

# PHAR 7632 Chapter 5

## Analysis of Urine Data

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### Analysis of Urine Data

#### Student Objectives for this Chapter

After completing the material in this chapter each student should:-

- be able to draw the scheme and write the differential equations for a one compartment pharmacokinetic model with elimination of drug and metabolite into urine (parallel pathways of elimination)
- to use the appropriate integrated equations for this pharmacokinetic model to calculate amount of drug excreted into urine
- be able to plot cumulative amount excreted *versus* time, A.R.E. *versus* time and rate of excretion *versus* time (midpoint) and use these graphs to calculate pharmacokinetic parameters
- be able to define, use, and calculate the parameters:
  - $k_e$  (excretion rate constant)
  - $k_m$  (metabolism rate constant)
  - $U^\infty$  and  $M^\infty$
  - $f_e$  and  $f_m$
  - renal and non renal clearance
- be able to use  $f_e$ , the fraction excreted, to calculate overall elimination rate constants in patients with impaired renal function

So far we have looked at most of the information we can get from plasma data following a rapid intravenous dose of a drug using a one compartment model. There is another part of the model which can be sampled. Sometimes it is not possible to collect blood or plasma samples but we may be able to measure the amount of drug excreted into urine.

- we may not want to take repeated blood samples from certain patient populations, for example very young, pediatric patients
- the apparent volume of distribution maybe so large that plasma concentrations are too small to measure
- it may be important to determine the role of metabolism in the elimination of a drug. Analysis of urine data for unchanged drug and metabolite concentrations is essential to the quantitative study of drug metabolism

If we collect data for amount of drug excreted into urine it may be possible to determine the elimination rate constant or half-life and other pharmacokinetic parameters.

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# PHAR 7632 Chapter 5

## Analysis of Urine Data

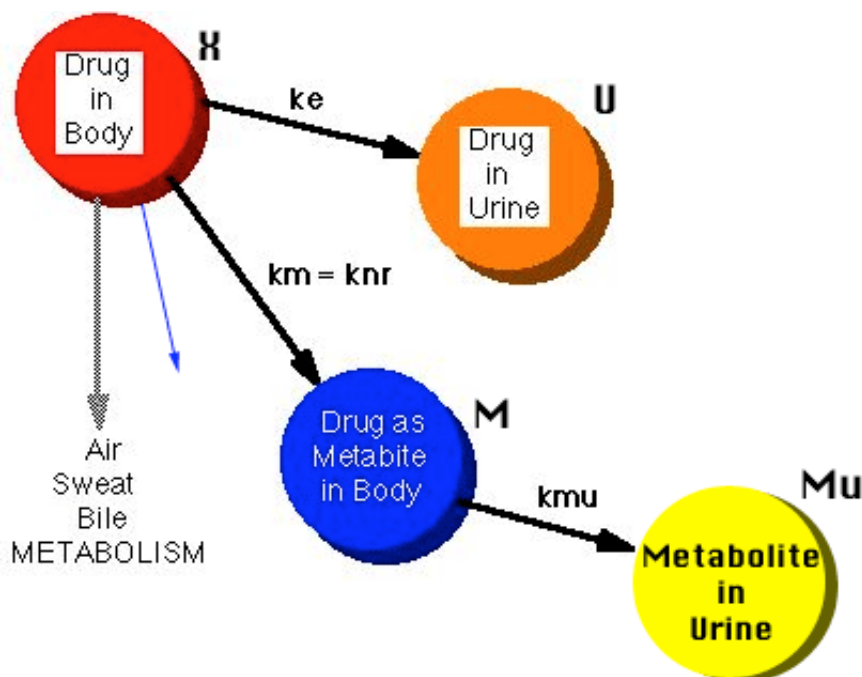
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### Metabolism and Excretion - Parallel Pathways

Although a few drugs are eliminated as unchanged drug into urine or alternately may be completely metabolized, most drugs are eliminated by excretion AND metabolism. There are often more than one excretion or metabolism pathway.

### Scheme or diagram

Schematically this can be represented as:-



**Figure 5.2.1 Diagram Illustrating Multiple Elimination Pathways with a One Compartment Model**

In Figure 5.2.1  $k_e$  is the excretion rate constant and  $k_m$  is the metabolism rate constant. Here we have two parallel pathways for elimination (with others as a shadow). We can write the differential equations for the four components shown in this diagram (X, U, M, Mu). There could be more pathways. It may be necessary to specify excretion by exhalation, in sweat, or as is commonly the case, more than one metabolic pathway.

## The Equations

### Drug in the Body, X

For  $X = V \cdot C_p$ , amount of drug in the body

$$\begin{aligned} \frac{V \cdot dC_p}{dt} &= \frac{dX}{dt} = -k_e \cdot V \cdot C_p - k_m \cdot V \cdot C_p \\ &= -(k_e + k_m) \cdot V \cdot C_p = -k_{el} \cdot V \cdot C_p \end{aligned}$$

#### Equation 5.2.1 Rate of Change of the Amount of Drug in the Body

Equation 5.2.1 includes terms for excretion and metabolism. The number (and type) of these elimination processes can be changed to accommodate a variety of possible routes of excretion or metabolism. Some of these processes may not be first order, however many can be represented by first order parameters.

The elimination rate constant,  $k_{el}$ , represents the sum of all the ('first-order') rate constants so we can substitute  $k_{el}$  for  $(k_e + k_m)$  in Equation 5.2.1 to give Equation 5.2.2.

$$\frac{V \cdot dC_p}{dt} = -k_{el} \cdot V \cdot C_p$$

#### Equation 5.2.2 Rate of Change of the Amount of Drug in the Body

Dividing by  $V$  gives the Equation 5.2.3, which is the same as Equation 4.4.1 in [Chapter 4](#).

$$\frac{dC_p}{dt} = -k_{el} \cdot C_p$$

#### Equation 5.2.3 Rate of Change of Drug Concentration

$$\frac{V \cdot dC_p}{dt} = \frac{dX}{dt} = -CL_R \cdot C_p - CL_M \cdot C_p = -CL \cdot C_p$$

#### Equation 5.2.4 Rate of Change of the Amount of Drug using Clearance Parameters

In Equation 5.2.4 the rate of elimination of drug from the central or plasma compartment is expressed in clearance terms, here, renal ( $CL_R$ ) and metabolic ( $CL_M$ ) clearance. The total body clearance ( $CL$ ) is equal to the sum of the clearance terms in the model. In Equation 5.2.4 total body clearance,  $CL = CL_R + CL_M$ .

