Analysis of Urine Data

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Objectives

- Draw scheme and understand diff. equations
- Recognize and use integrated equations
- Construct plots; U versus t, ARE versus t, and $\Delta U/\Delta t$ versus t
- Calculate excretion and metabolism rate constants
- Understand the use of fe and fm 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

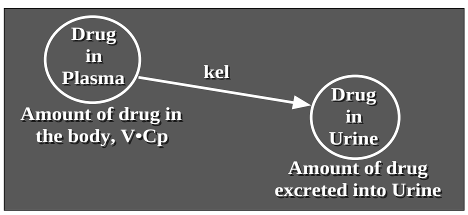
Why Urine Data?

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

Excretion Unchanged (Only)

Scheme or Diagram

- Assume no metabolism - not common



Differential Equation

$$\frac{dU}{dt} = -\frac{V \bullet Cp}{dt} = +kel \bullet Cp \bullet V$$

- NOTE:
  Dose = Amount in body + Amount Excreted
  Dose = V•Cp + U
  - ONLY because there is no metabolism

Plot Type

- Cumulative Amount Excreted into Urine

$$\frac{dU}{dt} = kel \bullet Cp \bullet V$$

Since $Cp = Cp^0 \bullet e^{-kel \bullet t}$ and $V \bullet Cp^0 = DOSE$

$$dU = DOSE \bullet kel \bullet e^{-kel \bullet t} \bullet dt$$

then

$$U = DOSE \bullet [1 - e^{-kel \bullet t}]$$

At $t = 0$; $U^0 = 0$ and $t = \infty$; $U^\infty = DOSE$

Cumulative Amount Excreted

- Using Laplace Transforms
  - The differential equations

$$\frac{V \bullet dCp}{dt} = \frac{dX}{dt} = -kel \bullet X \qquad \frac{dU}{dt} = kel \bullet X$$

  - Taking Laplace of Both Equations

$$s \bullet \overline{X} - DOSE = -kel \bullet \overline{X} \qquad s \bullet \overline{U} = kel \bullet \overline{X}$$

$$\overline{X} = \frac{DOSE}{s + kel} \qquad \overline{U} = \frac{kel \bullet \overline{X}}{s} = \frac{DOSE \bullet kel}{s \bullet (s + kel)}$$

Cumulative Amount Excreted

$$\overline{U} = \frac{kel \bullet \overline{X}}{s} = \frac{DOSE \bullet kel}{s \bullet (s + kel)}$$

- Taking the back transform
  - two roots i.e. 0 and -kel

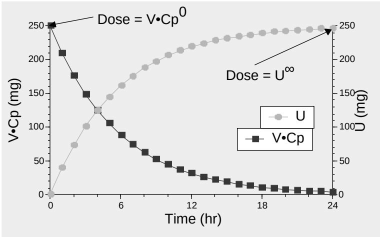
$$U = \frac{DOSE \bullet kel}{kel} + \frac{DOSE \bullet kel \bullet e^{-kel \bullet t}}{-kel}$$

$$U = DOSE - DOSE \bullet e^{-kel \bullet t}$$

$$U = DOSE \bullet \left[1 - e^{-kel \bullet t}\right]$$

Cumulative Amount Excreted

- More Qualitative



Plot Type

- Rate of Excretion (R/E)

$$\frac{dU}{dt} = kel \bullet Cp \bullet V = DOSE \bullet kel \bullet e^{-kel \bullet t}$$

- Taking the logs of both sides

$$\ln \frac{dU}{dt} = \ln(DOSE \bullet kel) - kel \bullet t$$

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

Plot Type

Rate of Excretion (R/E)

- ‘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 ΔU/Δt is average over sample interval

Plot Type

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

Since DOSE = Amount in Body + Amount Eliminated

$DOSE = V \bullet Cp^0 = V \bullet Cp + U = U^\infty$

$V \bullet Cp^0 \bullet e^{-kel \bullet t} + U = U^\infty$

$U^\infty \bullet e^{-kel \bullet t} + U = U^\infty$

$U^\infty - U = U^\infty \bullet e^{-kel \bullet t}$

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

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

Plot Type

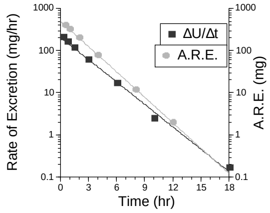
Amount Remaining to be Excreted (A.R.E.)

