Analysis of Urine Data

Objectives
- Draw scheme and understand differential equations
- Recognize and use integrated equations
- Construct plots; \(U\) versus \(t\), \(A\) versus \(t\), \(R\) versus \(t\), and \(\Delta U/\Delta t\) versus \(t\)
- Calculate excretion and metabolism rate constants
- Understand the use of \(f_e\) and \(f_m\) to make dose adjustments for patients with renal failure
- Define and use the parameter clearance

Analysis of Urine Data

- No Metabolism
  - Scheme
  - Differential Equations
  - Plot Types
- Parallel Pathways
  - Excretion
  - Metabolism
- Clearance
Why Urine Data?

- Avoid blood samples
  - Pediatrics
- Large V - Small concentrations
  - Analytical considerations

Excretion Unchanged (Only)

Scheme or Diagram
- Assume no metabolism - not common

\[
\text{Drug in Plasma} \quad \text{kel} \quad \text{Drug in Urine}
\]

\[
\text{Amount of drug in the body, } V \cdot C_p
\]

\[
\text{Amount of drug excreted into Urine}
\]

Differential Equation

\[
\frac{dU}{dt} = -V \cdot C_p \quad + \quad kel \cdot C_p \cdot V
\]

**NOTE:**
Dose = Amount in body + Amount Excreted
Dose = V \cdot C_p + U
- ONLY because there is no metabolism
Plot Type

- Cumulative Amount Excreted into Urine
  \[ \frac{dU}{dt} = ke_l \cdot Cp \cdot V \]
  
  Since \( Cp = Cp_0 \cdot e^{-ke_l \cdot t} \) and \( V \cdot Cp = \text{DOSE} \)
  
  \[ \frac{dU}{dt} = \text{DOSE} \cdot ke_l \cdot e^{-ke_l \cdot t} \cdot dt \]
  
  then
  
  \[ U = \text{DOSE} \cdot \left[ 1 - e^{-ke_l \cdot t} \right] \]
  
  At \( t = 0; U^0 = 0 \) and \( t = \infty; U^\infty = \text{DOSE} \)

Cumulative Amount Excreted

- Using Laplace Transforms
  - The differential equations
    \[ V \cdot \frac{dC_p}{dt} = \frac{dX}{dt} = -ke_l \cdot X \]
    \[ \frac{dU}{dt} = ke_l \cdot X \]
  - Taking Laplace of Both Equations
    \[ s \cdot X - \text{DOSE} = -ke_l \cdot X \]
    \[ s \cdot U = ke_l \cdot X \]
    
    \[ X = \frac{\text{DOSE}}{s + ke_l} \]
    \[ U = \frac{\text{kel} \cdot X}{s} = \frac{\text{DOSE} \cdot \text{kel}}{s \cdot (s + \text{kel})} \]

Cumulative Amount Excreted

- Taking the back transform
  - two roots i.e. 0 and -\( \text{kel} \)
    
    \[ U = \frac{\text{DOSE} \cdot \text{kel} + \text{DOSE} \cdot \text{kel} \cdot e^{-ke_l \cdot t}}{\text{kel}} \]
    \[ U = \text{DOSE} - \text{DOSE} \cdot e^{-ke_l \cdot t} \]
    \[ U = \text{DOSE} \cdot \left[ 1 - e^{-ke_l \cdot t} \right] \]
**Cumulative Amount Excreted**

- Dose = V*Cp
- Dose = U

**More Qualitative**

<table>
<thead>
<tr>
<th>V*Cp (mg)</th>
<th>U (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>250</td>
<td>250</td>
</tr>
</tbody>
</table>

**Time (hr)**

| 0 | 6 | 12 | 18 | 24 |

**Plot Type**

- Rate of Excretion (R/E)
  
  \[
dU/dt = k_e l*C_p * V = DOSE * k_e l * e^{-k_e l \cdot t}
\]

- Taking the logs of both sides
  
  \[
  \ln(dU/dt) = \ln(DOSE \cdot k_e l) - k_e l \cdot t
  \]

- Plot dU/dt versus t_{midpoint} on semi-log

**'Real' data may show considerable scatter**

- Early frequent samples difficult to obtain
- Data points independent
- Missed data points not a problem
- Plot versus midpoint time (average time)
  
  since \( \Delta U/\Delta t \) is average over sample interval
Plot Type

Amount Remaining to be Excreted (A.R.E.)