With more elimination pathways we sum all these process parameters to arrive at the elimination rate constant,  $k_{el}$ , or total body clearance,  $CL$ . Thus the equation for rate of elimination, either with rate constant parameters or clearance parameters, is the same as before in Chapter 4. The integrated equation is given in Equation 5.2.5 or 5.2.6

$$V \cdot C_p = \text{Dose} \cdot e^{-k_{el} \cdot t}$$

$$C_p = \frac{\text{Dose}}{V} \cdot e^{-k_{el} \cdot t}$$

**Equation 5.2.5**  $C_p$  versus time with  $k_{el}$  as the elimination rate parameter

$$C_p = \frac{\text{Dose}}{V} \cdot e^{-CL \cdot t / V}$$

**Equation 5.2.6**  $C_p$  versus time with  $CL$  as the elimination rate parameter

## Drug Excreted into Urine, U

The rate of excretion,  $dU/dt$ , can be derived from the model, Figure 5.7.1 in terms of  $k_e$  or  $CL_R$

$$\frac{dU}{dt} = k_e \cdot V \cdot C_p$$

$$\frac{dU}{dt} = CL_R \cdot C_p$$

**Equation 5.2.7** Rate of Change of Cumulative Amount Excreted into Urine

Then substituting for  $C_p$  ( $= (\text{Dose}/V) \cdot e^{-k_{el} \cdot t}$  or  $= (\text{Dose}/V) \cdot e^{-CL \cdot t / V}$ ) we get

$$\frac{dU}{dt} = k_e \cdot \cancel{V} \cdot \frac{\text{Dose}}{\cancel{V}} \cdot e^{-k_{el} \cdot t} = k_e \cdot \text{Dose} \cdot e^{-k_{el} \cdot t}$$

$$\frac{dU}{dt} = CL_R \cdot \frac{\text{Dose}}{V} \cdot e^{-CL \cdot t / V}$$

**Equation 5.2.8** Rate of Excretion of Unchanged Drug into Urine

after integrating [using Laplace transforms](#) we get:

$$U = \frac{k_e \cdot \text{Dose}}{k_{el}} \cdot [1 - e^{-k_{el} \cdot t}]$$

$$U = \frac{CL_R \cdot \text{Dose}}{CL} \cdot [1 - e^{-CL \cdot t / V}]$$

**Equation 5.2.9** Cumulative Amount Excreted as Unchanged Drug versus Time

Note:  $k_e$  or  $CL_R$  are in the numerator of Equation 5.2.9. As time approaches infinity the exponential term,  $e^{-k \cdot t}$ , approaches zero.

Setting the  $e^{-k_{el} \cdot t}$  term in Equation 5.2.9 to zero gives Equation 5.2.10 for the total amount of unchanged drug excreted in urine,  $U^\infty$

$$U^{\infty} = \frac{k_e \cdot \text{Dose}}{k_{el}}$$

Equation 5.2.10 Total Amount Excreted as Unchanged Drug into Urine

### Amount of Drug Metabolized in the body, M, and excreted into urine, Mu

For M, the amount of drug which has been metabolized the differential equations are:-

$$\frac{dM}{dt} = k_m \cdot V \cdot C_p - k_{mu} \cdot M$$

Equation 5.2.11 Rate of Change of Amount of Metabolite in the Central Compartment

AND

$$\frac{dMu}{dt} = +k_{mu} \cdot M$$

Equation 5.2.12 Rate of Excretion of Metabolite into Urine

After integrating Equation 5.2.9 [using Laplace transforms](#) we get Equation 5.2.13

$$\begin{aligned} Mu = & \frac{k_{mu} \cdot k_m \cdot \text{Dose}}{k_{el} \cdot k_{mu}} - \frac{k_{mu} \cdot k_m \cdot \text{Dose}}{k_{el} \cdot (k_{mu} - k_{el})} \cdot e^{-k_{el} \cdot t} \\ & + \frac{k_{mu} \cdot k_m \cdot \text{Dose}}{k_{mu} \cdot (k_{mu} - k_{el})} \cdot e^{-k_{mu} \cdot t} \end{aligned}$$

Equation 5.2.13 Cumulative Amount Excreted as Metabolite *versus* Time

Setting each exponential term,  $e^{-k \cdot t}$ , in Equation 5.2.13 to zero gives Equation 5.2.14 for the total amount excreted into urine as the metabolite.

$$Mu^{\infty} = \frac{\cancel{k_{mu}} \cdot k_m \cdot \text{Dose}}{k_{el} \cdot \cancel{k_{mu}}} = \frac{k_m \cdot \text{Dose}}{k_{el}}$$

Equation 5.2.14 Total Amount Excreted as Metabolite into Urine

Adding Equations 5.2.10 and 5.2.14 gives Equation 5.2.15.

$$\begin{aligned}U^{\infty} + Mu^{\infty} &= \frac{k_e \cdot \text{Dose}}{k_{el}} + \frac{k_m \cdot \text{Dose}}{k_{el}} \\ &= \frac{(k_e + k_m) \cdot \text{Dose}}{k_{el}} = \frac{\cancel{k_{el}} \cdot \text{Dose}}{\cancel{k_{el}}} = \text{Dose}\end{aligned}$$

**Equation 5.2.15 Mass Balance - Total Amount Eliminated equals Dose**

Notice the total amount of the drug excreted and metabolized adds up to the Dose. This is based on the assumption that we have information from all the pathways of elimination.

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## Analysis of Urine Data

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### Plotting and Analyzing Urine Data

#### Cumulative amount excreted *versus* time

Urine data is usually collected as drug concentration in the urine sample and the volume of the sample at the end of the collection interval. Multiplying these numbers together gives the amount of drug excreted during the collection interval as  $\Delta U$ . Accumulating these  $\Delta U$  values gives the cumulative amount of drug excreted up to the specified time,  $U$ . We can plot  $U$  *versus* time as the cumulative amount excreted *versus* time plot. As we lose drug from the body it will appear in urine. Earlier we wrote the differential equation for  $U$  and presented the integrated equation for  $U$ , Equation 5.2.9.