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

Example Data - Ampicillin (500 mg dose)

Time Interval (hr)	Δt (hr)	ΔU (mg)	U (mg)	t (mid-point) (hr)	ΔU/Δt (mg/hr)	A.R.E. (mg) [U^{inf}-U]
0-0.5	0.5	103	103	0.25	206	397
0.5-1	0.5	82	185	0.75	164	315
1-2	1	117	302	1.5	117	198
2-4	2	119	421	3	59.5	79
4-8	4	67	488	6	16.75	12
8-12	4	10	498	10	2.5	2
12-24	12	2	500	18	0.17	-
24-inf		-	500			

Example Data - Ampicillin (500 mg dose)



Calculations

- Rate of Excretion

$$kel = \frac{\ln 228 - \ln 10}{7.1 - 0} = 0.440\ hr^{-1}\ (t_{1/2} = 1.58\ hr)$$

- A.R.E.

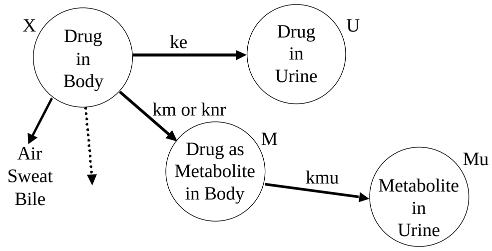
$$kel = \frac{\ln 500 - \ln 12.2}{8 - 0} = 0.464\ hr^{-1}\ (t_{1/2} = 1.49\ hr)$$

Metabolism and Excretion - Parallel Pathways

- Much more common
- Possibly multiple metabolic pathways
- Possibly multiple excretion pathways

Scheme or Diagram

- Metabolism and Excretion



Differential Equations

- For X (= V•Cp), Amount in the Body

$$\frac{V \cdot dCp}{dt} = \frac{dX}{dt} = -ke \cdot V \cdot Cp - km \cdot V \cdot Cp$$

$$= -(ke + km) \cdot V \cdot Cp = -kel \cdot X$$

$$\frac{dX}{dt} = -kel \cdot X$$

- For U, Amount Excreted into Urine

$$\frac{dU}{dt} = ke \cdot V \cdot Cp = ke \cdot X$$

Integrated Equation - Plasma Concentration

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

$$\frac{dCp}{dt} = -kel \cdot Cp$$

Integrate

$$Cp = \frac{DOSE}{V} \cdot e^{-kel \cdot t}$$

Integrated Equation - Amount in Urine

$$\frac{dU}{dt} = ke \bullet V \bullet Cp$$

$$\frac{dU}{dt} = ke \bullet DOSE \bullet e^{-kel \bullet t}$$

$$U = \frac{ke \bullet DOSE}{kel} \bullet \left[1 - e^{-kel \bullet t}\right]$$

Cumulative Amount Excreted

- Using Laplace Transforms
  - The differential equations

$$\frac{V \bullet dCp}{dt} = \frac{dX}{dt} = -kel \bullet X \qquad \frac{dU}{dt} = ke \bullet X$$

  - Taking Laplace of Both Equations

$$s \bullet \overline{X} - DOSE = -kel \bullet \overline{X} \qquad s \bullet \overline{U} = ke \bullet \overline{X}$$

$$\overline{X} = \frac{DOSE}{s + kel} \qquad \overline{U} = \frac{ke \bullet \overline{X}}{s} = \frac{DOSE \bullet ke}{s \bullet (s + kel)}$$

Cumulative Amount Excreted

$$\overline{U} = \frac{ke \bullet \overline{X}}{s} = \frac{DOSE \bullet ke}{s \bullet (s + kel)}$$

- Taking the back transform
  - two roots i.e. 0 and -kel

$$U = \frac{DOSE \bullet ke}{kel} + \frac{DOSE \bullet ke \bullet e^{-kel \bullet t}}{-kel}$$

$$U = \frac{DOSE \bullet ke}{kel} - \frac{DOSE \bullet ke \bullet e^{-kel \bullet t}}{kel}$$

$$U = \frac{ke \bullet DOSE}{kel} \bullet \left[1 - e^{-kel \bullet t}\right]$$

Integrated Equation - Amount of Metabolite in Body

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

Taking Laplace

$$s \cdot \overline{M} = km \cdot \overline{X} - kmu \cdot \overline{M}$$

$$\overline{M} = \frac{km \cdot \overline{X}}{s + kmu} = \frac{km \cdot Dose}{(s + kel) \cdot (s + kmu)}$$

Back Transform

$$M = \frac{km \cdot DOSE \cdot e^{-kel \cdot t}}{kmu - kel} + \frac{km \cdot DOSE \cdot e^{-kmu \cdot t}}{kel - kmu}$$

$$= \frac{km \cdot DOSE}{(kmu - kel)} \cdot \left[e^{-kel \cdot t} - e^{-kmu \cdot t}\right]$$