Since DOSE = Amount in Body + Amount Eliminated
DOSE = V\cdot Cp^0 = V\cdot Cp + U = U^\infty
V\cdot Cp^0 e^{-kt} + U = U^\infty
U^\infty - U = V\cdot e^{-kt}

\ln(U^\infty - U) = \ln(U^\infty) - kel t

Plot (U^\infty - U) versus time on semi-log graph paper

Plot Type

Amount Remaining to be Excreted (A.R.E.)

- Missed sample invalidates this analysis
- Errors cumulative - poor U^\infty value makes all points poor
- Can result in smoother curve
  - Interpretation of slope may be difficult

Example Data - Ampicillin (500 mg dose)

<table>
<thead>
<tr>
<th>Time Interval (hr)</th>
<th>\Delta t (hr)</th>
<th>\Delta U (mg)</th>
<th>U (mg)</th>
<th>t (mid-point) (hr)</th>
<th>\Delta U/\Delta t (mg/hr)</th>
<th>A.R.E. (mg)</th>
<th>[U^\infty - U]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.5</td>
<td>0.5</td>
<td>103</td>
<td>103</td>
<td>0.25</td>
<td>206</td>
<td>397</td>
<td></td>
</tr>
<tr>
<td>0.5-1</td>
<td>0.5</td>
<td>82</td>
<td>185</td>
<td>0.75</td>
<td>164</td>
<td>315</td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>1</td>
<td>117</td>
<td>302</td>
<td>1.5</td>
<td>117</td>
<td>198</td>
<td></td>
</tr>
<tr>
<td>2-4</td>
<td>2</td>
<td>421</td>
<td>3</td>
<td>59.5</td>
<td>79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-8</td>
<td>4</td>
<td>488</td>
<td>6</td>
<td>16.75</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-12</td>
<td>4</td>
<td>498</td>
<td>10</td>
<td>2.5</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-24</td>
<td>12</td>
<td>300</td>
<td>18</td>
<td>0.17</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-Inf</td>
<td>-</td>
<td>500</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Example Data - Ampicillin (500 mg dose)

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Rate of Excretion (mg/hr)</th>
<th>ΔU/Δt A.R.E. (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>1000</td>
<td></td>
</tr>
</tbody>
</table>

Calculations

- **Rate of Excretion**
  \[ k_e = \frac{\ln 228 - \ln 10}{\frac{7.1}{2}} = 0.440 \text{ hr}^{-1} \] \( t_{1/2} = 1.58 \text{ hr} \)

- **A.R.E.**
  \[ k_e = \frac{\ln 500 - \ln 12.2}{\frac{8}{2}} = 0.464 \text{ hr}^{-1} \] \( t_{1/2} = 1.49 \text{ hr} \)

Metabolism and Excretion - Parallel Pathways

- Much more common
- Possibly multiple metabolic pathways
- Possibly multiple excretion pathways
Scheme or Diagram

- Metabolism and Excretion

\[ \text{Drug in Body} \xrightarrow{\text{ke}} \text{Drug in Urine} \]
\[ \text{Air} \xrightarrow{\text{km or knr}} \text{Drug as Metabolite in Body} \]
\[ \text{Sweat Bile} \xrightarrow{\text{km or knr}} \text{Metabolite in Urine} \]

Differential Equations

- For \( X = V \cdot Cp \), Amount in the Body
\[
\frac{dV}{dt} \cdot \frac{dCp}{dt} = -ke \cdot V \cdot Cp - km \cdot V \cdot Cp
\]
\[
= -(ke + km) \cdot V \cdot Cp = -ke \cdot X
\]
\[
\frac{dX}{dt} = -ke \cdot X
\]

- For \( U \), Amount Excreted into Urine
\[
\frac{dU}{dt} = ke \cdot V \cdot Cp = ke \cdot X
\]

Integrated Equation - Plasma Concentration

\[
\frac{V \cdot dCp}{dt} = -(ke + km) \cdot V \cdot Cp
\]
\[
\frac{dCp}{dt} = -ke \cdot Cp
\]

Integrate

\[
Cp = \frac{\text{DOSE}}{V} \cdot e^{-ke \cdot t}
\]
Integrated Equation - Amount in Urine
\[
\frac{dU}{dt} = k_e \cdot V \cdot C_p \\
\frac{dU}{dt} = k_e \cdot \text{DOSE} \cdot e^{-k_e t} \\
U = \frac{k_e \cdot \text{DOSE}}{k_e} \left[ 1 - e^{-k_e t} \right]
\]