The linear plot of cumulative amount excreted into urine as unchanged drug *versus* time is shown below. Notice that the value of  $U^\infty$  is NOT EQUAL to the dose, it is somewhat less than dose, unless all of the dose is excreted into urine as unchanged drug. The remaining portion of the dose should be found as metabolites and from other routes of excretion.

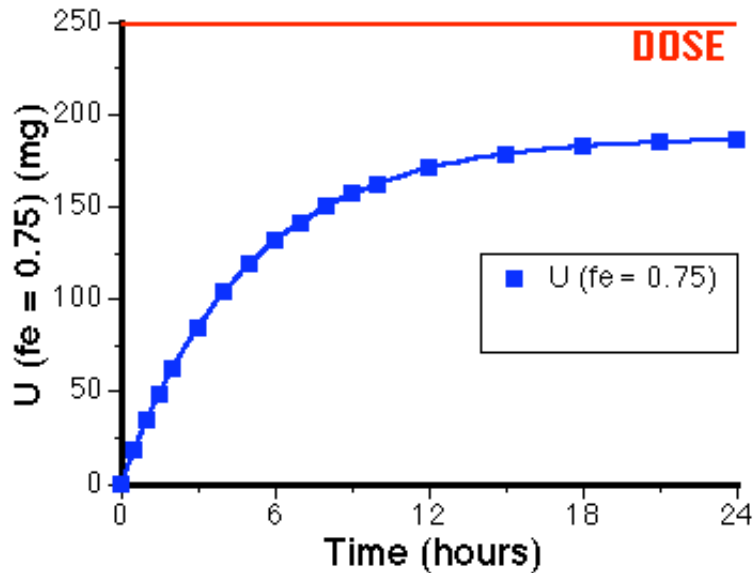
The equation for the cumulative amount excreted *versus* time is shown below in Equation 5.3.1.

$$U = \frac{k_e \cdot \text{Dose}}{k_{el}} \cdot [1 - e^{-k_{el} \cdot t}]$$

$$U = \frac{CL_R \cdot \text{Dose}}{CL} \cdot [1 - e^{-CL \cdot t/V}]$$

**Equation 5.3.1 Cumulative Amount excreted into Urine *versus* Time**

This translates into the plot shown in Figure 5.3.1. Notice that the total amount excreted as unchanged drug,  $U^\infty$ , is less than the dose administered in this plot.



**Figure 5.3.1** Linear Plot of  $U$  versus Time showing Approach to  $U^\infty$  not equal to DOSE

Click on the figure to view the Java Applet window  
Java Applet as a [Semi-log Plot](#)

Cumulative amount excreted plots are basically descriptive in nature. At most, you can get a general sense of how much drug is excreted, an estimate of  $U^\infty$  and an approximate estimate of  $t_{1/2}$ .

### Rate of excretion (R/E)

Equation 5.2.8 on the previous page represents the rate of excretion of unchanged drug into urine as an exponential function.

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

#### Equation 5.3.2 Rate of Excretion of Unchanged Drug into Urine

Since urine data is collected over an interval of time the data is represented as  $\Delta U$  rather than  $dU$ . Also, since  $\Delta U$  is collected over a discrete time interval the time point for this interval should be the midpoint of the interval,  $t_{\text{midpoint}}$ . Equation 5.3.2 can be replaced by Equation 5.3.3 to better represent the data collected. It may look like a strange way of plotting the data, but actually it's quite convenient to use because urine data results are collected as an amount of drug excreted during a time interval. The amount excreted is the product of the volume of urine voided and the concentration of drug in the sample. This is a rate measurement.

$$\frac{\Delta U}{\Delta t} = ke \bullet Dose \bullet e^{-kel \bullet t_{\text{midpoint}}}$$

#### Equation 5.3.3 Rate of Excretion of Unchanged Drug versus midpoint time

Taking the  $\ln$  of both sides gives Equation 5.3.4, an equation for a straight line. Plotting  $\ln[\Delta U/\Delta t]$  versus  $t_{\text{midpoint}}$  provides  $kel$  from the slope and  $ke$  from the intercept divided by the Dose

$$\ln \left[ \frac{\Delta U}{\Delta t} \right] = \ln [k_e \cdot \text{Dose}] - k_{el} \cdot t_{\text{midpoint}}$$

Equation 5.3.4. Natural log of Rate of Excretion *versus* Time

Note: The intercept (on semi-log graph paper) is  $k_e \cdot \text{DOSE}$ .

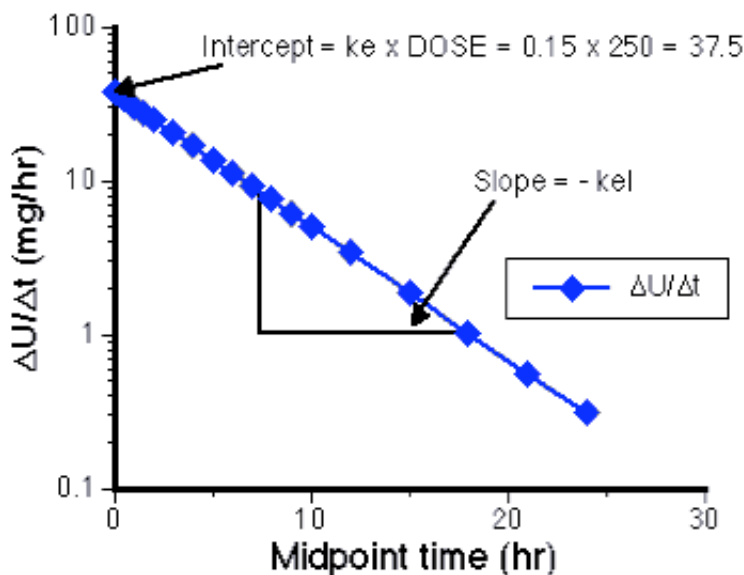


Figure 5.3.2. Semi-log Plot of  $\Delta U/\Delta t$  *versus* Time<sub>midpoint</sub> Showing Slope = -  $k_{el}$

with  $f_e = 0.75$ ,  $k_{el} = 0.2 \text{ hr}^{-1}$ ;  $k_e = 0.15 \text{ hr}^{-1}$

Click on the figure to view the Java Applet window  
Java Applet as a [Linear Plot](#)

Rate of excretion plots can be very useful in the determination of the parameters such as  $k_{el}$ ,  $k_e$  and  $f_e$ . There can be a little more scatter than with the ARE plot, below. Analysis of 'real' data may show considerable scatter in the rate of excretion plot. Thus, positioning the straight line on a semi-log plot may be difficult. In practical terms it is difficult to get a lot of early times points unless the subjects are catheterized and even then early times may be difficult to interpret. This means that this method can be difficult to use with drugs which have short half-lives. However, a significant advantage of the rate of excretion plot is that each data point is essentially independent, especially if the bladder is fully voided for each sample. A missed sample or data points is not critical to the analysis.