Integrated Equation - Amount Metabolized

$$\frac{dMu}{dt} = kmu \cdot M$$

Taking Laplace

$$s \cdot \overline{Mu} = kmu \cdot \overline{M}$$

$$\overline{Mu} = \frac{kmu \cdot \overline{M}}{s} = \frac{kmu \cdot km \cdot Dose}{s \cdot (s + kel) \cdot (s + kmu)}$$

Back Transform

$$Mu = \frac{\cancel{kmu} \cdot km \cdot DOSE}{kel \cdot \cancel{kmu}} + \frac{kmu \cdot km \cdot DOSE \cdot e^{-kel \cdot t}}{-kel \cdot (kmu - kel)}$$

$$+ \frac{kmu \cdot km \cdot DOSE \cdot e^{-kmu \cdot t}}{-kmu \cdot (kel - kmu)}$$

Total Amount Excreted or Metabolized

$$\text{At } t = \infty, \; e^{-kel \cdot t} = e^{-kmu \cdot t} = 0$$

$$U^{\infty} = \frac{ke \cdot DOSE}{kel}$$

and

$$Mu^{\infty} = \frac{km \cdot DOSE}{kel}$$

$$\text{Note: } U^{\infty} + Mu^{\infty} = DOSE$$

Fraction Excreted or Metabolized

- Excretion in Urine

$$fe = \frac{U^{\infty}}{DOSE} = \frac{ke}{kel}$$

- Metabolite Excreted into Urine

$$fm = \frac{Mu^{\infty}}{DOSE} = \frac{km}{kel}$$

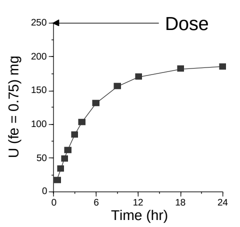
Note: fe + fm = 1

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

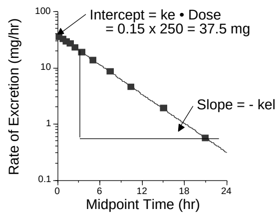
$$U = \frac{ke \bullet DOSE}{kel} \bullet \left[1 - e^{-kel \bullet t}\right]$$



Note:
Dose $\neq U^{\infty}$

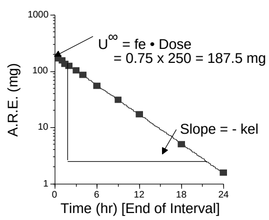
Rate of Excretion

$$\ln\left[\frac{\Delta U}{\Delta t}\right] = \ln(ke \bullet DOSE) - kel \bullet t$$



Amount Remaining to be Excreted

$$\ln\left(U^{\infty} - U\right) = \ln(fe \bullet DOSE) - kel \bullet t$$



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

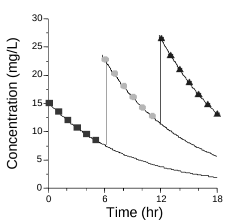
Example Calculation

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

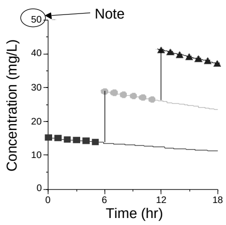
Example Calculation

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

Renal Clearance

- Amount cleared by the kidney per time is dU/dt
- Divide by Cp to obtain the volume cleared
- Thus:

$$CL_R = \frac{dU}{dt} \bullet \frac{1}{Cp}$$

Renal Clearance, CL_R

$$CL_R = \frac{dU}{dt} \bullet \frac{1}{Cp}$$

$$\text{Since } \frac{dU}{dt} = ke \bullet V \bullet Cp$$

$$CL_R = \frac{ke \bullet V \bullet Cp}{Cp} = ke \bullet V$$

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

- $CL = kel \bullet V$
- $CL_R = ke \bullet V$
- $CL_M = km \bullet V$
- $CL = CL_R + CL_M$

Alternate Calculation

- Integrating from 0 to ∞

$$\frac{dU}{dt} = CL_R \bullet Cp$$

$$U^{\infty} = CL_R \bullet \int_0^{\infty} Cp \bullet dt = CL_R \bullet AUC$$

$$CL_R = \frac{U^{\infty}}{AUC}$$

Clearance Equations

$$CL_R = \frac{U^{\infty}}{AUC}$$

$$CL_M = \frac{Mu^{\infty}}{AUC}$$

Total Body Clearance → CL

Total amount cleared → $DOSE$

$$CL = \frac{DOSE}{AUC}$$

Total Concentration (?) → AUC