Cumulative Amount Excreted

- Using Laplace Transforms
  - The differential equations
    \[
    V \cdot \frac{dC_p}{dt} = \frac{dX}{dt} = -k_e \cdot X \\
    \frac{dU}{dt} = k_e \cdot X
    \]
  - Taking Laplace of Both Equations
    \[
    s \cdot X - \text{DOSE} = -k_e \cdot X \\
    s \cdot U = k_e \cdot X
    \]
    \[
    X = \frac{\text{DOSE}}{s + k_e} \\
    U = \frac{k_e \cdot X}{s} = \frac{\text{DOSE} \cdot k_e}{s(s + k_e)}
    \]

Cumulative Amount Excreted

- Taking the back transform
  - Two roots i.e. 0 and -k_e
    \[
    U = \frac{\text{DOSE} \cdot k_e}{k_e} - \frac{\text{DOSE} \cdot k_e \cdot e^{k_e t}}{-k_e} \\
    U = \frac{\text{DOSE} \cdot k_e}{k_e} - \frac{\text{DOSE} \cdot k_e \cdot e^{k_e t}}{k_e} \\
    U = \frac{k_e \cdot \text{DOSE}}{k_e} \left[ 1 - e^{-k_e t} \right]
    \]
Integrated Equation - A mount of M etabolite in Body

\[ \frac{dM}{dt} = km \cdot X - kmu \cdot M \]

Taking Laplace

\[ s \cdot \hat{M} = \frac{km \cdot X}{s + km} - \frac{km \cdot \text{Dose}}{(s + kel) \cdot (s + kmu)} \]

Back Transform

\[ M = \frac{km \cdot \text{Dose} \cdot e^{-kel t}}{kmu - kel} + \frac{km \cdot \text{Dose} \cdot e^{kmu t}}{kel - kmu} \]

\[ M = \frac{km \cdot \text{Dose} \cdot e^{-kel t}}{kmu - kel} + \left[ e^{kmu t} - e^{-kel t} \right] \]

Integrated Equation - A mount M etabolized

\[ \frac{dM_u}{dt} = kmu \cdot M \]

Taking Laplace

\[ s \cdot \hat{M}_u = \frac{kmu \cdot M}{s} - \frac{kmu \cdot \text{Dose}}{s \cdot (s + kel) \cdot (s + kmu)} \]

Back Transform

\[ M_u = \frac{kmu \cdot \text{Dose} \cdot e^{-kel t}}{kel \cdot \text{Dose}} + \frac{kmu \cdot km \cdot \text{Dose} \cdot e^{kmu t}}{kel \cdot \text{Dose} \cdot (kmu - kel)} \]

\[ M_u = \frac{kmu \cdot km \cdot \text{Dose} \cdot e^{kmu t}}{kel \cdot \text{Dose} \cdot (kmu - kel)} \]

Total A mount E xcreted or M etabolized

At \( t = \infty \), \( e^{-kel t} = e^{kmu t} = 0 \)

\[ U^\infty = \frac{ke \cdot \text{DOSE}}{kel} \]

and

\[ M_u^\infty = \frac{km \cdot \text{DOSE}}{kel} \]

Note: \( U^\infty + M_u^\infty = \text{DOSE} \)
Fraction Excreted or Metabolized

- Excretion in Urine
  \[ fe = \frac{U}{DOSE} \cdot \frac{ke}{kel} \]

- Metabolite Excreted into Urine
  \[ fm = \frac{Ma}{DOSE} \cdot \frac{km}{kel} \]

Note: \( fe + fm = 1 \)

Plots

- Cumulative Amount Excreted into Urine versus Time
  - Linear Graph
  - Time at end of Interval

- Rate of Excretion versus Time
  - Semi-log Graph
  - Time at middle of Interval

- Amount Remaining to be Excreted versus Time
  - Semi-log Graph
  - Time at end of Interval

Cumulative Amount Excreted

\[ U = \frac{ke \cdot DOSE}{kel} \left[ 1 - e^{-kel} \right] \]
Rate of Excretion

\[ \Delta U = \ln(k_e \cdot \text{Dose}) - k_e \cdot t \]

Intercept = \(k_e \cdot \text{Dose} = 0.15 \times 250 = 37.5\) mg

Slope = \(-k_e\)