**NOTE:** This plot is rate of excretion *versus* midpoint of the collection interval, time.

**Amount remaining to be excreted (ARE)**

The third plot is the amount remaining to be excreted, the ARE plot. The equation for this plot can be derived from Equation 5.3.1.

$$U = \frac{ke \cdot Dose}{kel} \cdot [1 - e^{-kel \cdot t}]$$

**Equation 5.3.5 Cumulative amount excreted versus time**

$$\text{Since } U^\infty = \frac{ke \cdot Dose}{kel}$$

**Equation 5.3.6 Total Amount Excreted as Unchanged Drug,  $U^\infty$**

Equation 5.3.5 can be rewritten in terms of  $U^\infty$ .

$$U = U^\infty \cdot [1 - e^{-kel \cdot t}]$$

**Equation 5.3.7 Cumulative amount excreted versus time**

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

**Equation 5.3.8 Cumulative amount excreted versus time**

Rearranging Equation 5.3.8 gives Equation 5.3.9.

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

**Equation 5.3.9 Amount Remaining to be Excreted as Unchanged Drug versus Time**

Taking the log of both sides give the straight line equation. Plotting  $\ln[U^\infty - U]$  versus time provides  $kel$  from the slope and  $U^\infty$  from the intercept.

$$\ln[U^\infty - U] = \ln[U^\infty] - kel \cdot t$$

**Equation 5.3.10 Ln(ARE) versus time**

where

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

**Equation 5.3.11  $U^\infty$**

Note  $ke$  and  $fe$

Thus:

$$\ln(U^\infty - U) = \ln(f_e \cdot \text{Dose}) - k_{el} \cdot t$$

Equation 5.3.12 ARE *versus* time

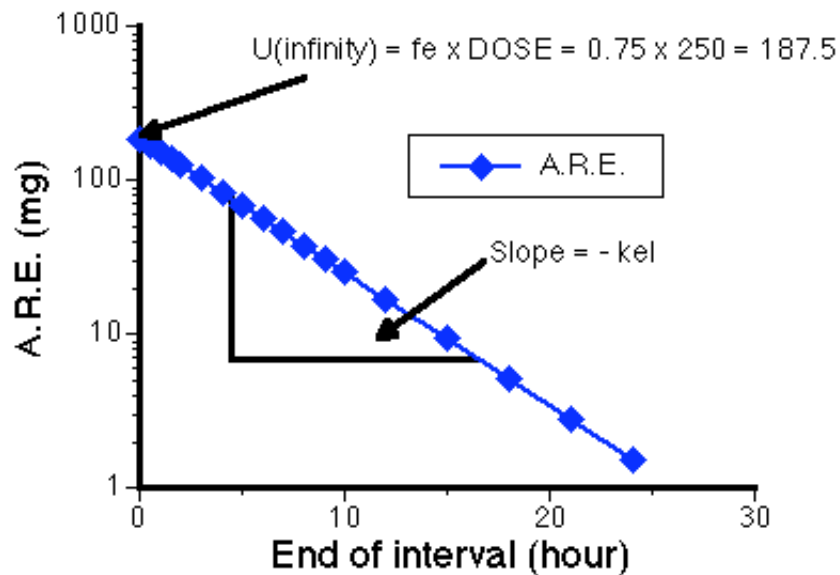


Figure 5.3.3 Semi-log Plot of ARE *versus* time

Note ke

Click on the figure to view the Java Applet window  
Java Applet as a [Linear Plot](#)

Amount remaining to be excreted (ARE) plots use the  $U^\infty$  value to estimate each data point. Error in any data is accumulated into  $U^\infty$  and thus each ARE value. This can lead to curved lines (instead of the expected straight lines) or an inability to use the method (with a missing sample). With good data these plots may be somewhat smoother.

**For practice** you can use these urine data collected after an IV bolus dose and [estimate pharmacokinetic parameters](#).

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### Fraction Excreted or Metabolized, $f_e$ or $f_m$

The equations provided on the two previous pages provide two new parameters, the fraction excreted unchanged in urine,  $f_e$ , and the fraction metabolized,  $f_m$

$$f_e = \frac{k_e}{k_{el}} = \frac{U^\infty}{\text{Dose}}$$

**Equation 5.4.1 Fraction Excreted into Urine as Unchanged Drug**

and

$$f_m = \frac{k_m}{k_{el}} = \frac{Mu^\infty}{\text{Dose}}$$

**Equation 5.4.2 Fraction Excreted into Urine as a Metabolite**

Equation 5.4.2 could be repeated for any number of metabolites. Note:

$$f_e + f_{m_1} + f_{m_2} + \dots = 1$$

#### Calculator 5.4.1 Estimate $f_e$ and $f_m$ using Equations 5.4.1 and 5.4.2

Calculate  $f_e$  given Dose and  $U^\infty$

Dose (mg)	<input type="text" value="100"/>
$U^\infty$ (mg)	<input type="text" value="75"/>
	<input type="button" value="Calculate &lt;math&gt;f_e&lt;/math&gt; and &lt;math&gt;f_m&lt;/math&gt;"/>
<b><math>f_e</math> (no units) is:</b>	<input type="text"/>
<b><math>f_m</math> (no units) is:</b>	<input type="text"/>

### Renal function

We can now use this information to start to understand dosage adjustments for patients with poor kidney function. These patients will have reduced ability to excrete some drugs. That is the  $k_e$  value for a drug will be lower in these patients than in normal patients. Depending on the value of  $f_e$  this may have a large effect on  $k_{el}$  or it may be insignificant. Fortunately there are a number of clinical tests for renal function which can be used. One common one is creatinine clearance. Creatinine is formed in the body and is excreted almost entirely by filtration in the kidney. The normal creatinine clearance value is similar to the glomerular filtration rate of 120 to 130 ml/min. We can measure the  $CL_{Cr}$  prior to drug treatment and adjust the dosage accordingly.

