta X}$
- $m = \frac{Y_2 - Y_1}{X_2 - X_1}$
- $Y = mX + b$

- $-k = \frac{\Delta \ln C}{\Delta t}$
- $-k = \ln C_2 - \ln C_1 / t_2 - t_1$
- $\ln C_p = -kt + C_0$
- Antilog: $C_p = C_0 e^{-kt}$
Using MDF

\[ C_t = C_0 e^{-kt} \]

If given by instantaneous input the highest concentration occurs at \( t=0 \).

\[ \therefore C_0 = \frac{F \cdot Dose}{V_D} \]

\[ C_t = \frac{F \cdot Dose}{V_D} \left( \frac{1 - e^{-n \cdot k \cdot \tau}}{1 - e^{-k \cdot \tau}} \right) e^{-kt} \]
At “n” doses

\[ C_t = \frac{F \cdot Dose}{V_D} \left( \frac{1 - e^{-n \cdot k \cdot \tau}}{1 - e^{-k \cdot \tau}} \right) e^{-kt} \]

Multiple Dosing Function
Bolus Dosing

SS is reached
Using MDF to Determine Steady State Concentrations

\[
MDF = \left( \frac{1 - e^{-n \cdot k \cdot \tau}}{1 - e^{-k \cdot \tau}} \right)
\]

When \( n = \text{large number} \) \( e^{-nk\tau} \) approaches 0

\[
MDF_{n \uparrow} \approx \left( \frac{1 - 0}{1 - e^{-k \cdot \tau}} \right) \approx \frac{1}{1 - e^{-k \cdot \tau}}
\]
At Steady State = Accumulation Index/Factor

\[ R_{ac} = \frac{1}{1 - e^{-k\tau}} \]

Relates the concentrations in the dosing interval at steady state to the values after a single dose.
Accumulation

- used to “fast forward” from first dose concentrations to steady-state concentrations
Using $R_{ac}$

- Fast Forward to steady-state
  - Concentration for single dose $X$ $R_{ac}$ = Concentration at steady-state
  - Equation for single dose $x$ $R_{ac}$ = Equation at Steady-State
Determinants of Accumulation

- Frequency of Administration ($\tau$) relative to
- Half-life ($t_{1/2}$)

\[
\frac{1}{2} \frac{t}{\tau} \quad \text{OR} \quad \frac{1}{k\tau}
\]
Example

- Given $t_{1/2} = 6$ hrs & $\text{Tau} = 6$ hrs, what happens when:
  - $\text{Tau}=t_{1/2}$
  - $\text{Tau}>t_{1/2}$; eg. Tau is 5 times greater than $t_{1/2}$
  - $\text{Tau}<t_{1/2}$; eg. Tau is 1/3 of $t_{1/2}$
- Calculate $R_{ac}$

$$R_{ac} = \frac{1}{1 - e^{-k\tau}}$$
### Application of Accumulation Index (Rac)

<table>
<thead>
<tr>
<th>Prediction</th>
<th>t1/2 (hrs)</th>
<th>Tau (hrs)</th>
<th>k</th>
<th>Rac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tau = t1/2</td>
<td>6</td>
<td>6</td>
<td>0.1155</td>
<td>2.000294</td>
</tr>
<tr>
<td>Tau 5 x &gt; t1/2</td>
<td>6</td>
<td>30</td>
<td>0.1155</td>
<td>1.032283</td>
</tr>
<tr>
<td>Tau 1/3 t1/2</td>
<td>6</td>
<td>2</td>
<td>0.1155</td>
<td>4.848237</td>
</tr>
</tbody>
</table>

\[
t_{1/2} = \frac{0.693}{k}; \quad k = \frac{0.693}{t_{1/2}}
\]

\[
R_{ac} = \frac{1}{1 - e^{-k\tau}}
\]
Application of $R_{ac}$
Prediction: $\tau$ relative to $t_{1/2}$

- When $\tau = t_{1/2}$: 2
- When $\tau > t_{1/2}$: No or less accumulation
- When $\tau < t_{1/2}$: More accumulation
Example: $t_{1/2} = 6$ hours