Amount Remaining to be Excreted

\[ \ln(U^\infty - U) = \ln(f_e \cdot \text{Dose}) - k_e \cdot t \]

\(U^\infty = f_e \cdot \text{Dose} = 0.75 \times 250 = 187.5\) mg

Fraction Excreted

- Renal Function
- Drug excretion related to Renal Function
- Creatinine Clearance - Normal 120 - 130 ml/min
- \(CL_{Cr}\) calculated from Serum_{Cr}
- Estimate Elimination Rate Constant
- Calculate Dosing Regimen
Example Calculation

- Vancomycin $fe = 0.95$
- Normal $kel = 0.116 \text{ hr}^{-1} (t_{1/2} = 6 \text{ hr})$
- $ke = fe \cdot kel = 0.110 \text{ hr}^{-1}$
- $km = kel - ke = 0.006 \text{ hr}^{-1}$
- Patient $ke = 0.110 \cdot 0.1 = 0.011 \text{ hr}^{-1}$
- Patient $kel = 0.011 + 0.006 = 0.017 \text{ hr}^{-1}$  
  ($t_{1/2} = 41 \text{ hr}$)
- NOTE: $t_{1/2} = 6 \text{ hr} \rightarrow t_{1/2} = 41 \text{ hr}$

Example Calculation

- Erythromycin $fe = 0.15$
- Normal $kel = 0.58 \text{ hr}^{-1} (t_{1/2} = 1.2 \text{ hr})$
- $ke = fe \cdot kel = 0.087 \text{ hr}^{-1}$
- $km = kel - ke = 0.493 \text{ hr}^{-1}$
- Patient $ke = 0.087 \cdot 0.1 = 0.009 \text{ hr}^{-1}$
- Patient $kel = 0.009 + 0.493 = 0.502 \text{ hr}^{-1}$  
  ($t_{1/2} = 1.4 \text{ hr}$)
- NOTE: $t_{1/2} = 1.2 \text{ hr} \rightarrow t_{1/2} = 1.4 \text{ hr}$

Cp for Patient with normal $CL_{Cr}$
Hypothetical Cp for Patient with low $CL_{Cr}$

Summary So Far!
- From the first section (no metabolism)
  - Forget the equations!
  - Remember the shape of the graphs
- From the second section - elimination by excretion and metabolism
  - Remember the ‘key’ equations
  - Remember the shape and use of graphs
    - Cumulative - qualitative
    - R/E - for $kel$ and $ke$ - midpoint time
    - ARE - for $kel$ if no lost data

Clearance, CL
- Volume of plasma completely cleared of drug per unit time
- Units of volume per time - ml/min, L/hr
- Consider an organ (e.g. kidney) that removes all of the drug which reaches it
  - Renal clearance would equal renal blood or plasma flow rate
Renal Clearance

- Amount cleared by the kidney per time is \( \frac{dU}{dt} \).
- Divide by \( Cp \) to obtain the volume cleared.
- Thus:

\[
CL_R = \frac{\frac{dU}{dt}}{Cp}
\]

Renal Clearance, \( CL_R \)

\[
CL_R = \frac{\frac{dU}{dt}}{Cp}
\]

Since \( \frac{dU}{dt} = k_e \cdot V \cdot Cp \)

\[
CL_R = \frac{k_e \cdot V \cdot Cp}{Cp} = k_e \cdot V
\]
Organ Clearance

- Can be related to Efficiency of Organ of Elimination
- and Blood Flow
- Used to investigate mechanism of excretion or metabolism
- Related to kidney or liver pathology

Total Body Clearance, CL

- \( CL = k_e \cdot V \)
- \( CL_R = ke \cdot V \)
- \( CL_M = km \cdot V \)
- \( CL = CL_R + CL_M \)

Alternate Calculation

- Integrating from 0 to \( \infty \)
  \[
  \frac{dU}{dt} = CL_e \cdot C_P
  \]
  \[
  U^\infty = CL_e \cdot \int C_P \cdot dt = CL_e \cdot AUC
  \]
  \[
  CL_e = \frac{U^\infty}{AUC}
  \]
Clearance Equations

\[ \text{CL}_e = \frac{U^e}{AUC} \]
\[ \text{CL}_{mu} = \frac{Mu^e}{AUC} \]
\[ \text{CL} = \frac{\text{DOSE}}{AUC} \]

Total Body Clearance

Total amount cleared

Total Concentration (?)