For example. Vancomycin  $f_e = 0.95$  (Dose 500 mg;  $V = 33L$ ;  $C_p^0 = 15 \text{ mg/L}$ )

The normal  $k_{el} = 0.116 \text{ hr}^{-1}$  ( $t_{1/2} = 6 \text{ hr}$ )

Equation 5.4.1, the equation for  $f_e$ , leads to:

$$k_e = f_e \cdot k_{el} = 0.95 \cdot 0.116 = 0.110 \text{ hr}^{-1}$$

$$k_m = f_m \cdot k_{el} = 0.05 \cdot 0.116 = 0.006 \text{ hr}^{-1}$$

If we now consider a patient with a creatinine clearance of 12 to 13 ml/min. That is, about 1/10 th of the normal kidney function,  $k_e$  should then be about 1/10 of normal in this patient.

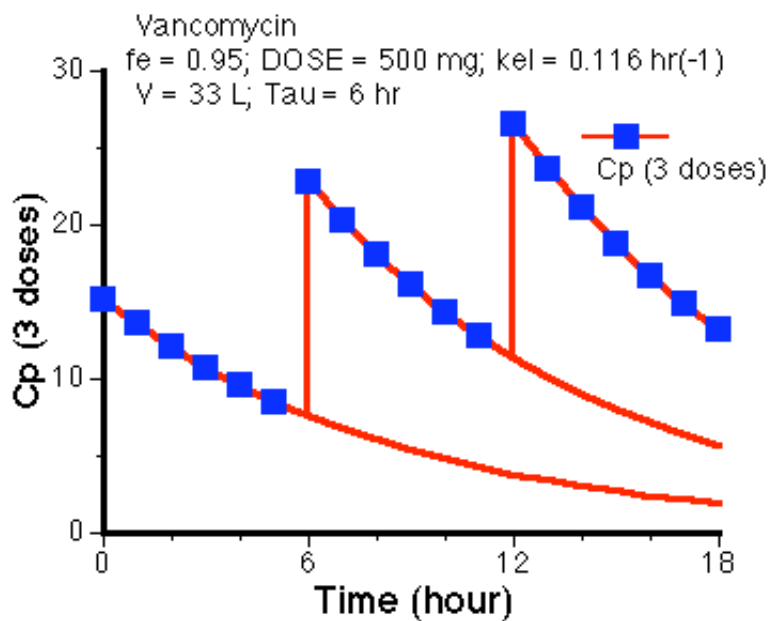
therefore

$$k_e^{\text{patient}} = 0.011 \text{ hr}^{-1}$$

Now assuming  $k_m$  is unchanged

$$\begin{aligned} k_{el}^{\text{patient}} &= k_e^{\text{patient}} + k_m \\ &= 0.011 + 0.006 \text{ hr}^{-1} \\ &= 0.017 \text{ hr}^{-1} \quad (t_{1/2} = 41 \text{ hour}) \end{aligned}$$

Thus the half-life changes from 6 hours to 41 hours in this patient with impaired renal function. Therefore it takes seven times longer for the body to eliminate half the dose. If repeated doses were given based on a normal half-life the levels in this patient would rapidly reach toxic concentrations.



**Figure 5.4.1 Plot of  $C_p$  versus Time after Multiple Doses in Normal Patient**

Compare Figure 5.4.1 with Figure 5.4.2

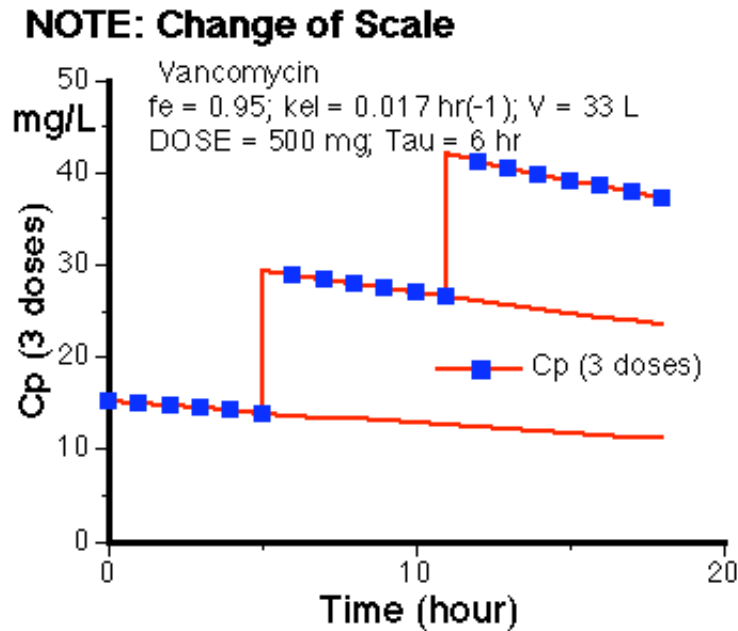


Figure 5.4.2 Plot of  $C_p$  versus Time after Multiple Doses

Click on the figure to view the Java Applet window  
 Java Applet as a [Semi-log Plot](#)