- If $\tau$ is 6 hours $R_{ac} = 2$, $C_{SS} \approx 2 \times$ first dose
- If $\tau$ is 30 hours ($\sim >5$ times $t_{1/2}$) $R_{ac} \rightarrow 1$
  no accumulation; all of the drug will be eliminated from the first dose before the second is given.
- If $\tau$ is 2 hours ($1/3$ $t_{1/2}$) the $R_{ac}$ would be 4.8. Conc, $C_{SS} \sim 5 \times$ first dose
Application of $R_{ac}$

Calculation of Loading Dose

$$LD = MD \times R_{ac}$$

$\tau = t_{1/2}$  \quad $R_{ac} = 2$  \quad $\therefore LD = MD \times 2$

$\tau > t_{1/2}$  \quad $R_{ac} \rightarrow 1$  \quad $\therefore LD = MD$

$\tau < t_{1/2}$  \quad $R_{ac} \rightarrow $ large number  \quad $\therefore$ large LD
Example – Drug X

- Loading Dose (LD) can be calculated using $R_{ac}$, where $LD = MD \times R_{ac}$
  - Drug X with $t_{1/2} < Tau$
  - $t_{1/2} = 1$ hr
  - Tau = 8 hrs
  - To achieve target $C_{ss}$, we must give $MD = 750$ mg/day OR 250 mg q 8 hours

$$R_{ac} = \frac{1}{1 - e^{-k\tau}}$$
Drug X: $t_{1/2} < \tau$

- MD 750 mg/day OR 250 mg q 8 hrs
  $\tau = 8$ hours
  $t_{1/2} = 1$ hr

\[
R_{ac} = \frac{1}{1 - e^{-k\tau}}
\]

\[
R_{ac} = \frac{1}{1 - e^{-0.693*8}} = 1.0
\]

$\therefore$ No accumulation
Drug X

- Time to steady-state ~ 5 hours
- No need for loading dose
  \[ LD = MD \times R_{ac} = 250 \text{ mg (normal MD)} \]
Example – Drug Y

- Loading Dose (LD) can be calculated using $R_{ac}$, where $LD = MD \times R_{ac}$
  - Drug Y with $t_{1/2} = \text{Tau}$
  - $t_{1/2} = 8$ hr
  - Tau = 8 hrs
  - To achieve target $C_{ss}$, we must give $MD = 750$ mg/day OR 250 mg q 8 hours

$$R_{ac} = \frac{1}{1 - e^{-kt}}$$
Drug Y: $t_{1/2} = \tau$

- MD 750 mg/day or 250 mg q 8 hrs
  - $\tau = 8$ hours
  - $t_{1/2} = 8$ hr

\[
R_{ac} = \frac{1}{1 - e^{-k\tau}}
\]

\[
R_{ac} = \frac{1}{1 - e^{-0.087*8}} = 2.0
\]
Drug Y

- Time to steady-state ~ 40 hours
- LD = MD * R_{ac} = 500 mg
Example – Drug Z

- Loading Dose (LD) can be calculated using $R_{ac}$, where $LD = MD \times R_{ac}$
  - Drug Z with $t_{1/2} > \text{Tau}$
  - $t_{1/2} = 24$ hr
  - Tau = 8 hrs
  - To achieve target $C_{ss}$, we must give $MD = 750$ mg/day OR 250 mg q 8 hours

$$R_{ac} = \frac{1}{1 - e^{-k\tau}}$$
Drug Z: \( t_{1/2} > \tau \)