**Calculator 5.4.2 Calculate  $k_{el}$  and  $t_{1/2}$  in a patient with impaired renal function**

Normal Elimination Rate Constant ( $\text{hr}^{-1}$ )	<input type="text" value="0.116"/>	
Normal Fraction excreted unchanged, $f_e$	<input type="text" value="0.95"/>	
Percent Renal Function in Patient of Interest	<input type="text" value="10"/>	
<input type="button" value="Calculate &lt;math&gt;k_m&lt;/math&gt;, &lt;math&gt;k_e&lt;/math&gt; and &lt;math&gt;k_{el}&lt;/math&gt; in this patient"/>		
Normal half-life $t_{1/2}$ (hr) is:	<input type="text"/>	$t_{1/2} = \ln(2)/k_{el}$
Normal $k_e$ value ( $\text{hr}^{-1}$ ) is:	<input type="text"/>	$k_e = f_e \cdot k_{el}$
Normal $k_m$ value ( $\text{hr}^{-1}$ ) is:	<input type="text"/>	$k_m = k_{el} - k_e$
<b>Patient <math>k_e</math> value (<math>\text{hr}^{-1}</math>) is:</b>	<input type="text"/>	$k_e(\text{patient}) = k_e \cdot \text{percent renal function}$
<b>Patient <math>k_m</math> value (<math>\text{hr}^{-1}</math>) is:</b>	<input type="text"/>	$k_m(\text{patient}) = k_m$
<b>Patient <math>k_{el}</math> value (<math>\text{hr}^{-1}</math>) is:</b>	<input type="text"/>	$k_{el}(\text{patient}) = k_e(\text{patient}) + k_m$
<b>Patient <math>t_{1/2}</math> value (hr) is:</b>	<input type="text"/>	$t_{1/2}(\text{patient}) = \ln(2)/k_{el}(\text{patient})$

**Another example**

For another drug, erythromycin,  $f_e = 0.15$  (Dose = 250 mg) the normal  $k_{el} = 0.58 \text{ hr}^{-1}$  ( $t_{1/2} = 1.2 \text{ hr}$ )

$$k_e^{\text{normal}} = 0.58 \times 0.15 = 0.087 \text{ hr}^{-1}$$

$$k_m = 0.58 \times 0.85 = 0.493 \text{ hr}^{-1}$$

if the patient  $k_e$  is reduced by a tenth

the  $k_e^{\text{patient}} = 0.009 \text{ hr}^{-1}$

and again assuming that  $k_m$  is unchanged

$$\begin{aligned}k_{e|p}^{\text{patient}} &= k_e^{\text{patient}} + k_m \\ &= 0.009 + 0.493 \text{ hr}^{-1} \\ &= 0.502 \text{ hr}^{-1} \quad (t_{1/2} = 1.4 \text{ hour})\end{aligned}$$

Thus the half-life changes from 1.2 hour to 1.4 hours.

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## References

- Bennett et al. 1977 Annuals of Int. Medicine 186, 754
- Bennett et al. 1974 J.A.M.A. 230 1544

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### Clearance

Clearance can be defined as the volume of plasma which is completely cleared of drug per unit time but this isn't always a clear explanation of this important parameter. The symbol is CL and common units are ml/min, L/hr, i.e. volume per time. One way of looking at clearance is to consider the drug being eliminated from the body ONLY via the kidneys. [If we were to also assume that all of the drug that reaches the kidneys is removed from the plasma then we have a situation where the clearance of the drug is equal to the plasma flow rate to the kidneys. All of the plasma reaching the kidneys would be cleared of drug]. The amount cleared by the body per unit time is  $dX/dt$  ( $= dU/dt$ ), the rate of excretion (also the rate of elimination in this example). To calculate the volume which contains that amount of drug we can divide by  $C_p$ . That is the volume = amount/concentration. This is the same as [Equation 4.10.2](#) in Chapter 4.

$$CL = -\frac{dX}{dt} \cdot \frac{1}{C_p} = \frac{dU}{dt} \cdot \frac{1}{C_p}$$

**Equation 5.5.1 Clearance as the Ratio of Rate of Excretion to  $C_p$**

For this particular example where elimination = excretion and  $k_{el} = k_e$  we can derive another equation for clearance which may be useful.

Since

$$\frac{dU}{dt} = k_{el} \cdot V \cdot C_p [= k_e \cdot V \cdot C_p]$$

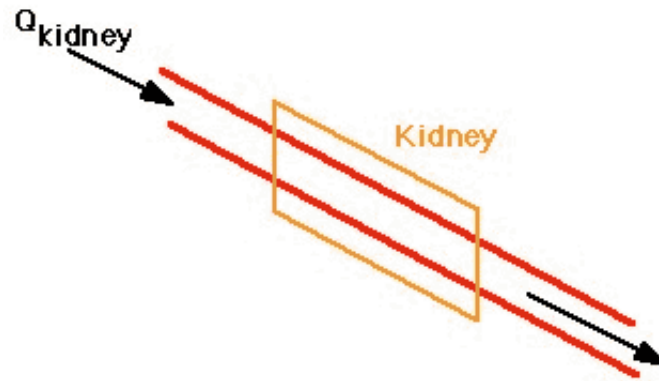
**Equation 5.5.2 Rate of Excretion**

$$CL = \frac{k_{el} \cdot V \cdot C_p}{C_p} = k_{el} \cdot V$$

**Equation 5.5.3 Clearance calculated from  $k_{el}$  and  $V$**

As we have defined the term here CL is the total body clearance. We have assumed that the drug is cleared totally by excretion in urine. Below we will see that the total body clearance can be divided into clearance due to renal excretion and that due to other processes such as metabolism.

Clearance is a useful term when talking of drug elimination since it can be related to the efficiency of the organs of elimination and blood flow to the organ of elimination. It is useful in investigating mechanisms of elimination and renal or hepatic function in cases of reduced clearance of test substances. The units of clearance, volume/time (e.g. ml/min) may be easier to visualize, compared with elimination rate constant (units 1/time, e.g. 1/hr) although half-life (in units of time) are probably even easier. Some people view clearance as a primary pharmacokinetic parameter along with the apparent volume of distribution.



**Figure 5.5.1 Drug clearance via the Kidney**

If the kidney removes all of the drug presented by blood flow then the renal clearance will be equal to renal blood flow,  $Q_{\text{renal}} (= Q_{\text{kidney}})$ .

When a drug is eliminated by more than one pathway total body clearance,  $CL$ , can be separated into various clearance terms describing these pathways. Thus, total body clearance might be split into clearance due to renal excretion,  $CL_r$  and clearance due to another pathway such as metabolism,  $CL_m$ .

$$CL_r = k_e \cdot V$$

**Equation 5.5.4 Renal Clearance from  $k_e$  and  $V$**

and

$$CL_m = k_m \cdot V$$

**Equation 5.5.5 Metabolic or Hepatic Clearance from  $k_m$  and  $V$**

Note

$$CL = k_{el} \cdot V$$

**Equation 5.5.6 Total Body Clearance from  $k_{el}$  and  $V$**

## Clearance can also be Calculated using AUC

Another more general method of calculating clearance can be derived from the basic definition, Equation 5.5.1. For renal clearance we can write:

$$\frac{dU}{dt} = CL_r \cdot C_p$$

**Equation 5.5.7 Renal Clearance**

Integrating both sides gives

$$U^{\infty} = CL_R \cdot \int_{t=0}^{t=\infty} C_p \cdot dt = CL_R \cdot AUC$$

**Equation 5.5.8 Renal Clearance Integrated Equation**

Rearranging gives

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

**Equation 5.5.9 Renal Clearance calculated from  $U^{\infty}$  and AUC**

Hepatic or metabolic clearance can be derived in a similar fashion.

$$CL_m = \frac{M^{\infty}}{AUC}$$

**Equation 5.5.10 Hepatic Clearance calculated from  $M^{\infty}$  and AUC**

Since the total amount eliminated is the dose (or at least  $F \cdot \text{Dose}$ ) total body clearance can also be calculated from the AUC.

$$CL = \frac{\text{Dose}}{AUC}$$

**Equation 5.5.11 Total body clearance Calculated from Dose and AUC**

Unlike Equations 5.5.4, 5 and 6 which use model derived parameter values. Equations 5.5.9, 10 and 11 use the model independent parameters AUC and Dose,  $U^{\infty}$  or  $M^{\infty}$ .

## Variable Renal Clearance

Equation 5.5.7 can be useful in determining if renal clearance is consistent throughout or between dosing intervals. Plotting  $\Delta U/\Delta t$  versus  $C_{p_{\text{midpoint}}}$  for the collection interval,  $\Delta t$ , should provide a straight line if renal clearance is constant. Dividing  $\Delta U/\Delta t$  by  $C_{p_{\text{midpoint}}}$  provides estimates of renal clearance for each collection period (Equation 5.5.1).

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### References

- Clearance has been discussed on [the PharmPK listserv](#).

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# PHAR 7632 Chapter 5

## Analysis of Urine Data

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### Example Calculation of Urine Analysis Plots

After an IV dose of 300 mg, total urine samples were collected and assayed for drug concentration. Thus the data collected is the volume of urine collected and the drug concentration in urine during each interval. These are the data in columns 1, 2 and 3 of Table 5.6.1.

**Table 5.6.1. Example Data Analysis of Drug in Urine Data**

Time Interval (hr)	Urine Volume (ml)	Urine Concentration (mg/ml)	Amount Excreted $\Delta U$ (mg)	Cumulative Amount Excreted U (mg)	Midpoint Time $t_{midpt}$ (hr)	Rate of Excretion $\Delta U/\Delta t$ (mg/hr)	A.R.E. (mg)
0 - 2	50	1.666	83.3	83.3			116.8
					1	41.7	
2 - 4	46	1.069	49.2	132.5			67.7
					3	24.6	
4 - 6	48	0.592	28.4	160.9			39.2
					5	14.2	
6 - 8	49	0.335	16.4	177.3			22.8
					7	8.2	
8 - 10	46	0.210	9.7	187			13.2
					9	4.8	
10 - 12	48	0.116	5.6	192.5			7.6
					11	2.8	
12 - 18	134	0.047	6.3	198.8			1.3
					15	1	
18 - 24	144	0.009	1.3	200.1			-
					21	0.2	
24 - $\infty$	-	-	-	200.1			

## Completing the Table

- Multiplying column 2 by column 3 gives  $\Delta U$ , column 4, the amount excreted during the interval.
- Accumulating the  $\Delta U$  amounts in column 4 gives the cumulative amount excreted,  $U$ , up to the end of the current time interval. The total amount excreted,  $U^\infty$  is found at the bottom of column 5, that is 500 mg.
- The rate of excretion,  $\Delta U/\Delta t$ , is calculated by dividing the  $\Delta U$  amount by the length of the time interval,  $\Delta t$ .
- A.R.E. in the last column is calculated by subtracting the value for  $U$  in each row from  $U^\infty$ .

## The Data Plots

### Cumulative Amount Excreted into Urine Plot

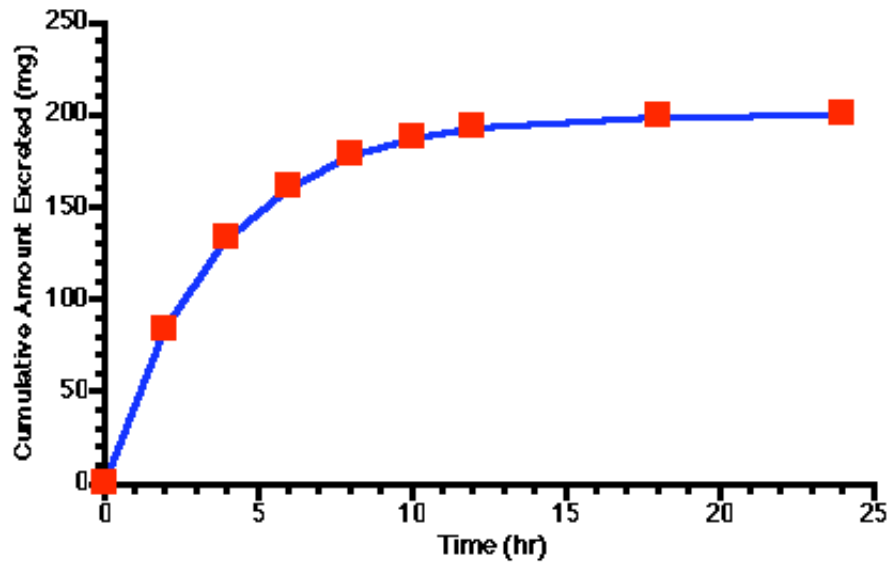


Figure 5.6.1 Linear Plot of Cumulative Amount Excreted *versus* Time

The plot in Figure 5.6.1 shows  $U$  rapidly increasing at first then leveling off to  $U^\infty (= 200 \text{ mg})$ . NOTE:  $U^\infty \neq \text{DOSE}$  for this set of data. Notice that  $U^\infty/2$  (100 mg) is excreted in about 3 hours which gives an estimate of the elimination half-life. Otherwise this plot is a qualitative representation of the data.