- MD 750 mg/day or 250 mg q 8 hrs
  \( \tau = 24 \) hours
- \( t_{1/2} = 8 \) hr

\[
R_{ac} = \frac{1}{1 - e^{-k\tau}}
\]

\[
R_{ac} = \frac{1}{1 - e^{-0.029\times8}} = 4.8
\]
Drug Z

- Time to steady-state ~ 5 days

\[ LD = MD \times R_{ac} = 1200 \text{ mg} \]
Calculation of LD

<table>
<thead>
<tr>
<th>Prediction</th>
<th>$t_{1/2}$ (hrs)</th>
<th>Tau (hrs)</th>
<th>$k$</th>
<th>Rac</th>
<th>$3t_{1/2}$ (hrs)</th>
<th>$5t_{1/2}$ (hrs)</th>
<th>MD (mg)</th>
<th>LD (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{1/2} &lt; \tau$</td>
<td>1</td>
<td>8</td>
<td>0.693</td>
<td>1.003926</td>
<td>3</td>
<td>5</td>
<td>250</td>
<td>250.9816</td>
</tr>
<tr>
<td>$t_{1/2} = \tau$</td>
<td>8</td>
<td>8</td>
<td>0.086625</td>
<td>2.000294</td>
<td>24</td>
<td>40</td>
<td>250</td>
<td>500.0736</td>
</tr>
<tr>
<td>$t_{1/2} &gt; \tau$</td>
<td>24</td>
<td>8</td>
<td>0.028875</td>
<td>4.848237</td>
<td>72</td>
<td>120</td>
<td>250</td>
<td>1212.059</td>
</tr>
</tbody>
</table>

\[ t_{1/2} = \frac{0.693}{k}; k = \frac{0.693}{t_{1/2}} \]

\[ R_{ac} = \frac{1}{1 - e^{-k\tau}} \]

\[ LD = MD \times R_{ac} \]
Maintenance of Concentrations within TR

- \( C_{ss,avg} \)
- Fluctuation within a dosing interval (\( \tau \))
  determined by:
  - \(-\tau\)
  - \(-t_{1/2}\)
  - rate of drug input
- Peak to Trough Ratio (P:T)

\[
\frac{Css_{\text{max}}}{Css_{\text{min}}} = \frac{1}{e^{-k\tau}}
\]
Peak to Trough Ratio: $C_{\text{max}}$

$$C_{\text{max}} = \frac{F \cdot \text{Dose}}{V_D}$$

Therefore, at steady-state

$$C_{\text{ss,max}} = \frac{F \cdot \text{Dose}}{V_D} \left( \frac{1}{1 - e^{-k\tau}} \right)$$
Peak to Trough Ratio: $C_{\text{min}}$

$$C_{\text{ss, min}} = C_{\text{ss, max}} \cdot e^{-k\tau}$$
Peak to Trough Ratio

\[
\frac{Css, \text{ max}}{Css, \text{ min}} = \frac{F \cdot \text{Dose}}{V_D} \left( \frac{1}{1 - e^{-k\tau}} \right) \cdot e^{-k\tau}
\]

\[
= \frac{1}{e^{-k\tau}}
\]

Peak to trough ratio depends upon \( t_{1/2} \) and dose interval
Peak to Trough Ratio

- $\tau = t_{1/2}$  \( P:T = 2 \)
- $\tau > t_{1/2}$  \( P:T \) will be large  \( \therefore \) large fluctuations
- $\tau < t_{1/2}$  \( P:T \) will be small, as $\tau \to 0$ there is no fluctuation like constant infusion
Example: \( t_{1/2} = 6 \) hours

- \( \tau = t_{1/2} \), eg. \( \tau = 6 \) hrs, \( P:T=2 \), \( C_{ss,\text{max}} \) will be twice \( C_{ss,\text{min}} \)

- \( \tau > t_{1/2} \), eg. \( \tau = 24 \) hrs, \( P:T=16 \), \( C_{ss,\text{max}} \) will be \( 16 \times C_{ss,\text{min}} \)

- \( \tau < t_{1/2} \), eg. \( \tau = 2 \) hrs, \( P:T=1.3 \), \( C_{ss,\text{max}} \) will be \( 1/3 \) larger than \( C_{ss,\text{min}} \)