## Calculation Using Rate of Excretion Data

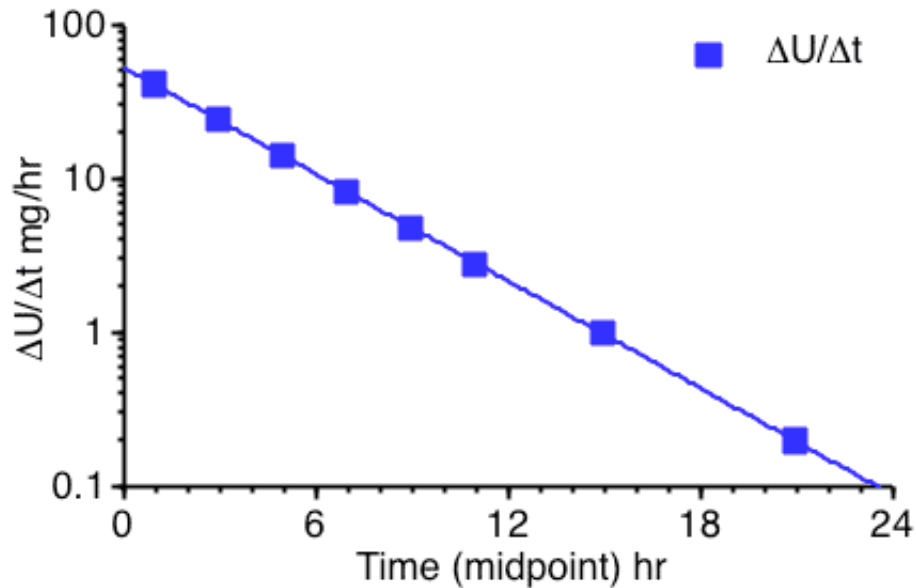


Figure 5.6.2 Semi-log Plot of Rate of Excretion *versus* Time

The plots in Figures 5.6.2 and 5.6.3 (below) are more useful for calculating parameter values. A straight line can be drawn through the data on each semi-log plot. The elimination rate constant,  $k_{el}$ , can be determined from the slope of this line and  $k_e$  or  $f_e$  determined from the intercept.

Figure 5.6.2 provides a semi-log plot of  $\Delta U/\Delta t$  *versus*  $t_{\text{midpoint}}$ . As you can see this gives a reasonably straight line plot.

Estimating the intercept value to be 53 mg/hr and if the line crosses the axis at 23.6 hr where the rate of excretion is 0.1 mg/hr a value for  $k_{el}$  can be estimated.

$$k_{el} = \frac{\ln(53) - \ln(0.1)}{23.6 - 0} = \frac{3.970 - -2.303}{23.6} = 0.266 \text{ hr}^{-1}$$

and  $k_e$  can be determined from the intercept.

$$k_e = \frac{\text{intercept}}{\text{dose}} = \frac{53}{300} = 0.177 \text{ hr}^{-1}$$

Thus  $f_e = k_e/k_{el} = 0.177/0.266 = 0.665$ .

This plot can be used to estimate  $k_{el}$ ,  $k_e$  and  $f_e$ . A disadvantage of this type of plot is that the error present in "real" data can obscure the straight line and lead to results which lack precision. Also it can be difficult to collect frequent, accurately timed urine samples. This is especially true when the elimination half-life is small.

## Calculation Using A.R.E. Data

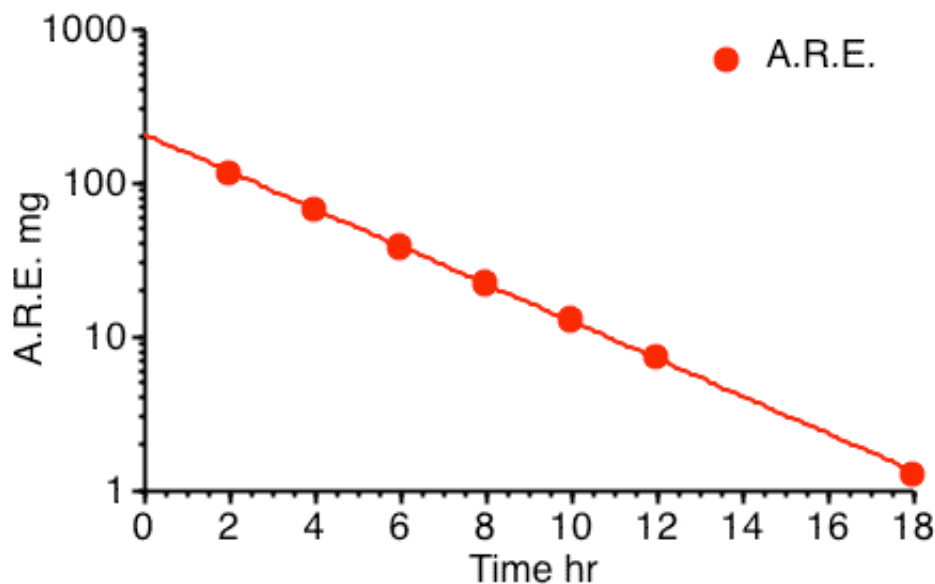


Figure 5.6.3 Semi-log Plot of A.R.E. versus Time

The A.R.E. data are plotted as red circles on Figure 5.6.3 above. Estimating the intercept value to be 210 mg and if the line crosses the axis at 19 hr where the A.R.E. is 1 mg a value for  $k_{el}$  can be estimated.

$$k_{el} = \frac{\ln(210) - \ln(1)}{19 - 0} = \frac{5.347 - 0}{19} = 0.281 \text{ hr}^{-1}$$

and  $f_e$  can be determined from the intercept.

$$f_e = \frac{\text{intercept}}{\text{dose}} = \frac{210}{300} = 0.7$$

Thus  $k_e = f_e \cdot k_{el} = 0.7 \times 0.281 = 0.197 \text{ hr}^{-1}$

One disadvantage of this approach is that the errors are cumulative, with collection interval, and the total error is incorporated into the  $U^\infty$  values and therefore into each A.R.E. value. Another problem is that total (all) urine collections are necessary. One missed sample means errors in all the results calculated.

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**For practice** you can use these urine data collected after an IV bolus dose and [estimate pharmacokinetic parameters](#).

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