\( P: Tratio = \frac{1}{e^{-k\tau}} \)
Rate of Drug Input

- PO administration results in a slower rate of input
- Peak conc occur later and are smaller
- P:T is also smaller
- Equations become complex, but more accurate
Average Concentration at Steady-State

\[ C_{ss,avg} = \frac{AUC_{ss}(0-\tau)}{\tau} \]
Determinants of $\text{Css,avg}$

$$C_{ss(t)} = \frac{F \cdot \text{Dose}}{V_D} \left( \frac{1}{1 - e^{-k\tau}} \right) e^{-kt}$$

$$\int_0^\tau C_{ss(t)} = AUC_{ss, (0-\tau)} = \frac{F \cdot \text{Dose}}{V_D} \int_0^\tau \left( \frac{1}{1 - e^{-k\tau}} \right) e^{-kt}$$

$$AUC_{ss (0-\tau)} = \frac{F \cdot \text{Dose}}{V_D} \left( \frac{1}{k} \right) = \frac{F \cdot \text{Dose}}{V_D \cdot k} = \frac{F \cdot \text{Dose}}{\text{CL}}$$
Determinants of $C_{ss,avg}$

$$C_{ss,avg} = \frac{AUC_{ss(0-\tau)}}{\tau} = \frac{F \cdot \text{Dose}}{CL} = \frac{F \cdot \text{Dose}}{\tau}$$

- $F$
- $\text{Dose}/\tau$
- $CL$
Dosage Regimen Design

- **Dose Rate (Dose/τ)**
  - Rate of drug administered over time
  - Daily Dose (ie. 1 G Q8, Dose/τ=3 G/d)

- **Dose Interval (τ)**
  - How often given
  - How small the pieces are
## Examples

<table>
<thead>
<tr>
<th>Dose/τ</th>
<th>τ</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 G/day</td>
<td>6 hours</td>
<td>250 mg Q6</td>
</tr>
<tr>
<td>1 G/day</td>
<td>12 hours</td>
<td>500 mg Q12</td>
</tr>
<tr>
<td>2 G/day</td>
<td>6 hours</td>
<td>500 mg Q6</td>
</tr>
<tr>
<td>2 G/day</td>
<td>12 hours</td>
<td>1 G Q12</td>
</tr>
</tbody>
</table>
When to alter Dose/τ

- Is Css,avg in acceptable range?

\[ \text{Css, avg} = \frac{F \cdot \text{Dose}}{\tau} = \frac{\text{Drug In}}{\text{Drug Out}} \]

- Has there been a change in
  - F
  - CL

- The only thing we can control is Dose/τ
Determinants of P:T

\[ \frac{C_{ss, \text{max}}}{C_{ss, \text{min}}} = \frac{1}{e^{-k\tau}} \]

\[ k = \frac{CL}{V_D} \]

• Half-life; k
  • CL
  • V

• The only thing we control is \( \tau \)
When to alter $\tau$

- Is P:T clinically acceptable?

$$\frac{C_{ss, \text{max}}}{C_{ss, \text{min}}} = \frac{1}{e^{-k\tau}}$$

- Has there been a change in
  - $\text{-CL}$
  - $\text{-V}$

- The only thing we control is $\tau$
Examples

Increase Dose Rate

- 250mg Q6
- 500mg Q6

- Concentration (mg/L)
- Time (hrs)

- Css,min = 3.0
- Css,avg = 2.1
- P:T = 1.9
- Css,max = 5.6
- Css,min = 1.5
- Css,avg = 4.2
- Css,max = 2.8
Determinants of $C_{ss,avg}$

$$C_{ss,avg} = \frac{AUC_{ss(0-\tau)}}{\tau} = \frac{F \cdot Dose}{CL\cdot\tau} = \frac{F \cdot Dose}{\tau \cdot CL}$$

- $F$
- $Dose/\tau$; increase $Dose/\tau$, increase $C_{ss,avg}$
- $CL$
Increase Dose Interval

<table>
<thead>
<tr>
<th>Dosage Interval</th>
<th>Concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250mg Q6</td>
<td>Css,max=3.6, Css,avg=2.1, Css,min=1.52</td>
</tr>
<tr>
<td>500mg Q12</td>
<td>Css,max=2.77, Css,avg=2.1, Css,min=1.08</td>
</tr>
</tbody>
</table>

P:T = 3.3 for 250mg Q6, P:T = 1.9 for 500mg Q12.
Determinants of P:T

\[ \frac{C_{ss, \text{max}}}{C_{ss, \text{min}}} = \frac{1}{e^{-k\tau}} \]

\[ k = \frac{CL}{V_D} \]

- CL
- \(V_D\)
- Only thing we can control is Tau (\(\tau\))
- P:T too small, increase dose interval
- i.e. give less often eg. q 6h to q 12h
Decreased Volume

Concentration (mg/L) vs. Time (hrs)

- **250mgQ6**
  - $C_{ss,\text{max}} = 3.6$
  - $P:T = 3.3$
  - $C_{ss,\text{avg}} = 2.1$
  - $C_{ss,\text{min}} = 1.5$

- **Decreased V**
  - $C_{ss,\text{max}} = 2.8$
  - $P:T = 1.9$
  - $C_{ss,\text{min}} = 1.1$
Determinants of $C_{ss,\text{avg}}$

$$C_{ss,\text{avg}} = \frac{AUC_{ss(0-\tau)}}{\tau} = \frac{F \cdot \text{Dose}}{CL} = \frac{F \cdot \text{Dose}}{\tau} \cdot \frac{\tau}{CL}$$

- $F$
- Dose/$\tau$
- CL
Determinants of P:T

\[
\frac{C_{ss, \text{max}}}{C_{ss, \text{min}}} = \frac{1}{e^{-k\tau}} \quad k = \frac{CL}{V_D}
\]

- CL
- \(V_D\); decreased \(V_D\) will increase \(k\) (steeper slope) and increase P:T ratio
- Tau (\(\tau\))
Decreased Clearance

- Css,max = 2.8
- Css,max = 4.8
- P:T = 1.3
- Css,avg = 2.1
- Css,avg = 4.2
- Css,min = 1.5
- Css,min = 3.6

Graph showing concentration over time for 250mg Q6 and Decreased CL conditions.
Determinants of $C_{ss,avg}$

$$C_{ss,avg} = \frac{AUC_{ss(0-\tau)}}{\tau} = \frac{F \cdot Dose}{CL} = \frac{F \cdot Dose}{\tau}$$

- $F$
- $Dose/\tau$
- $CL$; decreased $CL$ will increase $C_{ss,avg}$
Determinants of P:T

\[
\frac{C_{ss, \text{max}}}{C_{ss, \text{min}}} = \frac{1}{e^{-k\tau}} \quad k = \frac{CL}{V_D}
\]

- CL; decreased CL, will decrease k (flatter slope), and decrease P:T ratio
- \( V_D \)
- \( \text{Tau} (\tau) \)
When to change Dose Rate

Is $C_{ss,avg}$ in the target range?

Yes → No change in DR

No

Is $C_{ss,avg}$ too high or too low?

Too High → ↓ DR

Too Low → ↑ DR
P:T fluctuation

Conc.

<table>
<thead>
<tr>
<th>Time</th>
<th>Longer Tau</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shorter Tau</td>
<td></td>
</tr>
</tbody>
</table>

- **Conc.**
- **Time**
- **Longer Tau**
- **Shorter Tau**
When to change Dose Interval

Is P:T clinically acceptable?

Yes → No change in DI

No

Too Small:

Is P:T too great or too small?

Too Great:

↓ DI (Give more often)

↑ DI (Give less often)
P:T fluctuation

Conc.

Shorter Tau

Time

Longer Tau
P:T ratio (fluctuation) too small?

![Graph showing concentration over time with peak and trough levels.](image-url)
P:T ratio (fluctuation) too small?

Action is to increase or lengthen the dosing interval (tau)

Result is to increase P:T ratio
P:T ratio (fluctuation) too large?

Diagram:
- Conc: Concentration
- Peak
- Trough
- Tau
- Time
- Next dose
- Next dose
P:T ratio (fluctuation) too large?

- Reflects faster k
  - steeper slope
- Reflects shorter $t_{1/2}$
- Action is to decrease or shorten the dosing interval (tau)
  - Result is to decrease P:T ratio